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H.R.5546 - National Childhood Vaccine Injury Act of 1986

99th Congress (1985-1986)

Sponsor: Rep. Waxman, Henry A. [D-CA-24] (Introduced 09/18/1986)

Committees: House - Energy and Commerce; Ways and Means | Senate - Labor and Human Resources

Committee Reports: H.Rept 99-908 Part 1

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(Measure passed House, amended)
National Childhood Vaccine Injury Act of 1986 - **Title I: Vaccines - Subtitle 1: National Vaccine Program** - Amends the Public Health Service Act to establish in the Department of Health and Human Services a National Vaccine Program to: (1) direct vaccine research and development within the Federal Government; (2) ensure the production and procurement of safe and effective vaccines; (3) direct the distribution and use of vaccines; and (4) coordinate governmental and nongovernmental activities. Requires the Director of the Program to report to specified congressional committees.

Establishes the National Vaccine Advisory Committee to recommend: (1) ways to encourage the availability of an adequate supply of vaccines; and (2) research priorities.

Authorizes appropriations for FY 1987 through 1991.

Subtitle 2: National Vaccine Injury Compensation Program - **Part A: Program Requirements** - Establishes the National Vaccine Injury Compensation Program as an alternative remedy to judicial action for specified vaccine-related injuries.

Prescribes the contents of any petition for compensation.

Grants U.S. district courts authority to determine eligibility and compensation. Requires the district court in which the petition is filed to designate a special master to serve as an adjunct to the court. Sets forth the responsibilities of the court.

Lists factors to be considered when determining the amount of a compensation award. Sets forth a table of injuries deemed vaccine-related for compensation purposes. Permits the Secretary of Health and Human Services to: (1) promulgate regulations to revise such table; and (2) recommend changes to the vaccines covered by the table.

Provides that compensation awarded under the Program shall be paid out of the National Vaccine Injury Compensation Trust Fund. Limits awards for actual and projected pain and suffering and emotional distress to $250,000. Prohibits awards for punitive damages.

Establishes the Advisory Commission on Childhood Vaccines to: (1) advise the Secretary on the implementation of the Program; (2) recommend changes to the Vaccine Injury Table; and (3) recommend research priorities.

Part B: Additional Remedies - Sets forth procedures under which the person who filed a petition for compensation under the program may elect to file a civil action for damages.

Provides that no vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death: (1) resulting from unavoidable side effects; or (2) solely due to the manufacturer's failure to provide direct warnings. Provides that a manufacturer may be held liable where: (1) such manufacturer engaged in the fraudulent or intentional withholding of information; or (2) such manufacturer failed to exercise due care. Permits punitive damages in such civil actions under certain circumstances.

Part C: Assuring a Safer Childhood Vaccination Program in the United States - Requires each health care provider who administers a vaccine listed in the Vaccine Injury Table to record certain information with respect to each such vaccine. Requires each health care provider and vaccine manufacturer to report certain information to the Secretary.

Requires the Secretary to develop certain vaccine information materials for distribution to the legal representatives of any child receiving a vaccine listed in the Vaccine Injury Table.

Directs the Secretary to promote the development of safer childhood vaccines.

Sets forth recordkeeping and reporting requirements for vaccine manufacturers. Imposes civil and criminal penalties for destroying, altering, or concealing any such report or record.

Part D: General Provisions - Allows any person to commence a civil action against the Secretary where the Secretary allegedly has failed to perform a duty under this Act. Provides for judicial review of the Secretary's regulatory actions in a court of appeals of the United States.

Allows the Secretary to provide licensing for unpatented vaccines for naturally occurring human infectious diseases under certain circumstances.

Requires the Secretary to conduct studies on pertussis, rubella, and radiculoneuritis vaccines and publish the results of such studies.

Directs the Secretary to study the risks to children associated with each vaccine listed in the Vaccine Injury Table and establish guidelines respecting the administration of such vaccines. Directs the Secretary to periodically review and revise such guidelines.

Directs the Secretary to review the warnings, use instructions, and precautionary information presently used by manufacturers of vaccines listed in the Vaccine Injury Table. Directs the Secretary to require manufacturers to revise and reissue any warning, instruction, or information found inadequate.

Grants the Secretary recall authority with respect to any licensed virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other licensed product which presents a danger to public health. Establishes civil penalties for recall violations.

Directs the Secretary to make annual reports to specified congressional committees on the impact this Act has on the supply of vaccines.

Title II: Miscellaneous - Provides that certain Federal provisions designed to reduce paperwork shall not apply to information required to carry out this Act.

Syllabus

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Timber & Lumber Co.,* 200 U. S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

BRUESEWITZ ET AL. *v.* WYETH LLC, FKA WYETH, INC., ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 09–152. Argued October 12, 2010—Decided February 22, 2011

The National Childhood Vaccine Injury Act of 1986 (NCVIA or Act) created a no-fault compensation program to stabilize a vaccine market adversely affected by an increase in vaccine-related tort litigation and to facilitate compensation to claimants who found pursuing legitimate vaccine-inflicted injuries too costly and difficult. The Act provides that a party alleging a vaccine-related injury may file a petition for compensation in the Court of Federal Claims, naming the Health and Human Services Secretary as the respondent; that the court must resolve the case by a specified deadline; and that the claimant can then decide whether to accept the court's judgment or reject it and seek tort relief from the vaccine manufacturer. Awards are paid out of a fund created by an excise tax on each vaccine dose. As a *quid pro quo,* manufacturers enjoy significant tort-liability protections. Most importantly, the Act eliminates manufacturer liability for a vaccine's unavoidable, adverse side effects.

Hannah Bruesewitz's parents filed a vaccine-injury petition in the Court of Federal Claims, claiming that Hannah became disabled after receiving a diphtheria, tetanus, and pertussis (DTP) vaccine manufactured by Lederle Laboratories (now owned by respondent Wyeth). After that court denied their claim, they elected to reject the unfavorable judgment and filed suit in Pennsylvania state court, alleging, *inter alia,* that the defective design of Lederle's DTP vaccine caused Hannah's disabilities, and that Lederle was subject to strict liability and liability for negligent design under Pennsylvania common law. Wyeth removed the suit to the Federal District Court. It granted Wyeth summary judgment, holding that the relevant Pennsylvania law was preempted by 42 U. S. C. §300aa–22(b)(1), which

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provides that "[n]o vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side-effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings." The Third Circuit affirmed.

Held: The NCVIA preempts all design-defect claims against vaccine manufacturers brought by plaintiffs seeking compensation for injury or death caused by a vaccine's side effects. Pp. 7–19.

(a) Section 300aa–22(b)(1)'s text suggests that a vaccine's design is not open to question in a tort action. If a manufacturer could be held liable for failure to use a different design, the "even though" clause would do no work. A vaccine side effect could always have been avoidable by use of a different vaccine not containing the harmful element. The language of the provision thus suggests the design is not subject to question in a tort action. What the statute establishes as a complete defense must be unavoidability (given safe manufacture and warning) with respect to the particular design. This conclusion is supported by the fact that, although products-liability law establishes three grounds for liability—defective manufacture, inadequate directions or warnings, and defective design—the Act mentions only manufacture and warnings. It thus seems that the Act's failure to mention design-defect liability is "by deliberate choice, not inadvertence." *Barnhart* v. *Peabody Coal Co.*, 537 U. S. 149, 168. Pp. 7–8.

(b) Contrary to petitioners' argument, there is no reason to believe that §300aa–22(b)(1)'s term "unavoidable" is a term of art incorporating Restatement (Second) of Torts §402A, Comment *k,* which exempts from strict liability rules "unavoidably unsafe products." "Unavoidable" is hardly a rarely used word, and cases interpreting comment *k* attach special significance only to the term "unavoidably unsafe products," not the word "unavoidable" standing alone. Moreover, reading the phrase "side effects that were unavoidable" to exempt injuries caused by flawed design would require treating "even though" as a coordinating conjunction linking independent ideas when it is a concessive, subordinating conjunction conveying that one clause weakens or qualifies the other. The canon against superfluity does not undermine this Court's interpretation because petitioners' competing interpretation has superfluity problems of its own. Pp. 8–12.

(c) The structure of the NCVIA and of vaccine regulation in general reinforces what §300aa–22(b)(1)'s text suggests. Design defects do not merit a single mention in the Act or in Food and Drug Administration regulations that pervasively regulate the drug manufacturing process. This lack of guidance for design defects, combined with

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the extensive guidance for the two liability grounds specifically mentioned in the Act, strongly suggests that design defects were not mentioned because they are not a basis for liability. The Act's mandates lead to the same conclusion. It provides for federal agency improvement of vaccine design and for federally prescribed compensation, which are other means for achieving the two beneficial effects of design-defect torts—prompting the development of improved designs, and providing compensation for inflicted injuries. The Act's structural *quid pro quo* also leads to the same conclusion. The vaccine manufacturers fund an informal, efficient compensation program for vaccine injuries in exchange for avoiding costly tort litigation and the occasional disproportionate jury verdict. Taxing their product to fund the compensation program, while leaving their liability for design defect virtually unaltered, would hardly coax them back into the market. Pp. 13–16.

561 F. 3d 233, affirmed.

SCALIA, J., delivered the opinion of the Court, in which ROBERTS, C. J., and KENNEDY, THOMAS, BREYER, and ALITO, JJ., joined. BREYER, J., filed a concurring opinion. SOTOMAYOR, J., filed a dissenting opinion, in which GINSBURG, J., joined. KAGAN, J., took no part in the consideration or decision of the case.

SUPREME COURT OF THE UNITED STATES

No. 09–152

RUSSELL BRUESEWITZ, ET AL., PETITIONERS *v.* WYETH LLC, FKA WYETH, INC., FKA WYETH LABORATORIES, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

[February 22, 2011]

JUSTICE SCALIA delivered the opinion of the Court.

We consider whether a preemption provision enacted in the National Childhood Vaccine Injury Act of 1986 (NCVIA)[1] bars state-law design-defect claims against vaccine manufacturers.

I

A

For the last 66 years, vaccines have been subject to the same federal premarket approval process as prescription drugs, and compensation for vaccine-related injuries has been left largely to the States.[2] Under that regime, the elimination of communicable diseases through vaccination became "one of the greatest achievements" of public health in the 20th century.[3] But in the 1970's and 1980's vac-

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[1] 42 U. S. C. §300aa–22(b)(1).

[2] See P. Hutt, R. Merrill, & L. Grossman, Food and Drug Law 912–913, 1458 (3d ed. 2007).

[3] Centers for Disease Control, Achievements in Public Health, 1900–1999: Impact of Vaccines Universally Recommended for Children, 48 Morbidity and Mortality Weekly Report 243, 247 (Apr. 2, 1999).

cines became, one might say, victims of their own success. They had been so effective in preventing infectious diseases that the public became much less alarmed at the threat of those diseases,[4] and much more concerned with the risk of injury from the vaccines themselves.[5]

Much of the concern centered around vaccines against diphtheria, tetanus, and pertussis (DTP), which were blamed for children's disabilities and developmental delays. This led to a massive increase in vaccine-related tort litigation. Whereas between 1978 and 1981 only nine product-liability suits were filed against DTP manufacturers, by the mid-1980's the suits numbered more than 200 each year.[6] This destabilized the DTP vaccine market, causing two of the three domestic manufacturers to withdraw; and the remaining manufacturer, Lederle Laboratories, estimated that its potential tort liability exceeded its annual sales by a factor of 200.[7] Vaccine shortages arose when Lederle had production problems in 1984.[8]

Despite the large number of suits, there were many complaints that obtaining compensation for legitimate vaccine-inflicted injuries was too costly and difficult.[9] A

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[4] See Mortimer, Immunization Against Infectious Disease, 200 Science 902, 906 (1978).

[5] See National Vaccine Advisory Committee, A Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities 2–3 (Dec. 2008) (hereinafter NVAC), http://www.hhs.gov/nvpo/nvac/documents/vaccine-safety-review.pdf (as visited Feb. 18, 2011, and available in Clerk of Court's case file).

[6] See Sing & Willian, Supplying Vaccines: An Overview of the Market and Regulatory Context, in Supplying Vaccines: An Economic Analysis of Critical Issues 45, 51–52 (M. Pauly, C. Robinson, S. Sepe, M. Sing, & M. William eds. 1996).

[7] See *id.,* at 52.

[8] See Centers for Disease Control, Diptheria-Tetanus-Pertussis Vaccine Shortage, 33 Morbidity and Mortality Weekly Report 695–696 (Dec. 14, 1984).

[9] See Apolinsky & Van Detta, Rethinking Liability for Vaccine Injury, 19 Cornell J. L. & Pub. Pol'y 537, 550–551 (2010); T. Burke, Lawyers,

significant number of parents were already declining vaccination for their children,[10] and concerns about compensation threatened to depress vaccination rates even further.[11] This was a source of concern to public health officials, since vaccines are effective in preventing outbreaks of disease only if a large percentage of the population is vaccinated.[12]

To stabilize the vaccine market and facilitate compensation, Congress enacted the NCVIA in 1986. The Act establishes a no-fault compensation program "designed to work faster and with greater ease than the civil tort system." *Shalala* v. *Whitecotton*, 514 U. S. 268, 269 (1995). A person injured by a vaccine, or his legal guardian, may file a petition for compensation in the United States Court of Federal Claims, naming the Secretary of Health and Human Services as the respondent.[13] A special master then makes an informal adjudication of the petition within (except for two limited exceptions) 240 days.[14] The Court of Federal Claims must review objections to the special master's decision and enter final judgment under a similarly tight statutory deadline.[15] At that point, a claimant has two options: to accept the court's judgment and forgo a traditional tort suit for damages, or to reject the judgment and seek tort relief from the vaccine manufacturer.[16]

Fast, informal adjudication is made possible by the Act's Vaccine Injury Table, which lists the vaccines covered under the Act; describes each vaccine's compensable,

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Lawsuits, and Legal Rights: The Battle over Litigation in American Society 146 (2002).

[10] Mortimer, *supra*, at 906.

[11] See Hagan, 45 Food Drug Cosm. L. J. 477, 479 (1990).

[12] See R. Merrill, Introduction to Epidemiology 65–68 (2010).

[13] See 42 U. S. C. §300aa–11(a)(1).

[14] See §300aa–12(d)(3).

[15] See §300aa–12(e), (g).

[16] See §300aa–21(a).

adverse side effects; and indicates how soon after vaccination those side effects should first manifest themselves.[17] Claimants who show that a listed injury first manifested itself at the appropriate time are prima facie entitled to compensation.[18] No showing of causation is necessary; the Secretary bears the burden of disproving causation.[19] A claimant may also recover for unlisted side effects, and for listed side effects that occur at times other than those specified in the Table, but for those the claimant must prove causation.[20] Unlike in tort suits, claimants under the Act are not required to show that the administered vaccine was defectively manufactured, labeled, or designed.

Successful claimants receive compensation for medical, rehabilitation, counseling, special education, and vocational training expenses; diminished earning capacity; pain and suffering; and $250,000 for vaccine-related deaths.[21] Attorney's fees are provided, not only for successful cases, but even for unsuccessful claims that are not frivolous.[22] These awards are paid out of a fund created by an excise tax on each vaccine dose.[23]

The *quid pro quo* for this, designed to stabilize the vaccine market, was the provision of significant tort-liability protections for vaccine manufacturers. The Act requires claimants to seek relief through the compensation program before filing suit for more than $1,000.[24] Manufacturers are generally immunized from liability for fail-

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[17] See §300aa–14(a); 42 CFR §100.3 (2009) (current Vaccine Injury Table).

[18] See 42 U. S. C. §§300aa–11(c)(1), 300aa–13(a)(1)(A).

[19] See §300aa–13(a)(1)(B).

[20] See §300aa–11(c)(1)(C)(ii).

[21] See §300aa–15(a).

[22] See §300aa–15(e).

[23] See §300aa–15(i)(2); 26 U. S. C. §§4131, 9510.

[24] See 42 U. S. C. §300aa–11(a)(2).

ure to warn if they have complied with all regulatory requirements (including but not limited to warning requirements) and have given the warning either to the claimant or the claimant's physician.[25] They are immunized from liability for punitive damages absent failure to comply with regulatory requirements, "fraud," "intentional and wrongful withholding of information," or other "criminal or illegal activity."[26] And most relevant to the present case, the Act expressly eliminates liability for a vaccine's unavoidable, adverse side effects:

> "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."[27]

B

The vaccine at issue here is a DTP vaccine manufactured by Lederle Laboratories. It first received federal approval in 1948 and received supplemental approvals in 1953 and 1970. Respondent Wyeth purchased Lederle in 1994 and stopped manufacturing the vaccine in 1998.

Hannah Bruesewitz was born on October 20, 1991. Her pediatrician administered doses of the DTP vaccine according to the Center for Disease Control's recommended childhood immunization schedule. Within 24 hours of her April 1992 vaccination, Hannah started to experience

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[25] See §300aa–22(b)(2), (c). The immunity does not apply if the plaintiff establishes by clear and convincing evidence that the manufacturer was negligent, or was guilty of fraud, intentional and wrongful withholding of information, or other unlawful activity. See §§300aa–22(b)(2), 300aa–23(d)(2).

[26] §300aa–23(d)(2).

[27] §300aa–22(b)(1).

seizures.[28] She suffered over 100 seizures during the next month, and her doctors eventually diagnosed her with "residual seizure disorder" and "developmental delay."[29] Hannah, now a teenager, is still diagnosed with both conditions.

In April 1995, Hannah's parents, Russell and Robalee Bruesewitz, filed a vaccine injury petition in the United States Court of Federal Claims, alleging that Hannah suffered from on-Table residual seizure disorder and encephalopathy injuries.[30] A Special Master denied their claims on various grounds, though they were awarded $126,800 in attorney's fees and costs. The Bruesewitzes elected to reject the unfavorable judgment, and in October 2005 filed this lawsuit in Pennsylvania state court. Their complaint alleged (as relevant here) that defective design of Lederle's DTP vaccine caused Hannah's disabilities, and that Lederle was subject to strict liability, and liability for negligent design, under Pennsylvania common law.[31]

Wyeth removed the suit to the United States District Court for the Eastern District of Pennsylvania, which granted Wyeth summary judgment on the strict-liability and negligence design-defect claims, holding that the Pennsylvania law providing those causes of action was preempted by 42 U. S. C. §300aa–22(b)(1).[32] The United States Court of Appeals for the Third Circuit affirmed.[33] We granted certiorari. 559 U. S. ___ (2010).

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[28] See *Bruesewitz* v. *Secretary of Health and Human Servs.*, No. 95–0266V, 2002 WL 31965744, *3 (Ct. Cl., Dec. 20, 2002).

[29] 561 F. 3d 233, 236 (CA3 2009).

[30] See *id.,* at *1.

[31] See 561 F. 3d at 237. The complaint also made claims based upon failure to warn and defective manufacture. These are no longer at issue.

[32] See *id.,* at 237–238.

[33] *Id.,* at 235.

II

A

We set forth again the statutory text at issue:

> "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."[34]

The "even though" clause clarifies the word that precedes it. It delineates the preventative measures that a vaccine manufacturer *must* have taken for a side-effect to be considered "unavoidable" under the statute. Provided that there was proper manufacture and warning, any remaining side effects, including those resulting from design defects, are deemed to have been unavoidable. State-law design-defect claims are therefore preempted.

If a manufacturer could be held liable for failure to use a different design, the word "unavoidable" would do no work. A side effect of a vaccine could *always* have been avoidable by use of a differently designed vaccine not containing the harmful element. The language of the provision thus suggests that the *design* of the vaccine is a given, not subject to question in the tort action. What the statute establishes as a complete defense must be unavoidability (given safe manufacture and warning) *with respect to the particular design*. Which plainly implies that the design itself is not open to question.[35]

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[34] 42 U. S. C. §300aa–22(b)(1).

[35] The dissent advocates for another possibility: "[A] side effect is 'unavoidable' . . . where there is no feasible alternative design that would eliminate the side effect of the vaccine without compromising its cost and utility." *Post*, at 15 (opinion of SOTOMAYOR, J.). The dissent makes no effort to ground that position in the text of §300aa–22(b)(1).

A further textual indication leads to the same conclusion. Products-liability law establishes a classic and well known triumvirate of grounds for liability: defective manufacture, inadequate directions or warnings, and defective design.[36] If all three were intended to be preserved, it would be strange to mention specifically only two, and leave the third to implication. It would have been much easier (and much more natural) to provide that manufacturers would be liable for "defective manufacture, defective directions or warning, and defective design." It seems that the statute fails to mention design-defect liability "by deliberate choice, not inadvertence." *Barnhart* v. *Peabody Coal Co.*, 537 U. S. 149, 168 (2003). *Expressio unius, exclusio alterius.*

B

The dissent's principal textual argument is mistaken. We agree with its premise that "'side effects that were unavoidable' must refer to side effects caused by a vaccine's *design*."[37] We do not comprehend, however, the second step of its reasoning, which is that the use of the conditional term "if" in the introductory phrase "if the injury or death resulted from side effects that were unavoidable" "plainly implies that some side effects stemming from a vaccine's design are 'unavoidable,' while

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We doubt that Congress would introduce such an amorphous test by implication when it otherwise micromanages vaccine manufacturers. See *infra*, at 13–14. We have no idea how much more expensive an alternative design can be before it "compromis[es]" a vaccine's cost or how much efficacy an alternative design can sacrifice to improve safety. Neither does the dissent. And neither will the judges who must rule on motions to dismiss, motions for summary judgment, and motions for judgment as a matter of law. Which means that the test would probably have no real-world effect.

[36] W. Keeton, D. Dobbs, R. Keeton, & D. Owen, Prosser and Keeton on Law of Torts 695 (5th ed. 1984); Restatement (Third) of Torts §2 (1999).

[37] *Post*, at 3.

others are avoidable."[38] That is not so. The "if" clause makes total sense whether the design to which "unavoidable" refers is (as the dissent believes) any feasible design (making the side effects of the design used for the vaccine at issue avoidable), or (as we believe) the particular design used for the vaccine at issue (making its side effects unavoidable). Under the latter view, the condition established by the "if" clause is that the vaccine have been properly labeled and manufactured; and under the former, that it have been properly *designed*, labeled, and manufactured. Neither view renders the "if" clause a nullity. Which of the two variants must be preferred is addressed by our textual analysis, and is in no way determined by the "if" clause.

Petitioners' and the dissent's textual argument also rests upon the proposition that the word "unavoidable" in §300aa–22(b)(1) is a term of art that incorporates comment *k* to Restatement (Second) of Torts §402A (1963–1964).[39] The Restatement generally holds a manufacturer strictly liable for harm to person or property caused by "any product in a defective condition unreasonably dangerous to the user."[40] Comment *k* exempts from this strict-liability rule "unavoidably unsafe products." An unavoidably unsafe product is defined by a hodge-podge of criteria and a few examples, such as the Pasteur rabies vaccine and experimental pharmaceuticals. Despite this lack of clarity, petitioners seize upon one phrase in the comment *k* analysis, and assert that by 1986 a majority of courts had made this a *sine qua non* requirement for an "unavoidably unsafe product": a case-specific showing that the product was "quite incapable of being made safer for

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[38] *Ibid.*

[39] See Brief for Petitioners 29.

[40] Restatement §402A, p. 347.

[its] intended . . . use."[41]

We have no need to consider the finer points of comment *k*. Whatever consistent judicial gloss that comment may have been given in 1986, there is no reason to believe that §300aa–22(b)(1) was invoking it. The comment creates a special category of "unavoidably unsafe products," while the statute refers to "side effects that were unavoidable." That the latter uses the adjective "unavoidable" and the former the adverb "unavoidably" does not establish that Congress had comment *k* in mind. "Unavoidable" is hardly a rarely used word. Even the cases petitioners cite as putting a definitive gloss on comment *k* use the precise phrase "unavoidably unsafe product";[42] none attaches special significance to the term "unavoidable" standing alone.

The textual problems with petitioners' interpretation do

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[41] *Id.,* Comment *k*, p. 353; Petitioners cite, *inter alia*, *Kearl* v. *Lederle Labs.*, 172 Cal. App. 3d 812, 828–830, 218 Cal. Rptr. 453, 463–464 (1985); *Belle Bonfils Memorial Blood Bank* v. *Hansen*, 665 P. 2d 118, 122 (Colo. 1983).

Though it is not pertinent to our analysis, we point out that a large number of courts disagreed with that reading of comment *k*, and took it to say that manufacturers did not face strict liability for side effects of properly manufactured prescription drugs that were accompanied by adequate warnings. See, *e.g., Brown* v. *Superior Court*, 227 Cal. Rptr. 768, 772–775 (Cal. App. 1986), (officially depublished), aff'd 44 Cal. 3d 1049, 751 P. 2d 470 (1988); *McKee* v. *Moore*, 648 P. 2d 21, 23 (Okla. 1982); *Stone* v. *Smith, Kline & French Labs.*, 447 So. 2d 1301, 1303–1304 (Ala. 1984); *Lindsay* v. *Ortho Pharm. Corp.*, 637 F. 2d 87, 90–91 (CA2 1980) (applying N. Y. law); *Wolfgruber* v. *Upjohn Co.*, 72 App. Div. 2d 59, 61, 423 N. Y. S. 2d 95, 96 (1979); *Chambers* v. *G. D. Searle & Co.*, 441 F. Supp. 377, 380–381 (D Md. 1975); *Basko* v. *Sterling Drug, Inc.*, 416 F. 2d 417, 425 (CA2 1969) (applying Conn. law).

[42] See, *e.g., Johnson* v. *American Cyanamid Co.*, 239 Kan. 279, 285, 718 P. 2d 1318, 1323 (1986); *Feldman* v. *Lederle Labs.*, 97 N. J. 429, 440, 446–447, 479 A. 2d 374, 380, 383–384 (1984); *Belle Bonfils Memorial Blood Bank supra*, at 121–123; *Cassisi* v. *Maytag Co.*, 396 So. 2d 1140, 1144, n. 4, 1146 (Fla. App. 1981); *Racer* v. *Utterman*, 629 S. W. 2d 387, 393 (Mo. App. 1981).

not end there. The phrase "even though" in the clause "even though the vaccine was properly prepared and [labeled]" is meant to signal the unexpected: unavoidable side effects persist *despite* best manufacturing and labeling practices.[43] But petitioners' reading eliminates any opposition between the "even though" clause—called a concessive subordinate clause by grammarians—and the word "unavoidable."[44] Their reading makes preemption turn equally on unavoidability, proper preparation, and proper labeling. Thus, the dissent twice refers to the requirements of proper preparation and proper labeling as "two additional prerequisites" for preemption independent of unavoidability.[45] The primary textual justification for the dissent's position depends on that independence.[46] But linking independent ideas is the job of a coordinating junction like "and," not a subordinating junction like "even though."[47]

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[43] The dissent's assertion that we treat "even though" as a synonym for "because" misses the subtle distinction between "because" and "despite." See *post,* at 17, n. 14. "Even though" is a close cousin of the latter. See Webster's New International Dictionary 709, 2631 (2d ed. 1957). The statement "the car accident was unavoidable despite his quick reflexes" indicates that quick reflexes could not avoid the accident, and leaves open two unstated possibilities: (1) that other, unstated means of avoiding the accident besides quick reflexes existed, but came up short as well; or (2) that quick reflexes were the only possible way to avoid the accident. Our interpretation of §300aa–22(b)(1) explains why we think Congress meant the latter in this context. (Incidentally, the statement "the car accident was unavoidable because of his quick reflexes" makes no sense.)

[44] See W. Follett, Modern American Usage: A Guide 61 (1966).

[45] *Post*, at 9, 17.

[46] *Post*, at 3–5.

[47] The dissent responds that these "additional prerequisites" act "in a concessive, subordinating fashion," *post,* at 17, n. 14 (internal quotation marks and brackets omitted). But that is no more true of the dissent's conjunctive interpretation of the present text than it is of *all* provisions that set forth additional requirements—meaning that we could eliminate "even though" from our English lexicon, its function being entirely

Petitioners and the dissent contend that the interpretation we propose would render part of §300aa–22(b)(1) superfluous: Congress could have more tersely and more clearly preempted design-defect claims by barring liability "if . . . the vaccine was properly prepared and was accompanied by proper directions and warnings." The intervening passage ("the injury or death resulted from side effects that were unavoidable even though") is unnecessary. True enough. But the rule against giving a portion of text an interpretation which renders it superfluous does not prescribe that a passage which could have been more terse does not mean what it says. The rule applies only if verbosity and prolixity can be eliminated by giving the offending passage, or the remainder of the text, a competing interpretation. That is not the case here.[48] To be sure, petitioners' and the dissent's interpretation gives independent meaning to the intervening passage (the supposed meaning of comment *k*); but it does so only at the expense of rendering the remainder of the provision superfluous. Since a vaccine is not "quite incapable of being made safer for [its] intended use" if manufacturing defects could have been eliminated or better warnings provided, the entire "even though" clause is a useless appendage.[49] It would suffice to say "if the injury or death resulted from side effects that were unavoidable"—full stop.

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performed by "and." No, we think "even though" has a distinctive concessive, subordinating role to play.

[48] Because the dissent has a superfluity problem of its own, its reliance on *Bates* v. *Dow Agrosciences LLC*, 544 U. S. 431 (2005), is misplaced. See *id.,* at 449 (adopting an interpretation that was "the only one that makes sense of each phrase" in the relevant statute).

[49] That is true regardless of whether §300aa–22(b)(1) incorporates comment *k*. See Restatement §402A, Comment *k*, pp. 353, 354 (noting that "unavoidably unsafe products" are exempt from strict liability "with the qualification that they are properly prepared and marketed, and proper warning is given").

III

The structure of the NCVIA and of vaccine regulation in general reinforces what the text of §300aa–22(b)(1) suggests. A vaccine's license spells out the manufacturing method that must be followed and the directions and warnings that must accompany the product.[50] Manufacturers ordinarily must obtain the Food and Drug Administration's (FDA) approval before modifying either.[51] Deviations from the license thus provide objective evidence of manufacturing defects or inadequate warnings. Further objective evidence comes from the FDA's regulations—more than 90 of them[52]—that pervasively regulate the manufacturing process, down to the requirements for plumbing and ventilation systems at each manufacturing facility.[53] Material noncompliance with any one of them, or with any other FDA regulation, could cost the manufacturer its regulatory-compliance defense.[54]

Design defects, in contrast, do not merit a single mention in the NCVIA or the FDA's regulations. Indeed, the FDA has never even spelled out in regulations the criteria it uses to decide whether a vaccine is safe and effective for its intended use.[55] And the decision is surely not an easy one. Drug manufacturers often could trade a little less efficacy for a little more safety, but the safest design is not always the best one. Striking the right balance between safety and efficacy is especially difficult with respect to vaccines, which affect public as well as individual health. Yet the Act, which in every other respect micromanages manufacturers, is silent on how to evaluate competing designs. Are manufacturers liable only for failing to em-

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[50] See 42 U. S. C. §262(a), (j); 21 CFR §§601.2(a), 314.105(b) (2010).
[51] See §601.12.
[52] See §§211.1 *et seq.*, 600.10–600.15, 600.21–600.22, 820.1 *et seq.*
[53] See §§211.46, 211.48.
[54] See 42 U. S. C. §300aa–22(b)(2).
[55] Hutt, Merrill, & Grossman, Food and Drug Law, at 685, 891.

ploy an alternative design that the FDA has approved for distribution (an approval it takes years to obtain[56])? Or does it suffice that a vaccine design has been approved in other countries? Or could there be liability for failure to use a design that exists only in a lab? Neither the Act nor the FDA regulations provide an answer, leaving the universe of alternative designs to be limited only by an expert's imagination.

Jurors, of course, often decide similar questions with little guidance, and we do not suggest that the absence of guidance alone suggests preemption. But the lack of guidance for design defects combined with the extensive guidance for the two grounds of liability specifically mentioned in the Act strongly suggests that design defects were not mentioned because they are not a basis for liability.

The mandates contained in the Act lead to the same conclusion. Design-defect torts, broadly speaking, have two beneficial effects: (1) prompting the development of improved designs, and (2) providing compensation for inflicted injuries. The NCVIA provides other means for achieving both effects. We have already discussed the Act's generous compensation scheme. And the Act provides many means of improving vaccine design. It directs the Secretary of Health and Human Services to promote "the development of childhood vaccines that result in fewer and less serious adverse reactions."[57] It establishes a National Vaccine Program, whose Director is "to achieve optimal prevention of human infectious diseases . . . and to achieve optimal prevention against adverse reactions."[58] The Program is to set priorities for federal vaccine research, and to coordinate federal vaccine safety and effi-

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[56] See Sing & William, Supplying Vaccines, at 66–67.

[57] 42 U. S. C. §300aa–27(a)(1).

[58] §300aa–1.

cacy testing.[59] The Act requires vaccine manufacturers and health-care providers to report adverse side effects,[60] and provides for monitoring of vaccine safety through a collaboration with eight managed-care organizations.[61] And of course whenever the FDA concludes that a vaccine is unsafe, it may revoke the license.[62]

These provisions for federal agency improvement of vaccine design, and for federally prescribed compensation, once again suggest that §300aa–22(b)(1)'s silence regarding design-defect liability was not inadvertent. It instead reflects a sensible choice to leave complex epidemiological judgments about vaccine design to the FDA and the National Vaccine Program rather than juries.[63]

And finally, the Act's structural *quid pro quo* leads to the same conclusion: The vaccine manufacturers fund from their sales an informal, efficient compensation program for vaccine injuries;[64] in exchange they avoid costly tort litigation and the occasional disproportionate jury verdict.[65] But design-defect allegations are the most speculative and difficult type of products liability claim to

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[59] See §§300aa–2(a)(1)–(3), 300aa–3.

[60] See §300aa–25(b).

[61] See NVAC 18–19.

[62] See 21 CFR §601.5(b)(1)(vi) (2010).

[63] The dissent quotes just part of this sentence, to make it appear that we believe complex epidemiological judgments ought to be assigned in that fashion. See *post*, at 26. We do not state our preference, but merely note that it is Congress's expressed preference—and in order to preclude the argument that it is absurd to think Congress enacted such a thing, we assert that the choice is reasonable and express some of the reasons why. Leaving it to the jury may (or may not) be reasonable as well; we express no view.

[64] See 42 U. S. C. §300aa–15(i)(2); Pub. L. 99–660, §323(a), 100 Stat. 3784. The dissent's unsupported speculation that demand in the vaccine market is inelastic, see *post*, at 24, n. 22, sheds no light on whether Congress regarded the tax as a *quid pro quo*, most Members of Congress being neither professional economists nor law-and-economics scholars.

[65] See 42 U. S. C. §§300aa–11(a)(2), 300aa–22.

litigate. Taxing vaccine manufacturers' product to fund the compensation program, while leaving their liability for design defect virtually unaltered, would hardly coax manufacturers back into the market.

The dissent believes the Act's mandates are irrelevant because they do not spur innovation in precisely the same way as state-law tort systems.[66] That is a novel suggestion. Although we previously have expressed doubt that Congress would quietly preempt product-liability claims without providing a federal substitute, see *Medtronic, Inc.* v. *Lohr*, 518 U. S. 470, 486–488 (1996) (plurality opinion), we have never suggested we would be skeptical of preemption unless the congressional substitute operated like the tort system. We decline to adopt that stance today. The dissent's belief that the FDA and the National Vaccine Program cannot alone spur adequate vaccine innovation is probably questionable, but surely beside the point.

IV

Since our interpretation of §300aa–22(b)(1) is the only interpretation supported by the text and structure of the NCVIA, even those of us who believe legislative history is a legitimate tool of statutory interpretation have no need to resort to it. In any case, the dissent's contention that it would contradict our conclusion is mistaken.

The dissent's legislative history relies on the following syllogism: A 1986 House Committee Report states that §300aa–22(b)(1) "sets forth the principle contained in Comment k of Section 402A of the Restatement of Torts (Second);"[67] in 1986 comment *k* was "commonly understood" to require a case-specific showing that "no feasible alternative design" existed; Congress therefore must have intended §300aa–22(b)(1) to require that showing.[68] The

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[66] See *post*, at 21–24.

[67] H. R. Rep. No. 99–908, pt. 1, p. 25 (1986) (hereinafter 1986 Report).

[68] *Post*, at 7–8.

syllogism ignores unhelpful statements in the Report and relies upon a term of art that did not exist in 1986.

Immediately after the language quoted by the dissent, the 1986 Report notes the difficulty a jury would have in faithfully assessing whether a feasible alternative design exists when an innocent "young child, often badly injured or killed" is the plaintiff.[69] Eliminating that concern is why the Report's authors "strongly believ[e] that Comment k is appropriate and necessary as the policy for civil actions seeking damages in tort."[70] The dissent's interpretation of §300aa–22(b)(1) and its version of "the principle in Comment K" adopted by the 1986 Report leave that concern unaddressed.

The dissent buries another unfavorable piece of legislative history. Because the Report believes that §300aa–22(b)(1) should incorporate "the principle in Comment K" and because the Act provides a generous no-fault compensation scheme, the Report counsels injured parties who cannot prove a manufacturing or labeling defect to "pursue recompense in the compensation system, not the tort system."[71] That counsel echoes our interpretation of §300aa–22(b)(1).

Not to worry, the dissent retorts, a Committee Report by a later Congress "authoritative[ly]" vindicates its interpretation.[72] Post-enactment legislative history (a contradiction in terms) is not a legitimate tool of statutory interpretation. See *Jones* v. *United States*, 526 U. S. 227, 238

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[69] 1986 Report, at 26; see *ibid.* ("[E]ven if the defendant manufacturer may have made as safe a vaccine as anyone reasonably could expect, a court or jury undoubtedly will find it difficult to rule in favor of the 'innocent' manufacturer if the equally 'innocent' child has to bear the risk of loss with no other possibility of recompense").

[70] *Ibid.*

[71] *Ibid.*

[72] *Post*, at 12. This is a courageous adverb since we have previously held that the only authoritative source of statutory meaning is the text that has passed through the Article I process. See *Exxon Mobil Corp.* v. *Allapattah Services, Inc.*, 545 U. S. 546, 568 (2005).

(1999); *United States* v. *Mine Workers*, 330 U. S. 258, 281–282 (1947). Real (pre-enactment) legislative history is persuasive to some because it is thought to shed light on what legislators understood an ambiguous statutory text to mean when they voted to enact it into law. See *Exxon Mobil Corp.* v. *Allapattah Services, Inc.*, 545 U. S. 546, 568 (2005). But post-enactment legislative history by definition "could have had no effect on the congressional vote," *District of Columbia* v. *Heller*, 554 U. S. 570, 605 (2008).

It does not matter that §300aa–22(b)(1) did not take effect until the later Congress passed the excise tax that funds the compensation scheme,[73] and that the supposedly dispositive Committee Report is attached to that funding legislation.[74] Those who voted on the relevant statutory language were not necessarily the same persons who crafted the statements in the later Committee Report; or if they were did not necessarily have the same views at that earlier time; and no one voting at that earlier time could possibly have been informed by those later statements. Permitting the legislative history of subsequent funding legislation to alter the meaning of a statute would set a dangerous precedent. Many provisions of federal law depend on appropriations or include sunset provisions;[75] they cannot be made the device for unenacted statutory revision.

That brings us to the second flaw in the dissent's syllogism: Comment *k* did not have a "commonly understood meaning"[76] in the mid-1980's. Some courts thought it required a case-specific showing that a product was "unavoidably unsafe"; many others thought it categorically exempted certain types of products from strict liability.[77]

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[73] Pub. L. 99–960, §323(a), 100 Stat. 3784.

[74] H. R. Rep. No. 100–391, pt. 1, p. 701 (1987).

[75] See, *e.g.,* Pub. L. 104–208, §§401, 403(a), 110 Stat. 3009–655 to 3009–656, 3009–659 to 3009–662, as amended, note following 8 U. S. C. §1324a (2006 ed., Supp. III) (E-Verify program expires Sept. 30, 2012).

[76] *Post*, at 8.

[77] See n. 39, *supra; post*, at 7–8, n. 5.

When "all (or nearly all) of the" relevant judicial decisions have given a term or concept a consistent judicial gloss, we presume Congress intended the term or concept to have that meaning when it incorporated it into a later-enacted statute. *Merck & Co.* v. *Reynolds*, 559 U. S. ___, ___ (2010) (SCALIA, J., concurring in part and concurring in judgment) (slip op., at 5). The consistent gloss represents the public understanding of the term. We cannot make the same assumption when widespread disagreement exists among the lower courts. We must make do with giving the term its most plausible meaning using the traditional tools of statutory interpretation. That is what we have done today.

* * *

For the foregoing reasons, we hold that the National Childhood Vaccine Injury Act preempts all design-defect claims against vaccine manufacturers brought by plaintiffs who seek compensation for injury or death caused by vaccine side effects. The judgment of the Court of Appeals is affirmed.

It is so ordered.

JUSTICE KAGAN took no part in the consideration or decision of this case.

SUPREME COURT OF THE UNITED STATES

No. 09–152

RUSSELL BRUESEWITZ, ET AL., PETITIONERS *v.* WYETH LLC, FKA WYETH, INC., FKA WYETH LABORATORIES, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

[February 22, 2011]

JUSTICE BREYER, concurring.

I join the Court's judgment and opinion. In my view, the Court has the better of the purely textual argument. But the textual question considered alone is a close one. Hence, like the dissent, I would look to other sources, including legislative history, statutory purpose, and the views of the federal administrative agency, here supported by expert medical opinion. Unlike the dissent, however, I believe these other sources reinforce the Court's conclusion.

I

House Committee Report 99–908 contains an "authoritative" account of Congress' intent in drafting the pre-emption clause of the National Childhood Vaccine Injury Act of 1986 (NCVIA or Act). See *Garcia* v. *United States*, 469 U. S. 70, 76 (1984) ("[T]he authoritative source for finding the Legislature's intent lies in the Committee Reports on the bill"). That Report says that, "if" vaccine-injured persons

> "cannot demonstrate under applicable law either that a vaccine was improperly prepared or that it was accompanied by improper directions or inadequate warnings [they] should pursue recompense in the

> compensation system, not the tort system." H. R. Rep. No. 99–908, pt. 1, p. 24 (1986) (hereinafter H. R. Rep.).

The Report lists two specific kinds of tort suits that the clause does not pre-empt (suits based on improper manufacturing and improper labeling), while going on to state that compensation for other tort claims, *e.g.*, design-defect claims, lies in "the [NCVIA's no-fault] compensation system, not the tort system." *Ibid.*

The strongest contrary argument rests upon the Report's earlier description of the statute as "set[ting] forth the principle contained in Comment k" (of the Restatement Second of Torts' *strict liability* section, 402A) that "a vaccine manufacturer should not be liable for injuries or deaths resulting from *unavoidable* side effects." *Id.*, at 23 (emphasis added). But the appearance of the word "unavoidable" in this last-mentioned sentence cannot provide petitioners with much help. That is because nothing in the Report suggests that the statute means the word "unavoidable" to summon up an otherwise unmentioned third exception encompassing suits based on design defects. Nor can the Report's reference to comment *k* fill the gap. The Report itself refers, not to comment *k*'s details, but only to its "*principle,*" namely, that vaccine manufacturers should *not* be held liable for unavoidable injuries. It says nothing at all about who—judge, jury, or federal safety agency—should decide whether a safer vaccine could have been designed. Indeed, at the time Congress wrote this Report, different state courts had come to very different conclusions about that matter. See Cupp, Rethinking Conscious Design Liability for Prescription Drugs: The *Restatement (Third)* Standard Versus a Negligence Approach, 63 Geo. Wash. L. Rev. 76, 79 (1994–1995) ("[C]ourts [had] adopted a broad range of conflicting interpretations" of comment *k*). Neither the word "unavoid-

able" nor the phrase "the principle of Comment k" tells us which courts' view Congress intended to adopt. Silence cannot tell us to follow those States where juries decided the design-defect question.

II

The legislative history describes the statute more generally as trying to protect the lives of children, in part by ending "the instability and unpredictability of the childhood vaccine market." H. R. Rep., at 7; see *ante,* at 2–3. As the Committee Report makes clear, routine vaccination is "one of the most spectacularly effective public health initiatives this country has ever undertaken." H. R. Rep., at 4. Before the development of routine whooping cough vaccination, for example, "nearly all children" in the United States caught the disease and more than 4,000 people died annually, most of them infants. U. S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, What Would Happen if We Stopped Vaccinations? http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm (all Internet materials as visited Feb. 17, 2011, and available in Clerk of Court's case file); Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, Reduced Diptheria Toxoid and Acellular Pertussis Vaccines, 55 Morbidity and Mortality Weekly Report, No. RR–3, p. 2 (Mar. 24, 2006) (hereinafter Preventing Tetanus) (statistics for 1934–1943), http://www.cdc.gov/mmwr/PDF/rr/rr5503.pdf; U. S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, Epidemiology and Prevention of Vaccine-Preventable Diseases 200 (11th ed. rev. May 2009). After vaccination became common, the number of annual cases of whooping cough declined from over 200,000 to about 2,300, and the number of deaths from about 4,000 to about 12. Preventing Tetanus 2; Childhood Immunizations, House Committee on Energy and Com-

merce, 99th Cong., 2d Sess., 10 (Comm. Print 1986) (hereinafter Childhood Immunizations).

But these gains are fragile; "[t]he causative agents for these preventable childhood illnesses are ever present in the environment, waiting for the opportunity to attack the unprotected individual." Hearing on S. 827 before the Senate Committee on Labor and Human Resources, 99th Cong., 2d Sess., pt. 2, pp. 20–21 (1985) (hereinafter Hearings) (testimony of the American Academy of Pediatrics); see California Dept. of Public Health, Pertussis Report (Jan. 7, 2011), www.cdph.ca.gov/programs/immunize/Documents/PertussisReport2011–01–07.pdf (In 2010, 8,383 people in California caught whooping cough, and 10 infants died). Even a brief period when vaccination programs are disrupted can lead to children's deaths. Hearings 20–21; see Gangarosa et al., Impact of Anti-Vaccine Movements on Pertussis Control: The Untold Story, 351 Lancet 356–361 (Jan. 31, 1998) (when vaccination programs are disrupted, the number of cases of whooping cough skyrockets, increasing by orders of magnitude).

In considering the NCVIA, Congress found that a sharp increase in tort suits brought against whooping cough and other vaccine manufacturers between 1980 and 1985 had "prompted manufacturers to question their continued participation in the vaccine market." H. R. Rep., at 4; Childhood Immunizations 85–86. Indeed, two whooping cough vaccine manufacturers withdrew from the market, and other vaccine manufacturers, "fac[ing] great difficulty in obtaining [product liability] insurance," told Congress that they were considering "a similar course of action." H. R. Rep., at 4; Childhood Immunizations 68–70. The Committee Report explains that, since there were only one or two manufacturers of many childhood vaccines, "[t]he loss of any of the existing manufacturers of childhood vaccines . . . could create a genuine public health hazard"; it "would present the very real possibility of vaccine short-

ages, and, in turn, increasing numbers of unimmunized children, and, perhaps, a resurgence of preventable diseases." H. R. Rep., at 5. At the same time, Congress sought to provide generous compensation to those whom vaccines injured—as determined by an expert compensation program. *Id.,* at 5, 24.

Given these broad general purposes, to read the preemption clause as preserving design-defect suits seems anomalous. The Department of Health and Human Services (HHS) decides when a vaccine is safe enough to be licensed and which licensed vaccines, with which associated injuries, should be placed on the Vaccine Injury Table. 42 U. S. C. §300aa–14; *ante,* at 3–4; A Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities 13–15, 32–34 (Dec. 2008), http://www.hhs.gov/nvpo/nvac/documents/vaccine-safety-review.pdf. A special master in the Act's compensation program determines whether someone has suffered an injury listed on the Injury Table and, if not, whether the vaccine nonetheless caused the injury. *Ante,* at 3–4; §300aa–13. To allow a jury in effect to second-guess those determinations is to substitute less expert for more expert judgment, thereby threatening manufacturers with liability (indeed, strict liability) in instances where any conflict between experts and nonexperts is likely to be particularly severe—instances where Congress intended the contrary. That is because potential tort plaintiffs are unlikely to bring suit unless the specialized compensation program has determined that they are not entitled to compensation (say, because it concludes that the vaccine did not cause the injury). Brief for United States as *Amicus Curiae* 28 ("99.8% of successful Compensation Program claimants have accepted their awards, foregoing any tort remedies against vaccine manufacturers"). It is difficult to reconcile these potential conflicts and the resulting tort liabilities with a statute that seeks to diminish

manufacturers' product liability while simultaneously augmenting the role of experts in making compensation decisions.

III

The United States, reflecting the views of HHS, urges the Court to read the Act as I and the majority would do. It notes that the compensation program's listed vaccines have survived rigorous administrative safety review. It says that to read the Act as permitting design-defect lawsuits could lead to a recurrence of "exactly the crisis that precipitated the Act," namely withdrawals of vaccines or vaccine manufacturers from the market, "disserv[ing] the Act's central purposes," and hampering the ability of the agency's "expert regulators, in conjunction with the medical community, [to] control the availability and withdrawal of a given vaccine." Brief for United States as *Amicus Curiae* 30, 31.

The United States is supported in this claim by leading public health organizations, including the American Academy of Pediatrics, the American Academy of Family Physicians, the American College of Preventive Medicine, the American Public Health Association, the American Medical Association, the March of Dimes Foundation, the Pediatric Infectious Diseases Society, and 15 other similar organizations. Brief for American Academy of Pediatrics et al. as *Amici Curiae* (hereinafter AAP Brief). The American Academy of Pediatrics has also supported the retention of vaccine manufacturer tort liability (provided that federal law structured state-law liability conditions in ways that would take proper account of federal agency views about safety). Hearings 14–15. But it nonetheless tells us here, in respect to the specific question before us, that the petitioners' interpretation of the Act would undermine its basic purposes by threatening to "halt the future production and development of childhood vaccines

in this country," *i.e.,* by "threaten[ing] a resurgence of the very problems which . . . caused Congress to intervene" by enacting this statute. AAP Brief 24 (internal quotation marks omitted).

I would give significant weight to the views of HHS. The law charges HHS with responsibility for overseeing vaccine production and safety. It is "likely to have a thorough understanding" of the complicated and technical subject matter of immunization policy, and it is comparatively more "qualified to comprehend the likely impact of state requirements." *Geier* v. *American Honda Motor Co., Inc.*, 529 U. S. 861, 883 (2000) (internal quotation marks omitted); see *Medtronic, Inc.* v. *Lohr*, 518 U. S. 470, 506 (1996) (BREYER, J., concurring in part and concurring in judgment) (the agency is in the best position to determine "whether (or the extent to which) state requirements may interfere with federal objectives"). HHS's position is particularly persuasive here because expert public health organizations support its views and the matter concerns a medical and scientific question of great importance: how best to save the lives of children. See *Skidmore* v. *Swift & Co.*, 323 U. S. 134 (1944).

In sum, congressional reports and history, the statute's basic purpose as revealed by that history, and the views of the expert agency along with those of relevant medical and scientific associations, all support the Court's conclusions. I consequently agree with the Court.

SUPREME COURT OF THE UNITED STATES

No. 09–152

RUSSELL BRUESEWITZ, ET AL., PETITIONERS *v.* WYETH LLC, FKA WYETH, INC., FKA WYETH LABORATORIES, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

[February 22, 2011]

JUSTICE SOTOMAYOR, with whom JUSTICE GINSBURG joins, dissenting.

Vaccine manufacturers have long been subject to a legal duty, rooted in basic principles of products liability law, to improve the designs of their vaccines in light of advances in science and technology. Until today, that duty was enforceable through a traditional state-law tort action for defective design. In holding that §22(b)(1) of the National Childhood Vaccine Injury Act of 1986 (Vaccine Act or Act), 42 U. S. C. §300aa–22(b)(1), pre-empts all design defect claims for injuries stemming from vaccines covered under the Act, the Court imposes its own bare policy preference over the considered judgment of Congress. In doing so, the Court excises 13 words from the statutory text, misconstrues the Act's legislative history, and disturbs the careful balance Congress struck between compensating vaccine-injured children and stabilizing the childhood vaccine market. Its decision leaves a regulatory vacuum in which no one ensures that vaccine manufacturers adequately take account of scientific and technological advancements when designing or distributing their products. Because nothing in the text, structure, or legislative history of the Vaccine Act remotely suggests that Congress intended such a result, I respectfully dissent.

I

A

Section 22 of the Vaccine Act provides "[s]tandards of responsibility" to govern civil actions against vaccine manufacturers. 42 U. S. C. §300aa–22. Section 22(a) sets forth the "[g]eneral rule" that "State law shall apply to a civil action brought for damages for a vaccine-related injury or death." §300aa–22(a). This baseline rule that state law applies is subject to three narrow exceptions, one of which, §22(b)(1), is at issue in this case. Section 22(b)(1) provides:

> "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings." §300aa–22(b)(1).

The provision contains two key clauses: "if the injury or death resulted from side effects that were unavoidable" (the "if" clause), and "even though the vaccine was properly prepared and was accompanied by proper directions and warnings" (the "even though" clause).

Blackletter products liability law generally recognizes three different types of product defects: design defects, manufacturing defects, and labeling defects (*e.g.*, failure to warn).[1] The reference in the "even though" clause to a "properly prepared" vaccine "accompanied by proper directions and warnings" is an obvious reference to two such defects—manufacturing and labeling defects. The plain terms of the "even though" clause thus indicate that

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[1] W. Keeton, D. Dobbs, R. Keeton, & D. Owen, Prosser and Keeton on Law of Torts 695 (5th ed. 1984).

§22(b)(1) applies only where neither kind of defect is present. Because §22(b)(1) is invoked by vaccine manufacturers as a defense to tort liability, it follows that the "even though" clause requires a vaccine manufacturer in each civil action to demonstrate that its vaccine is free from manufacturing and labeling defects to fall within the liability exemption of §22(b)(1).[2]

Given that the "even though" clause requires the absence of manufacturing and labeling defects, the "if" clause's reference to "side effects that were unavoidable" must refer to side effects caused by something other than manufacturing and labeling defects. The only remaining kind of product defect recognized under traditional products liability law is a design defect. Thus, "side effects that were unavoidable" must refer to side effects caused by a vaccine's *design* that were "unavoidable." Because §22(b)(1) uses the conditional term "if," moreover, the text plainly implies that some side effects stemming from a vaccine's design are "unavoidable," while others are avoidable. See Webster's Third New International Dictionary 1124 (2002) ("if" means "in the event that," "so long as," or "on condition that"). Accordingly, because the "if" clause (like the "even though" clause) sets forth a condition to invoke §22(b)(1)'s defense to tort liability, Congress must also have intended a vaccine manufacturer to demonstrate in each civil action that the particular side effects of a vaccine's design were "unavoidable."

Congress' use of conditional "if" clauses in two other provisions of the Vaccine Act supports the conclusion that §22(b)(1) requires an inquiry in each case in which a manufacturer seeks to invoke the provision's exception to

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[2] See *Silkwood* v. *Kerr-McGee Corp.*, 464 U. S. 238, 255 (1984); *Brown* v. *Earthboard Sports USA, Inc.*, 481 F. 3d 901, 912 (CA6 2007) ("'[F]ederal preemption is an affirmative defense upon which the defendants bear the burden of proof'" (quoting *Fifth Third Bank* v. *CSX Corp.*, 415 F. 3d 741, 745 (CA7 2005))).

state tort liability. In §22(b)(2), Congress created a presumption that, for purposes of §22(b)(1), "a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with" federal labeling requirements. 42 U. S. C. §300aa–22(b)(2). Similarly, in §23(d)(2), Congress created an exemption from punitive damages "[i]f . . . the manufacturer shows that it complied, in all material respects," with applicable federal laws, unless it engages in "fraud," "intentional and wrongful withholding of information" from federal regulators, or "other criminal or illegal activity." §300aa–23(d)(2). It would be highly anomalous for Congress to use a conditional "if" clause in §§22(b)(2) and 23(d)(2) to require a specific inquiry in each case while using the same conditional "if" clause in §22(b)(1) to denote a categorical exemption from liability. Cf. *Erlenbaugh* v. *United States*, 409 U. S. 239, 243 (1972) ("[A] legislative body generally uses a particular word with a consistent meaning in a given context").

Indeed, when Congress intends to pre-empt design defect claims categorically, it does so using categorical (*e.g.*, "all") and/or declarative language (*e.g.*, "shall"), rather than a conditional term ("if"). For example, in a related context, Congress has authorized the Secretary of Health and Human Services to designate a vaccine designed to prevent a pandemic or epidemic as a "covered countermeasure." 42 U. S. C. §§247d–6d(b), (i)(1), (i)(7)(A)(i). With respect to such "covered countermeasure[s]," Congress provided that subject to certain exceptions, "a covered person *shall* be immune from suit and liability under Federal and State law with respect to *all* claims for loss caused by, arising out of, relating to, or resulting from the administration to or the use by an individual of a covered countermeasure," §247d–6d(a)(1) (emphasis added), including specifically claims relating to

"the design" of the countermeasure, §247d–6d(a)(2)(B).

The plain text and structure of the Vaccine Act thus compel the conclusion that §22(b)(1) pre-empts some—but not all—design defect claims. Contrary to the majority's and respondent's categorical reading, petitioners correctly contend that, where a plaintiff has proved that she has suffered an injury resulting from a side effect caused by a vaccine's design, a vaccine manufacturer may invoke §22(b)(1)'s liability exemption only if it demonstrates that the side effect stemming from the particular vaccine's design is "unavoidable," and that the vaccine is otherwise free from manufacturing and labeling defects.[3]

B

The legislative history confirms petitioners' interpretation of §22(b)(1) and sheds further light on its pre-emptive scope. The House Energy and Commerce Committee Report accompanying the Vaccine Act, H. R. Rep. No. 99–908, pt. 1 (1986) (hereinafter 1986 Report), explains in relevant part:

> "*Subsection (b)—Unavoidable Adverse Side Effects; Direct Warnings*.—This provision sets forth the principle contained in Comment K of Section 402A of the Restatement of Torts (Second) that a vaccine manufacturer should not be liable for injuries or deaths resulting from unavoidable side effects even though the vaccine was properly prepared and accompanied by proper directions and warnings.
>
> "The Committee has set forth Comment K in this bill because it intends that the principle in Comment K regarding 'unavoidably unsafe' products, i.e., those products which in the present state of human skill and knowledge cannot be made safe, apply to the vac-

[3] This leaves the question of what precisely §22(b)(1) means by "unavoidable" side effects, which I address in the next section.

> cines covered in the bill and that such products not be the subject of liability in the tort system." *Id.*, at 25–26.

The Report expressly adopts comment *k* of §402A of the Restatement of Torts (Second) (1963–1964) (hereinafter Restatement), which provides that "unavoidably unsafe" products—*i.e.*, those that "in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use"—are not defective.[4] As "[a]n outstanding example" of an "[u]navoidably unsafe" product, comment *k* cites "the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected";

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[4] Comment *k* provides as follows:

"*Unavoidably unsafe products*. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk." Restatement 353–354.

"[s]ince the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve." *Id.*, at 353. Comment *k* thus provides that "seller[s]" of "[u]navoidably unsafe" products are "not to be held to strict liability" provided that such products "are properly prepared and marketed, and proper warning is given." *Ibid.*

As the 1986 Report explains, Congress intended that the "principle in Comment K regarding 'unavoidably unsafe' products" apply to the vaccines covered in the bill. 1986 Report 26. That intent, in turn, is manifested in the plain text of §22(b)(1)—in particular, Congress' use of the word "unavoidable," as well as the phrases "properly prepared" and "accompanied by proper directions and warnings," which were taken nearly verbatim from comment *k*. 42 U. S. C. §300aa–22(b)(1); see Restatement 353–354 ("Such a[n unavoidably unsafe] product, properly prepared, and accompanied by proper directions and warning, is not defective"). By the time of the Vaccine Act's enactment in 1986, numerous state and federal courts had interpreted comment *k* to mean that a product is "unavoidably unsafe" when, given proper manufacture and labeling, no feasible alternative design would reduce the safety risks without compromising the product's cost and utility.[5] Given Con-

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[5] See, *e.g.*, *Smith ex rel. Smith* v. *Wyeth Labs., Inc.*, No. Civ. A 84–2002, 1986 WL 720792, *5 (SD W. Va., Aug. 21, 1986) ("[A] prescription drug is not 'unavoidably unsafe' when its dangers can be eliminated through design changes that do not unduly affect its cost or utility"); *Kearl* v. *Lederle Labs.*, 172 Cal. App. 3d 812, 830, 218 Cal. Rptr. 453, 464 (1985) ("unavoidability" turns on "(i) whether the product was designed to minimize—to the extent scientifically knowable at the time it was distributed—the risk inherent in the product, and (ii) the availability . . . of any alternative product that would have *as effectively* accomplished the *full intended purpose* of the subject product"), disapproved in part by *Brown* v. *Superior Ct.*, 44 Cal. 3d 1049, 751 P. 2d 470 (1988); *Belle Bonfils Memorial Blood Bank* v. *Hansen*, 665 P. 2d 118,

gress' expressed intent to codify the "principle in Comment K," 1986 Report 26, the term "unavoidable" in §22(b)(1) is best understood as a term of art, which incorporates the commonly understood meaning of "unavoidably unsafe" products under comment *k* at the time of the Act's enactment in 1986. See *McDermott Int'l, Inc.* v. *Wilander*, 498 U. S. 337, 342 (1991) ("[W]e assume that when a statute uses . . . a term [of art], Congress intended it to have its established meaning"); *Morissette* v. *United States*, 342 U. S. 246, 263 (1952) (same).[6] Similarly, courts applying

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122 (Colo. 1983) ("[A]pplicability of comment k . . . depends upon the coexistence of several factors," including that "the product's benefits must not be achievable in another manner; and the risk must be unavoidable under the present state of knowledge"); see also 1 L. Frumer & M. Friedman, Products Liability §§8.07[1]–[2], pp. 8–277 to 8–278 (2010) (comment *k* applies "only to defects in design," and there "must be no feasible alternative design which on balance accomplishes the subject product's purpose with a lesser risk" (internal quotation marks omitted)). To be sure, a number of courts at the time of the Vaccine Act's enactment had interpreted comment *k* to preclude design defect claims categorically for certain kinds of products, see *Hill* v. *Searle Labs.*, 884 F. 2d 1064, 1068 (CA8 1989) (collecting cases), but as indicated by the sources cited above, the courts that had construed comment *k* to apply on a case-specific basis generally agreed on the basic elements of what constituted an "unavoidably unsafe" product. See also n. 8, *infra*. The majority's suggestion that "judges who must rule on motions to dismiss, motions for summary judgment, and motions for judgment as a matter of law" are incapable of adjudicating claims alleging "unavoidable" side effects, *ante*, at 7–8, n. 35, is thus belied by the experience of the many courts that had adjudicated such claims for years by the time of the Vaccine Act's enactment.

[6]The majority refuses to recognize that "unavoidable" is a term of art derived from comment *k*, suggesting that "'[u]navoidable' is hardly a rarely used word." *Ante*, at 10. In fact, however, "unavoidable" is an extremely rare word in the relevant context. It appears exactly *once* (*i.e.*, in §300aa–22(b)(1)) in the entirety of Title 42 of the U. S. Code ("Public Health and Welfare"), which governs, *inter alia*, Social Security, see 42 U. S. C. §301 *et seq.*, Medicare, see §1395 *et seq.*, and several other of the Federal Government's largest entitlement programs. The singular rarity in which Congress used the term supports the conclu-

comment *k* had long required manufacturers invoking the defense to demonstrate that their products were not only "unavoidably unsafe" but also properly manufactured and labeled.[7] By requiring "prope[r] prepar[ation]" and "proper directions and warnings" in §22(b)(1), Congress plainly intended to incorporate these additional comment *k* requirements.

The 1986 Report thus confirms petitioners' interpretation of §22(b)(1). The Report makes clear that "side effects that were unavoidable" in §22(b)(1) refers to side effects stemming from a vaccine's design that were "unavoidable." By explaining what Congress meant by the term "unavoidable," moreover, the Report also confirms that whether a side effect is "unavoidable" for purposes of §22(b)(1) involves a specific inquiry in each case as to whether the vaccine "in the present state of human skill and knowledge cannot be made safe," 1986 Report 26—*i.e.*, whether a feasible alternative design existed that would have eliminated the adverse side effects of the vaccine without compromising its cost and utility. See Brief for Kenneth W. Starr et al. as *Amici Curiae* 14–15 ("If a particular plaintiff could show that her injury at issue was avoidable . . . through the use of a feasible alternative design for a specific vaccine, then she would satisfy the plain language of the statute, because she would have demonstrated that the side effects were *not* unavoidable"). Finally, the Report confirms that the "even though" clause is properly read to establish two additional prerequisites—proper manufacturing and proper labeling—to qualify for

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sion that "unavoidable" is a term of art.

[7] See, *e.g.*, *Brochu* v. *Ortho Pharmaceutical Corp.*, 642 F. 2d 652, 657 (CA1 1981); *Needham* v. *White Labs., Inc.*, 639 F. 2d 394, 402 (CA7 1981); *Reyes* v. *Wyeth Labs.*, 498 F. 2d 1264, 1274–1275 (CA5 1974); *Davis* v. *Wyeth Labs.*, 399 F. 2d 121, 127–129 (CA9 1968); *Feldman* v. *Lederle Labs.*, 97 N. J. 429, 448, 479 A. 2d 374, 384 (1984); see also *Toner* v. *Lederle Labs.*, 112 Idaho 328, 336, 732 P. 2d 297, 305 (1987).

§22(b)(1)'s liability exemption.[8]

In addition to the 1986 Report, one other piece of the Act's legislative history provides further confirmation of the petitioners' textual reading of §22(b)(1). When Congress enacted the Vaccine Act in 1986, it did not initially include a source of payment for the no-fault compensation program the Act established. The Act thus "made the compensation program and accompanying tort reforms contingent on the enactment of a tax to provide funding

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[8]Respondent suggests an alternative reading of the 1986 Report. According to respondent, "the principle in Comment K" is simply that of nonliability for "unavoidably unsafe" products, and thus Congress' stated intent in the 1986 Report to apply the "principle in Comment K" to "the vaccines covered in the bill" means that Congress viewed the covered vaccines as a class to be "'unavoidably unsafe.'" 1986 Report 25–26; Brief for Respondent 42. The concurrence makes a similar argument. *Ante*, at 1–2 (opinion of BREYER, J.). This interpretation finds some support in the 1986 Report, which states that "if [injured individuals] cannot demonstrate under applicable law either that a vaccine was improperly prepared or that it was accompanied by improper directions or inadequate warnings [they] should pursue recompense in the compensation system, not the tort system." 1986 Report 26. It also finds some support in the pre-Vaccine Act case law, which reflected considerable disagreement in the courts over "whether comment k applies to pharmaceutical products across the board or only on a case-by-case basis." Ausness, Unavoidably Unsafe Products and Strict Products Liability: What Liability Rule Should be Applied to the Sellers of Pharmaceutical Products? 78 Ky. L. J. 705, 708, and n. 11 (1989–1990) (collecting cases). This interpretation, however, is undermined by the fact that Congress has never directed the Food and Drug Administration (FDA) or any other federal agency to review vaccines for optimal vaccine design, see *infra*, at 20–22, and n. 19, and thus it seems highly unlikely that Congress intended to eliminate the traditional mechanism for such review (*i.e.*, design defect liability), particularly given its express retention of state tort law in the Vaccine Act, see 42 U. S. C. §300aa–22(a). In any event, to the extent there is ambiguity as to how precisely Congress intended the "principle in Comment K" to apply to the covered vaccines, that ambiguity is explicitly resolved in petitioners' favor by the 1987 House Energy and Commerce Committee Report, H. R. Rep. No. 100–391, pt. 1, pp. 690–691 (hereinafter 1987 Report). See *infra* this page and 11–12.

for the compensation." 1987 Report 690. In 1987, Congress passed legislation to fund the compensation program. The House Energy and Commerce Committee Report[9] accompanying that legislation specifically stated that "the codification of Comment (k) of The Restatement (Second) of Torts was not intended to decide as a matter of law the circumstances in which a vaccine should be deemed unavoidably unsafe." *Id.*, at 691. The Committee noted that "[a]n amendment to establish . . . that a manufacturer's failure to develop [a] safer vaccine was not grounds for liability was rejected by the Committee during its original consideration of the Act." *Ibid.* In light of that rejection, the Committee emphasized that "there should be no misunderstanding that the Act undertook to decide as a matter of law whether vaccines were unavoidably unsafe or not," and that "[t]his question is left to the courts to determine in accordance with applicable law." *Ibid.*

To be sure, postenactment legislative history created by a subsequent Congress is ordinarily a hazardous basis from which to infer the intent of the enacting Congress. See *Sullivan* v. *Finkelstein*, 496 U. S. 617, 631–632 (1990) (SCALIA, J., concurring in part). But unlike ordinary postenactment legislative history, which is justifiably given little or no weight, the 1987 Report reflects the intent of the Congress that enacted the funding legislation necessary to give operative effect to the principal provisions of the Vaccine Act, including §22(b)(1).[10] Congress in

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[9] The Third Circuit's opinion below expressed uncertainty as to whether the 1987 Report was authored by the House Budget Committee or the House Energy and Commerce Committee. See 561 F. 3d 233, 250 (2009). As petitioners explain, although the Budget Committee compiled and issued the Report, the Energy and Commerce Committee wrote and approved the relevant language. Title IV of the Report, entitled "Committee on Energy and Commerce," comprises "two Committee Prints approved by the Committee on Energy and Commerce for inclusion in the forthcoming reconciliation bill." 1987 Report 377, 380.

[10] The majority suggests that the 1987 legislation creating the fund-

1987 had a number of options before it, including adopting an entirely different compensation scheme, as the Reagan administration was proposing;[11] establishing different limitations on tort liability, including eliminating design defect liability, as pharmaceutical industry leaders were advocating;[12] or not funding the compensation program at all, which would have effectively nullified the relevant portions of the Act. Because the tort reforms in the 1986 Act, including §22(b)(1), had no operative legal effect unless and until Congress provided funding for the compensation program, the views of the Congress that enacted that funding legislation are a proper and, indeed, authoritative guide to the meaning of §22(b)(1). Those views, as reflected in the 1987 Report, provide unequivocal confir-

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ing mechanism is akin to appropriations legislation and that giving weight to the legislative history of such legislation "would set a dangerous precedent." *Ante*, at 18. The difference, of course, is that appropriations legislation ordinarily funds congressional enactments that already have operative legal effect; in contrast, operation of the tort reforms in the 1986 Act, including §22(b)(1), was expressly conditioned on the enactment of a separate tax to fund the compensation program. See §323(a), 100 Stat. 3784. Accordingly, this Court's general reluctance to view appropriations legislation as modifying substantive legislation, see, *e.g.*, *TVA* v. *Hill*, 437 U. S. 153, 190 (1978), has no bearing here.

[11] See 1987 Report 700 (describing the administration's alternative proposal).

[12] See, *e.g.*, Hearings on Funding of the Childhood Vaccine Program before the Subcommittee on Select Revenue Measures of the House Committee on Ways and Means, 100th Cong., 1st Sess., 85 (1987) ("[T]he liability provisions of the 1986 Act should be amended to assure that manufacturers will not be found liable in the tort system if they have fully complied with applicable government regulations. In particular, manufacturers should not face liability under a 'design defect' theory in cases where plaintiffs challenge the decisions of public health authorities and federal regulators that the licensed vaccines are the best available way to protect children from deadly diseases" (statement of Robert B. Johnson, President, Lederle Laboratories Division, American Cyanamid Co.)).

mation of petitioners' reading of §22(b)(1).

In sum, the text, structure, and legislative history of the Vaccine Act are fully consistent with petitioners' reading of §22(b)(1). Accordingly, I believe §22(b)(1) exempts vaccine manufacturers from tort liability only upon a showing by the manufacturer in each case that the vaccine was properly manufactured and labeled, and that the side effects stemming from the vaccine's design could not have been prevented by a feasible alternative design that would have eliminated the adverse side effects without compromising the vaccine's cost and utility.

II

In contrast to the interpretation of §22(b)(1) set forth above, the majority's interpretation does considerable violence to the statutory text, misconstrues the legislative history, and draws the wrong conclusions from the structure of the Vaccine Act and the broader federal scheme regulating vaccines.

A

As a textual matter, the majority's interpretation of §22(b)(1) is fundamentally flawed in three central respects. First, the majority's categorical reading rests on a faulty and untenable premise. Second, its reading functionally excises 13 words from the statutory text, including the key term "unavoidable." And third, the majority entirely ignores the Vaccine Act's default rule preserving state tort law.

To begin, the majority states that "[a] side effect of a vaccine could *always* have been avoidable by use of a differently designed vaccine not containing the harmful element." *Ante*, at 7. From that premise, the majority concludes that the statute must mean that "the *design* of the vaccine is a given, not subject to question in the tort action," because construing the statute otherwise would

render §22(b)(1) a nullity. *Ibid.* A tort claimant, according to the majority, will always be able to point to a differently designed vaccine not containing the "harmful element," and if that were sufficient to show that a vaccine's side effects were not "unavoidable," the statute would preempt nothing.

The starting premise of the majority's interpretation, however, is fatally flawed. Although in the most literal sense, as the majority notes, a side effect can always be avoided "by use of a differently designed vaccine not containing the harmful element," *ibid.*, this interpretation of "unavoidable" would effectively read the term out of the statute, and Congress could not have intended that result. Indeed, §22(b)(1) specifically uses the conditional phrase "if the injury or death resulted from side effects that were unavoidable," which plainly indicates that Congress contemplated that there would be some instances in which a vaccine's side effects are "unavoidable" and other instances in which they are not. See *supra*, at 3. The majority's premise that a vaccine's side effects can always be "avoid[ed] by use of a differently designed vaccine not containing the harmful element," *ante*, at 7, entirely ignores the fact that removing the "harmful element" will often result in a less effective (or entirely ineffective) vaccine. A vaccine, by its nature, ordinarily employs a killed or weakened form of a bacteria or virus to stimulate antibody production;[13] removing that bacteria or virus might remove the "harmful element," but it would also necessarily render the vaccine inert. As explained above, the legislative history of the Vaccine Act and the cases interpreting comment *k* make clear that a side effect is

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[13] See American Academy of Pediatrics, Questions and Answers about Vaccine Ingredients (Oct. 2008), http://www.aap.org/immunization/families/faq/Vaccineingredients.pdf (all Internet materials as visited Feb. 18, 2011, and available in Clerk of Court's case file).

"unavoidable" for purposes of §22(b)(1) only where there is no feasible alternative design that would eliminate the side effect of the vaccine without compromising its cost and utility. See *supra*, at 7. The majority's premise—that side effects stemming from a vaccine's design are always avoidable—is thus belied by the statutory text and legislative history of §22(b)(1). And because its starting premise is invalid, its conclusion—that the design of a vaccine is not subject to challenge in a tort action—is also necessarily invalid.

The majority's reading suffers from an even more fundamental defect. If Congress intended to exempt vaccine manufacturers categorically from all design defect liability, it more logically would have provided: "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the vaccine was properly prepared and was accompanied by proper directions and warnings." There would have been no need for Congress to include the additional 13 words "the injury or death resulted from side effects that were unavoidable even though." See *TRW Inc.* v. *Andrews*, 534 U. S. 19, 31 (2001) (noting "cardinal principle of statutory construction that a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence, or word shall be superfluous, void, or insignificant" (internal quotation marks omitted)).

In *Bates* v. *Dow Agrosciences LLC*, 544 U. S. 431 (2005), this Court considered an analogous situation where an express pre-emption provision stated that certain States "'shall not impose or continue in effect any requirements for labeling or packaging in addition to or different from those required under this subchapter.'" *Id.*, at 436 (quoting 7 U. S. C. §136v(b) (2000 ed.)). The *Bates* Court stated:

> "Conspicuously absent from the submissions by [respondent] and the United States is any plausible alternative interpretation of 'in addition to or different from' that would give that phrase meaning. Instead, they appear to favor reading those words out of the statute, which would leave the following: 'Such State shall not impose or continue in effect any requirements for labeling or packaging.' This amputated version of [the statute] would no doubt have clearly and succinctly commanded the pre-emption of *all* state requirements concerning labeling. That Congress added the remainder of the provision is evidence of its intent to draw a distinction between state labeling requirements that are pre-empted and those that are not." 544 U. S., at 448–449.

As with the statutory interpretation rejected by this Court in *Bates*, the majority's interpretation of §22(b)(1) functionally excises 13 words out of the statute, including the key term "unavoidable." See *Duncan* v. *Walker*, 533 U. S. 167, 174 (2001) ("We are especially unwilling" to treat a statutory term as surplusage "when the term occupies so pivotal a place in the statutory scheme"). Although the resulting "amputated version" of the statutory provision "would no doubt have clearly and succinctly commanded the pre-emption of *all* state" design defect claims, the fact "[t]hat Congress added the remainder of the provision" is strong evidence of its intent not to pre-empt design defect claims categorically. *Bates*, 544 U. S., at 449; see also *American Home Prods. Corp.* v. *Ferrari*, 284 Ga. 384, 393, 668 S. E. 2d 236, 242 (2008) ("'If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly'" (quoting *Bates*, 544 U. S., at 449)), cert. pending, No. 08–1120.

Strikingly, the majority concedes that its interpretation

renders 13 words of the statute entirely superfluous. See *ante*, at 12 ("The intervening passage ('the injury or death resulted from side effects that were unavoidable even though') is unnecessary. True enough"). Nevertheless, the majority contends that "the rule against giving a portion of text an interpretation which renders it superfluous . . . applies only if verbosity and prolixity can be eliminated by giving the offending passage, or the remainder of the text, a competing interpretation." *Ibid.* According to the majority, petitioners' reading of §22(b)(1) renders the "even though" clause superfluous because, to reach petitioners' desired outcome, "[i]t would suffice to say 'if the injury or death resulted from side effects that were unavoidable'—full stop." *Ibid.* As explained above, however, the "even though" clause establishes two additional prerequisites—proper manufacturing and proper labeling—to qualify for §22(b)(1)'s exemption from liability. Contrary to the majority's contention, then, the "even though" clause serves an important function by limiting the scope of the preemption afforded by the preceding "if" clause.[14]

The majority's only other textual argument is based on

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[14] In this manner, the "even though" clause functions in a "concessive subordinat[ing]" fashion, *ante*, at 11, in accord with normal grammatical usage. According to the majority, however, the "even though" clause "clarifies the word that precedes it" by "delineat[ing]" the conditions that make a side effect "unavoidable" under the statute. *Ante*, at 7. The majority's interpretation hardly treats the clause as "concessive," and indeed strains the meaning of "even though." In the majority's view, proper manufacturing and labeling are the sole prerequisites that render a vaccine's side effects unavoidable. Thus, an injurious side effect is unavoidable *because* the vaccine was properly prepared and labeled, not "even though" it was. The two conjunctions are not equivalent: The sentence "I am happy *even though* it is raining" can hardly be read to mean that "I am happy *because* it is raining." In any event, the more fundamental point is that petitioners' interpretation actually gives meaning to the words "even though," whereas the majority concedes that its interpretation effectively reads those words entirely out of the statute. See *supra* this page.

the *expressio unius*, *exclusio alterius* canon. According to the majority, because blackletter products liability law generally recognizes three different types of product defects, "[i]f all three were intended to be preserved, it would be strange [for Congress] to mention specifically only two"—namely, manufacturing and labeling defects in the "even though" clause—"and leave the third to implication." *Ante*, at 8. The majority's argument, however, ignores that the default rule under the Vaccine Act is that state law is preserved. As explained above, §22(a) expressly provides that the "[g]eneral rule" is that "State law shall apply to a civil action brought for damages for a vaccine-related injury or death." 42 U. S. C. §300aa–22(a). Because §22(a) already preserves state-law design defect claims (to the extent the exemption in §22(b)(1) does not apply), there was no need for Congress separately and expressly to preserve design defect claims in §22(b)(1). Indeed, Congress' principal aim in enacting §22(b)(1) was not to preserve manufacturing and labeling claims (those, too, were already preserved by §22(a)), but rather, to federalize comment *k*-type protection for "unavoidably unsafe" vaccines. The "even though" clause simply functions to limit the applicability of that defense. The lack of express language in §22(b)(1) specifically preserving design defect claims thus cannot fairly be understood as impliedly (and categorically) pre-empting such traditional state tort claims, which had already been preserved by §22(a).[15]

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[15]This Court, moreover, has long operated on "the assumption that the historic police powers of the States are not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Altria Group, Inc.* v. *Good*, 555 U. S. ___, ___ (2008) (slip op., at 5) (internal quotation marks and alteration omitted). Given the long history of state regulation of vaccines, see Brief for Petitioners 3–6, the presumption provides an additional reason not to read §22(b)(1) as pre-empting all design defect claims, especially given Congress' inclusion of

The majority also suggests that if Congress wished to preserve design defect claims, it could have simply provided that manufacturers would be liable for "defective manufacture, defective directions or warning, and defective design." *Ante*, at 8 (internal quotation marks omitted). Putting aside the fact that §22(a) already preserves design defect claims (to the extent §22(b)(1) does not apply), the majority's proposed solution would not have fully effectuated Congress' intent. As the legislative history makes clear, Congress used the term "unavoidable" to effectuate its intent that the "principle in Comment K regarding 'unavoidably unsafe' products . . . apply to the vaccines covered in the bill." 1986 Report 26; see also 1987 Report 691. At the time of the Vaccine Act's enactment in 1986, at least one State had expressly rejected comment *k*,[16] while many others had not addressed the applicability of comment *k* specifically to vaccines or applied comment *k* to civil actions proceeding on a theory other than strict liability (*e.g.*, negligence[17]). A statute

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an express saving clause in the same statutory section, see 42 U. S. C. §300aa–22(a), and its use of the conditional "if" clause in defining the pre-emptive scope of the provision. See *Bates* v. *Dow Agrosciences LLC*, 544 U. S. 431, 449 (2005) ("In areas of traditional state regulation, we assume that a federal statute has not supplanted state law unless Congress has made such an intention clear and manifest" (internal quotation marks omitted)).

[16] See *Collins* v. *Eli Lilly Co.*, 116 Wis. 2d 166, 197, 342 N. W. 2d 37, 52 (1984) ("We conclude that the rule embodied in comment k is too restrictive and, therefore, not commensurate with strict products liability law in Wisconsin"). *Collins* did, however, "recognize that in some exigent circumstances it may be necessary to place a drug on the market before adequate testing can be done." *Ibid.* It thus adopted a narrower defense (based on "exigent circumstances") than that recognized in other jurisdictions that had expressly adopted comment *k*.

[17] See, *e.g.*, *Kearl*, 172 Cal. App. 3d, at 831, n. 15, 218 Cal. Rptr., at 465, n. 15 ("[T]he unavoidably dangerous product doctrine merely exempts the product from a strict liability design defect analysis; a plaintiff remains free to pursue his design defect theory on the basis of

that simply stated that vaccine manufacturers would be liable for "defective design" would be silent as to the availability of a comment *k*-type defense for "unavoidably unsafe" vaccines, and thus would not have fully achieved Congress' aim of extending greater liability protection to vaccine manufacturers by providing comment *k*-type protection in all civil actions as a matter of federal law.

B

The majority's structural arguments fare no better than its textual ones. The principal thrust of the majority's position is that, since nothing in the Vaccine Act or the FDA's regulations governing vaccines expressly mentions design defects, Congress must have intended to remove issues concerning the design of FDA-licensed vaccines from the tort system. *Ante*, at 13. The flaw in that reasoning, of course, is that the FDA's silence on design defects existed long before the Vaccine Act was enacted. Indeed, the majority itself concedes that the "FDA has never even spelled out in regulations the criteria it uses to decide whether a vaccine is safe and effective for its intended use."[18] *Ibid.* And yet it is undisputed that prior to the Act, vaccine manufacturers had long been subject to liability under state tort law for defective vaccine design. That the Vaccine Act did not itself set forth a comprehensive regulatory scheme with respect to design defects is thus best understood to mean not that Congress suddenly decided to change course *sub silentio* and pre-empt a

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negligence"); *Toner*, 112 Idaho, at 340, 732 P. 2d, at 309–310 ("The authorities universally agree that where a product is deemed unavoidably unsafe, the plaintiff is deprived of the advantage of a strict liability cause of action, but may proceed under a negligence cause of action").

[18] See 42 U. S. C. §262(a)(2)(C)(i)(I) ("The Secretary shall approve a biologics license application . . . on the basis of a demonstration that . . . the biological product that is the subject of the application is safe, pure, and potent").

longstanding, traditional category of state tort law, but rather, that Congress intended to leave the status quo alone (except, of course, with respect to those aspects of state tort law that the Act expressly altered). See 1987 Report 691 ("It is not the Committee's intention to preclude court actions under applicable law. The Committee's intent at the time of considering the Act . . . was . . . to leave otherwise applicable law unaffected, except as expressly altered by the Act").

The majority also suggests that Congress necessarily intended to pre-empt design defect claims since the aim of such tort suits is to promote the development of improved designs and provide compensation for injured individuals, and the Vaccine Act "provides other means for achieving both effects"—most notably through the no-fault compensation program and the National Vaccine Program. *Ante*, at 14, and nn. 57–60 (citing 42 U. S. C. §§300aa–1, 300aa–2(a)(1)–(3), 300aa–3, 300aa–25(b), 300aa–27(a)(1)). But the majority's position elides a significant difference between state tort law and the federal regulatory scheme. Although the Vaccine Act charges the Secretary of Health and Human Services with the obligation to "promote the development of childhood vaccines" and "make or assure improvements in . . . vaccines, and research on vaccines," §300aa–27(a), neither the Act nor any other provision of federal law places a legal *duty* on vaccine manufacturers to improve the design of their vaccines to account for scientific and technological advances. Indeed, the FDA does not condition approval of a vaccine on it being the most optimally designed among reasonably available alternatives, nor does it (or any other federal entity) ensure that licensed vaccines keep pace with technological and scientific advances.[19] Rather, the function of ensuring

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[19] See, *e.g.*, *Hurley* v. *Lederle Labs.*, 863 F. 2d 1173, 1177 (CA5 1988) ("[T]he FDA is a passive agency: it considers whether to approve

that vaccines are optimally designed in light of existing science and technology has traditionally been left to the States through the imposition of damages for design defects. Cf. *Bates*, 544 U. S., at 451 ("'[T]he specter of damage actions may provide manufacturers with added dynamic incentives to continue to keep abreast of all possible injuries stemming from use of their product[s] so as to forestall such actions through product improvement'"); *Wyeth* v. *Levine*, 555 U. S. ___, ___ (2009) (slip op., at 22–

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vaccine designs only if and when manufacturers come forward with a proposal"); *Jones* v. *Lederle Labs.*, 695 F. Supp. 700, 711 (EDNY 1988) ("[T]he agency takes the drugs and manufacturers as it finds them. While its goal is to oversee inoculation with the best possible vaccine, it is limited to reviewing only those drugs submitted by various manufacturers, regardless of their flaws"). Although the FDA has authority under existing regulations to revoke a manufacturer's biologics licenses, that authority can be exercised only where (as relevant here) "[t]he licensed product is not safe and effective for all of its intended uses." 21 CFR §601.5(b)(1)(vi) (2010); see §600.3(p) (defining "safety" as "relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time"). The regulation does not authorize the FDA to revoke a biologics license for a manufacturer's failure to adopt an optimal vaccine design in light of existing science and technology. See Conk, Is There a Design Defect in the Restatement (Third) of Torts: Products Liability? 109 Yale L. J. 1087, 1128–1129 (1999–2000) ("The FDA does not claim to review products for optimal design . . . . FDA review thus asks less of drug . . . manufacturers than the common law of products liability asks of other kinds of manufacturers"). At oral argument, counsel for *amicus* United States stated that the Centers for Disease Control and Prevention (CDC) routinely performs comparative analyses of vaccines that are already on the market. See Tr. of Oral Arg. 44–45; *id.*, at 52–53 (describing CDC's comparison of Sabin and Salk polio vaccines). Neither the United States nor any of the parties, however, has represented that CDC examines whether a safer alternative vaccine *could have been designed* given practical and scientific limits, the central inquiry in a state tort law action for design defect. CDC does not issue biologics licenses, moreover, and thus has no authority to require a manufacturer to adopt a different vaccine design.

23) (noting that the FDA has "traditionally regarded state law as a complementary form of drug regulation" as "[s]tate tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly").[20] The importance of the States' traditional regulatory role is only underscored by the unique features of the vaccine market, in which there are "only one or two manufacturers for a majority of the vaccines listed on the routine childhood immunization schedule." Brief for Respondent 55. The normal competitive forces that spur innovation and improvements to existing product lines in other markets thus operate with less force in the vaccine market, particularly for vaccines that have already been released and marketed to the public. Absent a clear statutory mandate to the contrary, there is no reason to think that Congress intended in the vaccine context to eliminate the traditional incentive and deterrence functions served by state tort liability in favor of a federal regulatory scheme providing only carrots and no sticks.[21] See *Levine*, 555 U. S., at ___ (slip op., at 18) ("The

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[20] Indeed, we observed in *Levine* that the FDA is perpetually understaffed and underfunded, see 555 U. S., at ___, n. 11 (slip op., at 22, n. 11), and the agency has been criticized in the past for its slow response in failing to withdraw or warn about potentially dangerous products, see, *e.g.*, L. Leveton, H. Sox, & M. Soto, Institute of Medicine, HIV and the Blood Supply: An Analysis of Crisis Decisionmaking (1995) (criticizing FDA response to transmission of AIDS through blood supply). These practical shortcomings reinforce the conclusion that "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Levine*, 555 U. S., at ___ (slip op., at 23).

[21] The majority mischaracterizes my position as expressing a general "skeptic[ism] of preemption unless the congressional substitute operate[s] like the tort system." *Ante*, at 16. Congress could, of course, adopt a regulatory regime that operates differently from state tort systems, and such a difference is not necessarily a reason to question Congress' pre-emptive intent. In the specific context of the Vaccine Act, however, the relevant point is that this Court should not lightly assume

case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there is between them." (internal quotation marks and alteration omitted)).

III

In enacting the Vaccine Act, Congress established a carefully wrought federal scheme that balances the competing interests of vaccine-injured persons and vaccine manufacturers. As the legislative history indicates, the Act addressed "two overriding concerns": "(a) the inadequacy—from both the perspective of vaccine-injured persons as well as vaccine manufacturers—of the current approach to compensating those who have been damaged by a vaccine; and (b) the instability and unpredictability of the childhood vaccine market." 1986 Report 7. When viewed in the context of the Vaccine Act as a whole, §22(b)(1) is just one part of a broader statutory scheme that balances the need for compensating vaccine-injured children with added liability protections for vaccine manufacturers to ensure a stable childhood vaccine market.

The principal innovation of the Act was the creation of the no-fault compensation program—a scheme funded entirely through an excise tax on vaccines.[22] Through that

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that Congress intended *sub silentio* to displace a longstanding species of state tort liability where, as here, Congress specifically included an express saving clause preserving state law, there is a long history of state-law regulation of vaccine design, and pre-emption of state law would leave an important regulatory function—*i.e.*, ensuring optimal vaccine design—entirely unaddressed by the congressional substitute.

[22]The majority's suggestion that "vaccine manufacturers fund from their sales" the compensation program is misleading. *Ante*, at 15. Although the manufacturers nominally pay the tax, the amount of the tax is specifically included in the vaccine price charged to purchasers. See CDC Vaccine Price List (Feb. 15, 2011), http://www.cdc.gov/

program, Congress relieved vaccine manufacturers of the burden of compensating victims of vaccine-related injuries in the vast majority of cases[23]—an extremely significant economic benefit that "functionally creat[es] a valuable insurance policy for vaccine-related injuries." Reply Brief for Petitioners 10. The structure and legislative history, moreover, point clearly to Congress' intention to divert would-be tort claimants into the compensation program, rather than eliminate a longstanding category of traditional tort claims. See 1986 Report 13 ("The Committee anticipates that the speed of the compensation program, the low transaction costs of the system, the no-fault nature of the required findings, and the relative certainty and generosity of the system's awards will divert a significant number of potential plaintiffs from litigation"). Indeed, although complete pre-emption of tort claims would have eliminated the principal source of the "unpredictability" in the vaccine market, Congress specifically chose *not* to pre-empt state tort claims categorically. See 42 U. S. C. §300aa–22(a) (providing as a "[g]eneral rule" that "State law shall apply to a civil action brought for damages for a vaccine-related injury or death"). That decision reflects Congress' recognition that court actions are essential

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vaccines/programs/vfc/cdc-vac-price-list.htm. Accordingly, the only way the vaccine manufacturers can be said to actually "fund" the compensation program is if the cost of the excise tax has an impact on the number of vaccines sold by the vaccine manufacturer. The majority points to no evidence that the excise tax—which ordinarily amounts to 75 cents per dose, 26 U. S. C. §4131(b)—has any impact whatsoever on the demand for vaccines.

[23] See Brief for United States as *Amicus Curiae* 28 ("Department of Justice records indicate that 99.8% of successful Compensation Program claimants have accepted their awards, foregoing any tort remedies against vaccine manufacturers"); S. Plotkin, W. Orenstein, & P. Offit, Vaccines 1673 (5th ed. 2008) (noting that "[v]irtually all . . . petitioners, even those who were not awarded compensation" under the compensation program, choose to accept the program's determination).

because they provide injured persons with significant procedural tools—including, most importantly, civil discovery—that are not available in administrative proceedings under the compensation program. See §§300aa–12(d)(2)(E), (d)(3). Congress thus clearly believed there was still an important function to be played by state tort law.

Instead of eliminating design defect liability entirely, Congress enacted numerous measures to reduce manufacturers' liability exposure, including a limited regulatory compliance presumption of adequate warnings, see §300aa–22(b)(2), elimination of claims based on failure to provide direct warnings to patients, §300aa–22(c), a heightened standard for punitive damages, §300aa–23(d)(2), and, of course, immunity from damages for "unavoidable" side effects, §300aa–22(b)(1). Considered in light of the Vaccine Act as a whole, §22(b)(1)'s exemption from liability for unavoidably unsafe vaccines is just one part of a broader statutory scheme that reflects Congress' careful balance between providing adequate compensation for vaccine-injured children and conferring substantial benefits on vaccine manufacturers to ensure a stable and predictable childhood vaccine supply.

The majority's decision today disturbs that careful balance based on a bare policy preference that it is better "to leave complex epidemiological judgments about vaccine design to the FDA and the National Vaccine Program rather than juries." *Ante*, at 15.[24] To be sure, reasonable minds can disagree about the wisdom of having juries weigh the relative costs and benefits of a particular vaccine design. But whatever the merits of the majority's

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[24] JUSTICE BREYER's separate concurrence is even more explicitly policy driven, reflecting his own preference for the "more expert judgment" of federal agencies over the "less expert" judgment of juries. *Ante*, at 5.

policy preference, the decision to bar all design defect claims against vaccine manufacturers is one that Congress must make, not this Court.[25] By construing §22(b)(1) to

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[25] Respondent notes that there are some 5,000 petitions alleging a causal link between certain vaccines and autism spectrum disorders that are currently pending in an omnibus proceeding in the Court of Federal Claims (Vaccine Court). Brief for Respondent 56–57. According to respondent, a ruling that §22(b)(1) does not pre-empt design defect claims could unleash a "crushing wave" of tort litigation that would bankrupt vaccine manufacturers and deplete vaccine supply. *Id.*, at 28. This concern underlies many of the policy arguments in respondent's brief and appears to underlie the majority and concurring opinions in this case. In the absence of any empirical data, however, the prospect of an onslaught of autism-related tort litigation by claimants denied relief by the Vaccine Court seems wholly speculative. As an initial matter, the special masters in the autism cases have thus far uniformly rejected the alleged causal link between vaccines and autism. See Brief for American Academy of Pediatrics et al. as *Amici Curiae* 20–21, n. 4 (collecting cases). To be sure, those rulings do not necessarily mean that no such causal link exists, cf. Brief for United States as *Amicus Curiae* 29 (noting that injuries have been added to the Vaccine Injury Table for existing vaccines), or that claimants will not ultimately be able to prove such a link in a state tort action, particularly with the added tool of civil discovery. But these rulings do highlight the substantial hurdles to recovery a claimant faces. See *Schafer* v. *American Cyanamid Co.*, 20 F. 3d 1, 5 (CA1 1994) ("[A] petitioner to whom the Vaccine Court gives nothing may see no point in trying to overcome tort law's yet more serious obstacles to recovery"). Trial courts, moreover, have considerable experience in efficiently handling and disposing of meritless products liability claims, and decades of tort litigation (including for design defect) in the prescription-drug context have not led to shortages in prescription drugs. Despite the doomsday predictions of respondent and the various *amici* cited by the concurrence, *ante*, at 6–7, the possibility of a torrent of meritless lawsuits bankrupting manufacturers and causing vaccine shortages seems remote at best. More fundamentally, whatever the merits of these policy arguments, the issue in this case is what Congress has decided, and as to that question, the text, structure, and legislative history compel the conclusion that Congress intended to leave the courthouse doors open for children who have suffered severe injuries from defectively designed vaccines. The majority's policy-driven decision to the contrary usurps Congress' role and deprives such vaccine-injured children of a key remedy that Congress intended them to have.

pre-empt all design defect claims against vaccine manufacturers for covered vaccines, the majority's decision leaves a regulatory vacuum in which no one—neither the FDA nor any other federal agency, nor state and federal juries—ensures that vaccine manufacturers adequately take account of scientific and technological advancements. This concern is especially acute with respect to vaccines that have already been released and marketed to the public. Manufacturers, given the lack of robust competition in the vaccine market, will often have little or no incentive to improve the designs of vaccines that are already generating significant profit margins. Nothing in the text, structure, or legislative history remotely suggests that Congress intended that result.

I respectfully dissent.

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Bruesewitz v. Wyeth's **Impact on the Vaccine Safety Debate**

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Childhood vaccines are extolled for effective prevention of dangerous diseases. However, a persistent anti-vaccine movement resists vaccination due to real and perceived links between vaccines and adverse health effects, including autism.[3] Closely related to the vaccine safety debate is the policy concern about balancing the need to compensate individuals who are harmed by vaccines and to prevent vaccine manufacturers from exiting the market due to the prospect of unmanageable tort liability. The recent Supreme Court decision in Bruesewitz v. Wyeth strikes a balance in favor of shielding vaccine manufacturers from design-defect liability and thus limits the options for claimants of certain vaccine-related injuries to recover compensation.[4]

The Bruesewitz decision held that design-defect claims against vaccine manufacturers are preempted under the National Childhood Vaccine Injury Act (NCVIA).[5] Despite the Court's focus on statutory interpretation, the public health policy implications and vaccine safety debate lurked beneath the surface of the Court's reasoning. Although the Court's decision has largely been lauded as a win for public health, some have criticized the decision as creating a dangerous regulatory vacuum for vaccine improvement and monitoring. This decision has significant ramifications for the vaccine compensation system, including the thousands of pending claims asserting a link between vaccines and autism.

The Current Vaccine Injury Compensation Program

In 1986, Congress enacted NCVIA and established the Vaccine Injury Compensation Program (VICP) in response to a destabilized vaccine market caused by manufacturer withdrawal due to increasing tort liability. The VICP is a no-fault program to compensate individuals who experience adverse reactions to vaccination and to protect vaccine manufacturers from certain types of liability to ensure a sufficient production of vaccine.[6] The VICP allows claimants to petition a vaccine court for an award paid from a fund created by excise taxes on vaccines. The vaccine court will issue an award if the adverse reaction is listed on the Vaccine Injury Table, which lists compensable injuries by vaccine type, without the petitioner needing to prove causation or fault. Alternatively, if the vaccine or injury is not included within the table, the vaccine court will issue an award if the claimant proves the vaccine caused the injury. The claimant may decide whether to accept the vaccine court's judgment or file a state tort claim against the manufacturer, unless the claim is preempted by NCVIA. Preempted claims may only be pursued in vaccine court and include claims relating to manufacturing defects, failures to warn and, after Bruesewitz, design-defects.

The Case: Bruesewitz v. Wyeth

The Bruesewitz case was filed by Russell and Robalee Bruesewitz, who claimed that their daughter, Hannah, experienced seizures and suffered permanent disabilities following the administration of a diphtheria-tetanus-pertussis vaccine when she was six months old.[7] Hannah's parents petitioned the vaccine court on her behalf, but they were denied an award.[8] The Bruesewitzes rejected the vaccine court's ruling, and filed a state claim alleging, among other things, that the vaccine manufactured by Lederle Laboratories (later purchased by Wyeth) had a defective design that caused their daughter's disabilities.[9]

The United States Supreme Court ruled that NCVIA preemptively bars all state-law design-defect claims against vaccine manufacturers.[10] Justice Scalia, writing for the majority, relied on a textual analysis of NCVIA's provision that no vaccine manufacturer is liable for a vaccine-related injury "if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."[11] The Court

noted the policy concern of NCVIA to stabilize the market to entice manufacturers to remain in the vaccine business and avert the vaccine shortages seen in the 1980s due to the threat of tort liability.[12] The majority concluded that allowing design-defect tort claims, "the most speculative and difficult type of products liability claim to litigate," would "hardly coax manufacturers back into the market."[13]

In her dissent, Justice Sotomayor argued that the text of the statute did contemplate design-defect claims because it provided liability protection only for "unavoidable" side effects.[14] Accordingly, the adverse side effects could have been avoided if the vaccine in question had been designed differently. The dissent expressed concern that the majority's decision creates a significant vacuum—the Food and Drug Administration's approval process does not require vaccines to be optimally designed or continuously improved, and state tort liability for design defects has traditionally provided this incentive.[15] The dissent further pointed to the lack of post-approval regulatory oversight and the lack of competition in the vaccine market as exacerbating the regulatory vacuum.[16]

Whether the majority's decision or the dissent's concerns are correct will be determined as the effect of a bar on state design-defect claims against vaccine manufacturers plays out. Regardless, the decision adds a new component to the vaccine safety debate and could affect the large number of current claims asserting that vaccines have caused autism in children.

The Impact

This case has significant ramifications for the approximately 5,000 pending claims in an omnibus proceeding before the vaccine court alleging that childhood vaccines caused autism. The Bruesewitz decision will likely restrict many of the claims to vaccine court and foreclose the possibility of a state tort law alternative for claims asserting that a defective design caused autism.

Claims asserting a link between vaccines and autism have not generally been compensated in vaccine court under NCVIA because autism is not listed on the Vaccine Injury Table and due to the lack of credible medical evidence that vaccines cause autism.[17] A vocal anti-vaccine movement still believes that vaccines, particularly the thimerosol-containing measles-mumps-rubella (MMR) vaccine, cause autism despite the lack of medical evidence,[18] likely due to the co-occurrence of the timing of standard vaccine administration and the emergence of symptoms of autism.

Public health officials voice concern over threats to the health of the population as herd immunity to communicable diseases declines with lower rates of vaccination. Recent measles outbreaks demonstrate the potential public health dangers associated with decisions to not vaccinate. An example is the 2008 measles outbreak in San Diego, spreading primarily among unvaccinated schoolchildren and infants too young to be vaccinated.[19]Bruesewitz may strengthen liability protections of vaccine manufacturers necessary to maintain vaccine supply, but it does little to combat the problem of declining immunization rates among the anti-vaccine movement.

Generally, the Court's decision has been hailed by public health commentators because it prevents the specter of a similar vaccine supply crisis that led to the passage of NCVIA. The position adopted by the Court was urged by the Department of Health and Human Services, the American Public Health Association, the American Academy of Pediatrics, and many other professional medical associations.[20] Nevertheless, like the dissent, some commentators have expressed concern that vaccine manufacturers will have few incentives to improve their vaccine designs. Both sides, and the Court, seem to recognize that the compensation scheme created by NCVIA was a significant and necessary public health achievement. In preempting state tort liability for design-defect claims, the Court may have been swayed by the success of the vaccine compensation program and the importance of the public health need for a stable vaccine supply.

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3 Donald G. McNeil Jr., A Multitude of Vaccine Benefits, Yet Controversy Persists, N. Y. Times,

Mar. 28, 2008, http://www.nytimes.com/ref/health/healthguide/esn-vaccinations-ess.html ; Inst. of Medicine, Immunization Safety Review: Vaccines and Autism (2004).

4 Bruesewitz v. Wyeth, Inc. , 131 S. Ct. 1068 (2011).

5 Id. at 1082; National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1 et. seq.

6 National Vaccine Injury Program, Health Resources and Services Administration available at http://www.hrsa.gov/vaccinecompensation/ (last accessed March 15, 2011).

7 Id.

8 Id. (The Bruesewitzs were awarded attorneys fees and costs by the vaccine court, but elected to pursue their claim in Pennsylvania state court).

9 Id.

10 Id. at 1082 (6-2 vote, with Justice Kagan sitting out).

11 42 U.S.C. § 300aa-22(b)(1) (2006).

12 Bruesewitz, 131 S. Ct. at 1072-73.

13 Id. at 1080.

14 Id., 131 S. Ct. at 1087 (Sotomayor, J., dissenting).

15 Id. at 1100-01 (Sotomayor, J., dissenting).

16 Id. at 1100-01 (Sotomayor, J., dissenting).

17 See, e.g. , Cedillo v. Sec'y of Health and Human Services, 617 F.3d 1328 (Fed. Cir. 2010); Hazlehurst v. Sec'y of Health and Human Services, 604 F.3d 1343 (Fed. Cir. 2010).

18 Editorial, Autism Fraud, N.Y. Times, January 12, 2011, at A28 (describing the British Medical Journal's finding that Dr. Andrew Wakefield's influential 1998 study finding a link between the MMR vaccine and autism was deliberately fraudulent. A report seven years after the Wakefield study indicated that the twelve original subjects' medical histories had been falsified in order to make vaccines culpable for injuries.)

19 CDC, 57 MMWR 203 (Feb. 29, 2008), http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5708a3.htm .

20 Bruesewitz , 131 S. Ct. at 1085 (Breyer, J., concurring).

HRSA
Health Resources & Services Administration

National Vaccine Injury Compensation Program

Vaccines save lives by preventing disease

In fact, the Centers for Disease Control and Prevention (CDC) named immunizations as one of the ten most important public health achievements of the 20th century.

Most people who get vaccines have no serious problems, but like any medicine, they can cause side effects - most of which are rare and mild. In very rare cases, a vaccine can cause a serious problem, such as a severe allergic reaction.

In those instances, the National Vaccine Injury Compensation Program (VICP) provides individuals with an opportunity to file a petition or claim for financial compensation.

The VICP is a no-fault alternative to the traditional legal system for resolving vaccine injury petitions.

The National Childhood Vaccine Injury Act of 1986 created the VICP, which began on October 1, 1988, after a series of lawsuits threatened to cause vaccine shortages and reduce U.S. vaccination rates.

The following three organizations have a role in the VICP.

- The VICP is administered through the Department of Health and Human Services (HHS).
- The Department of Justice (DOJ) represents HHS in Court.
- The U.S. Court of Federal Claims (the Court) makes the final decision regarding whether a petitioner should be compensated.

Any individual, of any age, who received a covered vaccine and believes he or she was injured as a result, can file a petition. Parents, legal guardians and legal representatives can file on behalf of children, disabled adults and individuals who are deceased.

Please note that, with limited exceptions, all petitions must be filed within 3 years after the first symptom of the alleged vaccine injury, or within 2 years of the death and 4 years after the first symptom of the alleged vaccine injury that resulted in death. For information about additional requirements that must be met in order to pursue compensation, visit the VICP website, www.hrsa.gov/vaccinecompensation.

Did you know?

The risk of experiencing a severe allergic reaction from one of these commonly administered vaccines covered by the VICP – MMR, Hepatitis B, Diphtheria, Tetanus, and Pertussis-- *is 1 or less than 1 out of 1 million doses*, according to the CDC.

The Court makes the final decision regarding whether a petitioner should be compensated and the amount of compensation.

For more information about the VICP

Visit the website:
www.hrsa.gov/vaccinecompensation

1-800-338-2382

National Vaccine Injury Compensation Program

Parklawn Building
5600 Fishers Lane
8N146B
Rockville, Maryland 20857

How the claims process works

1. An individual files a petition with the Court. The Court sends a copy of the petition to DOJ and HHS.
2. An HHS healthcare provider reviews the petition, determines if it meets the medical criteria for compensation and makes a preliminary recommendation to DOJ. The government's position is included in DOJ's report, which is submitted to the Court.
3. The report is presented to a court-appointed special master, who decides whether the petitioner should be compensated.
4. The special master's decision may be appealed.
5. Petitioners who reject the decision of the Court (or those who withdraw their claims after certain timelines are met) may file a claim in civil court against the vaccine manufacturer and/or the health care provider who administered the vaccine.

An individual may contact the Court for more information about filing a petition, including the requirements that must be satisfied to pursue compensation. The petition does not have to be filed by a lawyer but most people use a lawyer. If certain requirements are met, the VICP generally will pay lawyer's fees and other legal costs related to the petition, whether or not the petitioner is paid for a vaccine injury or death. Visit the Court's website for a list of attorneys willing to file VICP petitions.

U.S. Court of Federal Claims
717 Madison Place, N.W.
Washington, DC 20005
202-357-6400
www.uscfc.uscourts.gov

Vaccines covered by the VICP

In order for a category of vaccines to be covered by the VICP, the category of the vaccine must be recommended for routine administration to children by the Centers for Disease Control and Prevention and subject to an excise tax. There are no age restrictions on who may file a petition with the VICP. Petitions may be filed on behalf of infants, children and adolescents, or by adults receiving VICP-covered vaccines. The following vaccines are covered by the VICP:

- Diphtheria and Tetanus vaccines (e.g., DTaP, DTP, DT, Td, or TT)
- Pertussis vaccines (e.g., DTP, DTaP, P, Tdap, DTP-Hib)
- Measles, Mumps, and Rubella vaccines (e.g., MMR, MR, M, R)
- Polio vaccines (e.g., OPV or IPV)
- Hepatitis A vaccines (e.g., HAV)
- Hepatitis B vaccines (e.g.,HBV)
- Haemophilus influenza type b polysaccharide conjugate vaccines (e.g., Hib)
- Varicella vaccines (e.g., VZV) [herpes zoster (shingles) vaccine is not covered]
- Rotavirus vaccines (e.g.,RV)
- Pneumococcal conjugate vaccines (e.g., PCV)
- Seasonal influenza vaccines (e.g., IIV3 standard dose, IIV3 high dose, IIV4, RIV3, LAIV3, LAIV4)
- Human Papillomavirus vaccines (e.g., HPV)
- Meningococcal vaccines (e.g., MCV4, MPSV4, recombinant)

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Data & Statistics

The United States has the safest, most effective vaccine supply in history. In the majority of cases, vaccines cause no side effects, however they can occur, as with any medication—but most are mild. Very rarely, people experience more serious side effects, like allergic reactions.

In those instances, the National Vaccine Injury Compensation Program (VICP) allows individuals to file a petition for compensation.

What does it mean to be awarded compensation?
Being awarded compensation for a petition does not necessarily mean that the vaccine caused the alleged injury. In fact:

- Approximately 70 percent of all compensation awarded by the VICP comes as result of a negotiated settlement between the parties in which HHS has not concluded, based upon review of the evidence, that the alleged vaccine(s) caused the alleged injury.
- Attorneys are eligible for reasonable attorneys' fees, whether or not the petitioner is awarded compensation by the Court, if certain minimal requirements are met. In those circumstances, attorneys are paid by the VICP directly. By statute, attorneys may not charge any other fee, including a contingency fee, for his or her services in representing a petitioner in the VICP.

What reasons might a petition result in a negotiated settlement?

- Consideration of prior U.S. Court of Federal Claims decisions, both parties decide to minimize risk of loss through settlement
- A desire to minimize the time and expense of litigating a case
- The desire to resolve a petition quickly

How many petitions have been awarded compensation?
According to the CDC, from 2006 to 2017 over 3.4 billion doses of covered vaccines were distributed in the U.S. For petitions filed in this time period, 6,529 petitions were adjudicated by the Court, and of those 4,493 were compensated. This means for every 1 million doses of vaccine that were distributed, approximately 1 individual was compensated.

Since 1988, over 21,303 petitions have been filed with the VICP. Over that 30-year time period, 18,358 petitions have been adjudicated, with 6,947 of those determined to be compensable, while 11,411 were dismissed. Total compensation paid over the life of the program is approximately $4.2 billion.

VICP Adjudication Categories, by Alleged Vaccine
For Petitions Filed Since the Inclusion of Influenza as an Eligible Vaccine for Filings 01/01/2006 through 12/31/2017

Name of Vaccine Listed First in a Petition (other vaccines may be alleged or basis for compensation)	Number of Doses Distributed in the U.S., 01/01/2006 through 12/31/2017 (Source: CDC)	Compensable Concession	Compensable Court Decision	Compensable Settlement	Compensable Total	Dismissed/Non-Compensable Total	Grand Total
DT	794,777	1	0	5	6	4	10
DTaP	101,073,594	19	22	107	148	117	265
DTaP-Hep B-IPV	68,764,777	5	7	28	40	55	95
DTaP-HIB	1,135,474	0	1	2	3	2	5
DTaP-IPV	24,237,580	0	0	4	4	3	7
DTap-IPV-HIB	62,397,611	3	4	9	16	31	47
DTP	0	1	1	3	5	2	7
DTP-HIB	0	1	0	2	3	1	4
Hep A-Hep B	15,826,685	1	1	15	17	6	23
Hep B-HIB	4,787,457	1	1	2	4	1	5
Hepatitis A (Hep A)	176,194,118	8	6	43	57	33	90
Hepatitis B (Hep B)	185,428,393	8	11	67	86	79	165
HIB	119,947,400	2	1	9	12	10	22
HPV	111,677,552	14	14	109	137	180	317
Influenza	1,518,400,000	658	168	2,262	3,088	529	3,617
IPV	72,962,512	0	0	4	4	4	8
Measles	135,660	0	0	1	1	0	1
Meningococcal	94,113,218	2	5	39	46	11	57
MMR	101,501,714	23	14	88	125	127	252
MMR-Varicella	24,798,297	9	0	13	22	15	37
Mumps	110,749	0	0	0	0	0	0

Name of Vaccine Listed First in a Petition (other vaccines may be alleged or basis for compensation)	Number of Doses Distributed in the U.S., 01/01/2006 through 12/31/2017 (Source: CDC)	Compensable Concession	Compensable Court Decision	Compensable Settlement	Compensable Total	Dismissed/Non-Compensable Total	Grand Total
Nonqualified	0	0	0	3	3	36	39
OPV	0	1	0	0	1	5	6
Pneumococcal Conjugate	228,588,846	20	3	34	57	36	93
Rotavirus	107,678,219	17	4	22	43	14	57
Rubella	422,548	0	1	1	2	0	2
Td	65,170,306	10	6	61	77	27	104
Tdap	248,258,803	91	18	274	383	80	463
Tetanus	3,836,052	10	1	41	52	20	72
Unspecified	0	1	1	4	6	589	595
Varicella	116,063,014	8	7	30	45	19	64
Grand Total	3,454,269,356	914	297	3,282	4,493	2,036	6,529

Notes on the Adjudication Categories Table

The date range of 01/01/2006 through 12/31/2017 was selected to reflect petitions filed since the inclusion of influenza vaccine in July 2005. Influenza vaccine now is named in the majority of all VICP petitions.

In addition to the first vaccine alleged by a petitioner, which is the vaccine listed in this table, a VICP petition may allege other vaccines, which may form the basis of compensation.

Vaccine doses are self-reported distribution data provided by US-licensed vaccine manufacturers. The data provide an estimate of the annual national distribution and do not represent vaccine administration. In order to maintain confidentiality of an individual manufacturer or brand, the data are presented in an aggregate format by vaccine type. Flu doses are derived from CDC's FluFinder tracking system, which includes data provided to CDC by US-licensed influenza vaccine manufacturers as well as their first line distributors.

"Unspecified" means insufficient information was submitted to make an initial determination. The conceded "unspecified" petition was for multiple unidentified vaccines that caused abscess formation at the vaccination site(s), and the "unspecified" settlements were for multiple vaccines later identified in the Special Masters' decisions

Definitions

Compensable – The injured person who filed a petition was paid money by the VICP. Compensation can be achieved through a concession by the U.S. Department of Health and Human Services (HHS), a decision on the merits of the petition by a special master or a judge of the U.S. Court of Federal Claims (Court), or a settlement between the parties.

- **Concession**: HHS concludes that a petition should be compensated based on a thorough review and analysis of the evidence, including medical records and the scientific and medical literature. The HHS review concludes that the petitioner is entitled to compensation, including a determination either that it is more likely than not that the vaccine caused the injury or the evidence supports fulfillment of the criteria of the Vaccine Injury Table. The Court also determines that the petition should be compensated.
- **Court Decision**: A special master or the court, within the United States Court of Federal Claims, issues a legal decision after weighing the evidence presented by both sides. HHS abides by the ultimate Court decision even if it maintains its position that the petitioner was not entitled to compensation (e.g., that the injury was not caused by the vaccine).
  For injury petitions, compensable court decisions are based in part on one of the following determinations by the court:
  1. The evidence is legally sufficient to show that the vaccine more likely than not caused (or significantly aggravated) the injury; or
  2. The injury is listed on, and meets all of the requirements of, the Vaccine Injury Table, and HHS has not proven that a factor unrelated to the vaccine more likely than not caused or significantly aggravated the injury. An injury listed on the Table and meeting all Table requirements is given the legal presumption of causation. It should be noted that conditions are placed on the Table for both scientific and policy reasons.
- **Settlement**: The petition is resolved via a negotiated settlement between the parties. This settlement is not an admission by the United States or the Secretary of Health and Human Services that the vaccine caused the petitioner's alleged injuries, and, in settled cases, the Court does not determine that the vaccine caused the injury. A settlement therefore cannot be characterized as a decision by HHS or by the Court that the vaccine caused an injury. Petitions may be resolved by settlement for many reasons, including consideration of prior court decisions; a recognition by both parties that there is a risk of loss in proceeding to a decision by the Court making the certainty of settlement more desirable; a desire by both parties to minimize the time and expense associated with litigating a case to conclusion; and a desire by both parties to resolve a case quickly and efficiently.
- **Non-compensable/Dismissed**: The injured person who filed a petition was ultimately not paid money. Non-compensable Court decisions include the following:
  1. The Court determines that the person who filed the petition did not demonstrate that the injury was caused (or significantly aggravated) by a covered vaccine or meet the requirements of the Table (for injuries listed on the Table).
  2. The petition was dismissed for not meeting other statutory requirements (such as not meeting the filing deadline, not receiving a covered vaccine, and not meeting the statute's severity requirement).
  3. The injured person voluntarily withdrew his or her petition.

Petitions Filed, Compensated and Dismissed, by Alleged Vaccine, Since the Beginning of VICP, 10/01/1988 through 11/01/2019

Vaccines	Filed Injury	Filed Death	Filed Grand Total	Compensated	Dismissed
DTaP-IPV	12	0	12	4	3
DT	69	9	78	26	52
DTP	3,286	696	3,982	1,273	2,709
DTP-HIB	20	8	28	7	21
DTaP	461	84	545	231	253
DTaP-Hep B-IPV	89	38	127	42	55
DTaP-HIB	11	1	12	7	4
DTaP-IPV-HIB	44	21	65	14	32
Td	213	3	216	125	75
Tdap	749	6	755	398	79
Tetanus	141	2	143	76	47
Hepatitis A (Hep A)	104	7	111	58	33
Hepatitis B (Hep B)	707	61	768	279	423
Hep A-Hep B	36	0	36	18	7
Hep B-HIB	8	0	8	5	3
HIB	44	3	47	19	20
HPV	418	15	433	133	171
Influenza	5,592	176	5,768	3,251	524
IPV	269	14	283	8	270
OPV	282	28	310	158	152
Measles	143	19	162	55	107
Meningococcal	90	2	92	45	9
MMR	984	61	1,045	406	585
MMR-Varicella	53	2	55	23	13
MR	15	0	15	6	9
Mumps	10	0	10	1	9
Pertussis	4	3	7	2	5
Pneumococcal Conjugate	216	17	233	66	57
Rotavirus	98	5	103	62	25
Rubella	190	4	194	71	123
Varicella	103	9	112	66	31
Nonqualified1	104	9	113	3	104
Unspecified2	5,426	9	5,435	9	5,401
Grand Total	**19,991**	**1,312**	**21,303**	**6,947**	**11,411**

[1] Nonqualified petitions are those filed for vaccines not covered under the VICP.
[2] Unspecified petitions are those submitted with insufficient information to make a determination.

Petitions Filed

Fiscal Year	Total
FY 1988	24
FY 1989	148
FY 1990	1,492
FY 1991	2,718
FY 1992	189
FY 1993	140
FY 1994	107
FY 1995	180
FY 1996	84
FY 1997	104
FY 1998	120
FY 1999	411
FY 2000	164
FY 2001	215
FY 2002	958
FY 2003	2,592
FY 2004	1,214
FY 2005	735
FY 2006	325
FY 2007	410
FY 2008	417
FY 2009	397
FY 2010	448
FY 2011	386
FY 2012	401
FY 2013	504
FY 2014	633
FY 2015	803
FY 2016	1,120
FY 2017	1,243
FY 2018	1,238
FY 2019	1,282
FY 2020	101
Total	**21,303**

Adjudications

Generally, petitions are not adjudicated in the same fiscal year as filed.
On average, it takes 2 to 3 years to adjudicate a petition after it is filed.

Fiscal Year	Compensable	Dismissed	Total
FY 1989	9	12	21
FY 1990	100	33	133
FY 1991	141	447	588
FY 1992	166	487	653
FY 1993	125	588	713
FY 1994	162	446	608
FY 1995	160	575	735
FY 1996	162	408	570
FY 1997	189	198	387
FY 1998	144	181	325
FY 1999	98	139	237
FY 2000	125	104	229
FY 2001	86	88	174
FY 2002	104	104	208
FY 2003	56	100	156
FY 2004	62	247	309
FY 2005	60	229	289
FY 2006	69	193	262
FY 2007	82	136	218
FY 2008	147	151	298
FY 2009	134	257	391
FY 2010	180	329	509
FY 2011	266	1,740	2,006
FY 2012	265	2,533	2,798
FY 2013	369	649	1,018
FY 2014	370	192	562
FY 2015	517	137	654
FY 2016	697	179	876
FY 2017	695	185	880
FY 2018	539	189	728
FY 2019	630	143	773
FY 2020	38	11	49
Total	**6,947**	**11,411**	**18,358**

Awards Paid

Fiscal Year	Number of Compensated Awards	Petitioners' Award Amount	Attorneys' Fees/Costs Payments	Number of Payments to Attorneys (Dismissed Cases)	Attorneys' Fees/Costs Payments (Dismissed Cases)	Number of Payments to Interim Attorneys'	Interim Attorneys' Fees/Costs Payments	Total Outlays
FY 1989	6	$1,317,654.78	$54,107.14	0	$0.00	0	$0.00	$1,371,761.92
FY 1990	88	$53,252,510.46	$1,379,005.79	4	$57,699.48	0	$0.00	$54,689,215.73
FY 1991	114	$95,980,493.16	$2,364,758.91	30	$496,809.21	0	$0.00	$98,842,061.28
FY 1992	130	$94,538,071.30	$3,001,927.97	118	$1,212,677.14	0	$0.00	$98,752,676.41
FY 1993	162	$119,693,267.87	$3,262,453.06	272	$2,447,273.05	0	$0.00	$125,402,993.98
FY 1994	158	$98,151,900.08	$3,571,179.67	335	$3,166,527.38	0	$0.00	$104,889,607.13
FY 1995	169	$104,085,265.72	$3,652,770.57	221	$2,276,136.32	0	$0.00	$110,014,172.61
FY 1996	163	$100,425,325.22	$3,096,231.96	216	$2,364,122.71	0	$0.00	$105,885,679.89
FY 1997	179	$113,620,171.68	$3,898,284.77	142	$1,879,418.14	0	$0.00	$119,397,874.59
FY 1998	165	$127,546,009.19	$4,002,278.55	121	$1,936,065.50	0	$0.00	$133,484,353.24
FY 1999	96	$95,917,680.51	$2,799,910.85	117	$2,306,957.40	0	$0.00	$101,024,548.76
FY 2000	136	$125,945,195.64	$4,112,369.02	80	$1,724,451.08	0	$0.00	$131,782,015.74
FY 2001	97	$105,878,632.57	$3,373,865.88	57	$2,066,224.67	0	$0.00	$111,318,723.12
FY 2002	80	$59,799,604.39	$2,653,598.89	50	$656,244.79	0	$0.00	$63,109,448.07
FY 2003	65	$82,816,240.07	$3,147,755.12	69	$1,545,654.87	0	$0.00	$87,509,650.06
FY 2004	57	$61,933,764.20	$3,079,328.55	69	$1,198,615.96	0	$0.00	$66,211,708.71
FY 2005	64	$55,065,797.01	$2,694,664.03	71	$1,790,587.29	0	$0.00	$59,551,048.33
FY 2006	68	$48,746,162.74	$2,441,199.02	54	$1,353,632.61	0	$0.00	$52,540,994.37
FY 2007	82	$91,449,433.89	$4,034,154.37	61	$1,692,020.25	0	$0.00	$97,175,608.51
FY 2008	141	$75,716,552.06	$5,191,770.83	74	$2,531,394.20	2	$117,265.31	$83,556,982.40
FY 2009	131	$74,142,490.58	$5,404,711.98	36	$1,557,139.53	28	$4,241,362.55	$85,345,704.64
FY 2010	173	$179,387,341.30	$5,961,744.40	59	$1,933,550.09	22	$1,978,803.88	$189,261,439.67
FY 2011	251	$216,319,428.47	$9,572,042.87	403	$5,589,417.19	28	$2,001,770.91	$233,482,659.44
FY 2012	249	$163,491,998.82	$9,241,427.33	1,020	$8,649,676.56	37	$5,420,257.99	$186,803,360.70
FY 2013	375	$254,666,326.70	$13,543,099.70	704	$7,012,615.42	50	$1,454,851.74	$276,676,893.56
FY 2014	365	$202,084,196.12	$12,161,422.64	508	$6,824,566.68	38	$2,493,460.73	$223,563,646.17
FY 2015	508	$204,137,880.22	$14,445,776.29	118	$3,546,785.14	50	$3,089,497.68	$225,219,939.33

Fiscal Year	Number of Compensated Awards	Petitioners' Award Amount	Attorneys' Fees/Costs Payments	Number of Payments to Attorneys (Dismissed Cases)	Attorneys' Fees/Costs Payments (Dismissed Cases)	Number of Payments to Interim Attorneys'	Interim Attorneys' Fees/Costs Payments	Total Outlays
FY 2016	689	$230,140,251.20	$16,225,881.12	99	$2,741,830.10	59	$3,502,709.91	$252,610,672.33
FY 2017	706	$252,245,932.78	$22,045,785.00	131	$4,441,724.32	52	$3,363,464.24	$282,096,906.34
FY 2018	522	$199,658,492.49	$16,658,440.14	111	$5,091,269.45	58	$5,220,096.78	$226,628,298.86
FY 2019	653	$196,217,707.64	$18,991,247.55	102	$4,791,157.52	65	$5,457,545.23	$225,457,657.94
FY 2020	70	$12,388,361.18	$1,961,499.60	11	$497,915.36	9	$824,152.52	$15,671,928.66
Total	**6,912**	**$3,896,760,140.04**	**$208,024,693.57**	**5,463**	**$85,380,159.41**	**498**	**$39,165,239.47**	**$4,229,330,232.49**

NOTE: Some previous fiscal year data has been updated as a result of the receipt and entry of data from documents issued by the Court and system updates which included petitioners' costs reimbursements in outlay totals,

"Compensated" are petitions that have been paid as a result of a settlement between parties or a decision made by the U.S. Court of Federal Claims (Court). The # of awards is the number of petitioner awards paid, including the attorneys' fees/costs payments, if made during a fiscal year. However, petitioners' awards and attorneys' fees/costs are not necessarily paid in the same fiscal year as when the petitions/petitions are determined compensable. "Dismissed" includes the # of payments to attorneys and the total amount of payments for attorneys' fees/costs per fiscal year. The VICP will pay attorneys' fees/costs related to the petition, whether or not the petition/petition is awarded compensation by the Court, if certain minimal requirements are met. "Total Outlays" are the total amount of funds expended for compensation and attorneys' fees/costs from the Vaccine Injury Compensation Trust Fund by fiscal year.

Since influenza vaccines (vaccines administered to large numbers of adults each year) were added to the VICP in 2005, many adult petitions related to that vaccine have been filed, thus changing the proportion of children to adults receiving compensation.

Vaccine Injury Table

Applies Only to Petitions for Compensation Filed under the National Vaccine Injury Compensation Program on or after March 21, 2017

(a) In accordance with section 312(b) of the National Childhood Vaccine Injury Act of 1986, title III of Public Law 99-660, 100 Stat. 3779 (42 U.S.C. 300aa-1 note) and section 2114(c) of the Public Health Service Act, as amended (PHS Act) (42 U.S.C. 300aa-14(c)), the following is a table of vaccines, the injuries, disabilities, illnesses, conditions, and deaths resulting from the administration of such vaccines, and the time period in which the first symptom or manifestation of onset or of the significant aggravation of such injuries, disabilities, illnesses, conditions, and deaths is to occur after vaccine administration for purposes of receiving compensation under the Program. Paragraph (b) of this section sets forth additional provisions that are not separately listed in this Table but that constitute part of it. Paragraph (c) of this section sets forth the qualifications and aids to interpretation for the terms used in the Table. Conditions and injuries that do not meet the terms of the qualifications and aids to interpretation are not within the Table. Paragraph (d) of this section sets forth a glossary of terms used in paragraph (c).

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
I. Vaccines containing tetanus toxoid (*e.g.,* DTaP, DTP, DT, Td, or TT)	A. Anaphylaxis B. Brachial Neuritis	≤4 hours. 2-28 days (not less than 2 days and not more than 28 days).
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
II. Vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen(s) (*e.g.,* DTP, DTaP, P, DTP-Hib)	A. Anaphylaxis	≤4 hours.
	B. Encephalopathy or encephalitis	≤72 hours.
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
III. Vaccines containing measles, mumps, and rubella virus or any of its components (*e.g.,* MMR, MM, MMRV)	A. Anaphylaxis B. Encephalopathy or encephalitis	≤4 hours. 5-15 days (not less than 5 days and not more than 15 days).
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	D. Vasovagal syncope	≤1 hour.

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
IV. Vaccines containing rubella virus (*e.g.,* MMR, MMRV)	A. Chronic arthritis	7-42 days (not less than 7 days and not more than 42 days).
V. Vaccines containing measles virus (*e.g.,* MMR, MM, MMRV)	A. Thrombocytopenic purpura	7-30 days (not less than 7 days and not more than 30 days).
	B. Vaccine-Strain Measles Viral Disease in an immunodeficient recipient	
	—Vaccine-strain virus identified	Not applicable.
	—If strain determination is not done or if laboratory testing is inconclusive	≤12 months.
VI. Vaccines containing polio live virus (OPV)	A. Paralytic Polio	
	—in a non-immunodeficient recipient	≤30 days.
	—in an immunodeficient recipient	≤6 months.
	—in a vaccine associated community case	Not applicable.
	B. Vaccine-Strain Polio Viral Infection	
	—in a non-immunodeficient recipient	≤30 days.
	—in an immunodeficient recipient	≤6 months.
	—in a vaccine associated community case	Not applicable.
VII. Vaccines containing polio inactivated virus (*e.g.,* IPV)	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
VIII. Hepatitis B vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	C. Vasovagal syncope	≤1 hour.

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
IX. Haemophilus influenzae type b (Hib) vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	B. Vasovagal syncope	≤1 hour.
X. Varicella vaccines	A. Anaphylaxis	≤4 hours.
	B. Disseminated varicella vaccine-strain viral disease	
	—Vaccine-strain virus identified	Not applicable.
	—If strain determination is not done or if laboratory testing is inconclusive	7-42 days (not less than 7 days and not more than 42 days).
	C. Varicella vaccine-strain viral reactivation	Not applicable.
	D. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	E. Vasovagal syncope	≤1 hour.
XI. Rotavirus vaccines	A. Intussusception	1-21 days (not less than 1 day and not more than 21 days).
XII. Pneumococcal conjugate vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	B. Vasovagal syncope	≤1 hour.
XIII. Hepatitis A vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	B. Vasovagal syncope	≤1 hour.
XIV. Seasonal influenza vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
	D. Guillain-Barré Syndrome	3-42 days (not less than 3 days and not more than 42 days).
XV. Meningococcal vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
XVI. Human papillomavirus (HPV) vaccines	A. Anaphylaxis	≤4 hours.

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
XVII. Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by the Secretary of a notice of coverage	A. Shoulder Injury Related to Vaccine Administration	≤48 hours.
	B. Vasovagal syncope	≤1hour.

(b) *Provisions that apply to all conditions listed.* (1) Any acute complication or sequela, including death, of the illness, disability, injury, or condition listed in paragraph (a) of this section (and defined in paragraphs (c) and (d) of this section) qualifies as a Table injury under paragraph (a) except when the definition in paragraph (c) requires exclusion.

(2) In determining whether or not an injury is a condition set forth in paragraph (a) of this section, the Court shall consider the entire medical record.

(3) An idiopathic condition that meets the definition of an illness, disability, injury, or condition set forth in paragraph (c) of this section shall be considered to be a condition set forth in paragraph (a) of this section.

(c) *Qualifications and aids to interpretation.* The following qualifications and aids to interpretation shall apply to, define and describe the scope of, and be read in conjunction with paragraphs (a), (b), and (d) of this section:

(1) *Anaphylaxis.* Anaphylaxis is an acute, severe, and potentially lethal systemic reaction that occurs as a single discrete event with simultaneous involvement of two or more organ systems. Most cases resolve without sequela. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse. Other significant clinical signs and symptoms may include the following: Cyanosis, hypotension, bradycardia, tachycardia, arrhythmia, edema of the pharynx and/or trachea and/or larynx with stridor and dyspnea. There are no specific pathological findings to confirm a diagnosis of anaphylaxis.

(2) *Encephalopathy.* A vaccine recipient shall be considered to have suffered an encephalopathy if an injury meeting the description below of an acute encephalopathy occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.

(i) *Acute encephalopathy.* (A) For children less than 18 months of age who present:

(*1*) Without a seizure, an acute encephalopathy is indicated by a significantly decreased level of consciousness that lasts at least 24 hours.

(*2*) Following a seizure, an acute encephalopathy is demonstrated by a significantly decreased level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state—from a seizure or a medication.

(B) For adults and children 18 months of age or older, an acute encephalopathy is one that persists at least 24 hours and is characterized by at least two of the following:

(*1*) A significant change in mental status that is not medication related (such as a confusional state, delirium, or psychosis);

(*2*) A significantly decreased level of consciousness which is independent of a seizure and cannot be attributed to the effects of medication; and

(*3*) A seizure associated with loss of consciousness.

(C) The following clinical features in themselves do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, poor feeding, persistent inconsolable crying, bulging fontanelle, or symptoms of dementia.

(D) Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy and in the absence of other evidence of an acute encephalopathy seizures shall not be viewed as the first symptom or manifestation of an acute encephalopathy.

(ii) *Exclusionary criteria for encephalopathy.* Regardless of whether or not the specific cause of the underlying condition, systemic disease, or acute event (including an infectious organism) is known, an encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by:

(A) An underlying condition or systemic disease shown to be unrelated to the vaccine (such as malignancy, structural lesion, psychiatric illness, dementia, genetic disorder, prenatal or perinatal central nervous system (CNS) injury); or

(B) An acute event shown to be unrelated to the vaccine such as a head trauma, stroke, transient ischemic attack, complicated migraine, drug use (illicit or prescribed) or an infectious disease.

(3) *Encephalitis.* A vaccine recipient shall be considered to have suffered encephalitis if an injury meeting the description below of acute encephalitis occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.

(i) *Acute encephalitis.* Encephalitis is indicated by evidence of neurologic dysfunction, as described in paragraph (c)(3)(i)(A) of this section, plus evidence of an inflammatory process in the brain, as described in paragraph (c)(3)(i)(B) of this section.

(A) Evidence of neurologic dysfunction consists of either:

(*1*) One of the following neurologic findings referable to the CNS: Focal cortical signs (such as aphasia, alexia, agraphia, cortical blindness); cranial nerve abnormalities; visual field defects; abnormal presence of primitive reflexes (such as Babinski's sign or sucking reflex); or cerebellar dysfunction (such as ataxia, dysmetria, or nystagmus); or

(*2*) An acute encephalopathy as set forth in paragraph (c)(2)(i) of this section.

(B) Evidence of an inflammatory process in the brain (central nervous system or CNS inflammation) must include cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells (WBC)/mm^3 in children >2 months of age and adults; >15 WBC/mm3 in children <2 months of age); or at least two of the following:

(*1*) Fever (temperature ≥ 100.4 degrees Fahrenheit);

(*2*) Electroencephalogram findings consistent with encephalitis, such as diffuse or multifocal nonspecific background slowing and periodic discharges; or

(*3*) Neuroimaging findings consistent with encephalitis, which include, but are not limited to brain/spine magnetic resonance imaging (MRI) displaying diffuse or multifocal areas of hyperintense signal on T2-weighted, diffusion-weighted image, or fluid-attenuation inversion recovery sequences.

(ii) *Exclusionary criteria for encephalitis.* Regardless of whether or not the specific cause of the underlying condition, systemic disease, or acute event (including an infectious organism) is known, encephalitis shall not be considered to be a condition set forth in the Table if it is shown that the encephalitis was caused by:

(A) An underlying malignancy that led to a paraneoplastic encephalitis;

(B) An infectious disease associated with encephalitis, including a bacterial, parasitic, fungal or viral illness (such as herpes viruses, adenovirus, enterovirus, West Nile Virus, or human immunodeficiency virus), which may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing; or

(C) Acute disseminated encephalomyelitis (ADEM). Although early ADEM may have laboratory and clinical characteristics similar to acute encephalitis, findings on MRI are distinct with ADEM displaying evidence of acute demyelination (scattered, focal, or multifocal areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; gray matter involvement may also be seen but is a minor component); or

(D) Other conditions or abnormalities that would explain the vaccine recipient's symptoms.

(4) *Intussusception.* (i) For purposes of paragraph (a) of this section, intussusception means the invagination of a segment of intestine into the next segment of intestine, resulting in bowel obstruction, diminished arterial blood supply, and blockage of the venous blood flow. This is characterized by a sudden onset of abdominal pain that may be manifested by anguished crying, irritability, vomiting, abdominal swelling, and/or passing of stools mixed with blood and mucus.

(ii) For purposes of paragraph (a) of this section, the following shall not be considered to be a Table intussusception:

(A) Onset that occurs with or after the third dose of a vaccine containing rotavirus;

(B) Onset within 14 days after an infectious disease associated with intussusception, including viral disease (such as those secondary to non-enteric or enteric adenovirus, or other enteric viruses such as Enterovirus), enteric bacteria (such as Campylobacter jejuni), or enteric parasites (such as Ascaris lumbricoides), which may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing;

(C) Onset in a person with a preexisting condition identified as the lead point for intussusception such as intestinal masses and cystic structures (such as polyps, tumors, Meckel's diverticulum, lymphoma, or duplication cysts);

(D) Onset in a person with abnormalities of the bowel, including congenital anatomic abnormalities, anatomic changes after abdominal surgery, and other anatomic bowel abnormalities caused by mucosal

hemorrhage, trauma, or abnormal intestinal blood vessels (such as Henoch Scholein purpura, hematoma, or hemangioma); or

(E) Onset in a person with underlying conditions or systemic diseases associated with intussusception (such as cystic fibrosis, celiac disease, or Kawasaki disease).

(5) *Chronic arthritis.* Chronic arthritis is defined as persistent joint swelling with at least two additional manifestations of warmth, tenderness, pain with movement, or limited range of motion, lasting for at least 6 months.

(i) Chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:

(A) Medical documentation recorded within 30 days after the onset of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and

(B) Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination; and

(C) Medical documentation of an antibody response to the rubella virus.

(ii) The following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/determatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's Syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders, and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's Syndrome, blood disorders, or arthralgia (joint pain), or joint stiffness without swelling.

(6) *Brachial neuritis.* This term is defined as dysfunction limited to the upper extremity nerve plexus (*i.e.,* its trunks, divisions, or cords). A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is typically followed in days or weeks by weakness in the affected upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature. Atrophy of the affected muscles may occur. The neuritis, or plexopathy, may be present on the same side or on the side opposite the injection. It is sometimes bilateral, affecting both upper extremities. A vaccine recipient shall be considered to have suffered brachial neuritis as a Table injury if such recipient manifests all of the following:

(i) Pain in the affected arm and shoulder is a presenting symptom and occurs within the specified time-frame;

(ii) Weakness;

(A) Clinical diagnosis in the absence of nerve conduction and electromyographic studies requires weakness in muscles supplied by more than one peripheral nerve.

(B) Nerve conduction studies (NCS) and electromyographic (EMG) studies localizing the injury to the brachial plexus are required before the diagnosis can be made if weakness is limited to muscles supplied by a single peripheral nerve.

(iii) Motor, sensory, and reflex findings on physical examination and the results of NCS and EMG studies, if performed, must be consistent in confirming that dysfunction is attributable to the brachial plexus; and

(iv) No other condition or abnormality is present that would explain the vaccine recipient's symptoms.

(7) *Thrombocytopenic purpura.* This term is defined by the presence of clinical manifestations, such as petechiae, significant bruising, or spontaneous bleeding, and by a serum platelet count less than 50,000/mm^3 with normal red and white blood cell indices. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with other causes such as hypersplenism, autoimmune disorders (including alloantibodies from previous transfusions) myelodysplasias, lymphoproliferative disorders, congenital thrombocytopenia or hemolytic uremic syndrome. Thrombocytopenic purpura does not include cases of immune (formerly called idiopathic) thrombocytopenic purpura that are mediated, for example, by viral or fungal infections, toxins or drugs. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with disseminated intravascular coagulation, as observed with bacterial and viral infections. Viral infections include, for example, those infections secondary to Epstein Barr virus, cytomegalovirus, hepatitis A and B, human immunodeficiency virus, adenovirus, and dengue virus. An antecedent viral infection may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing. However, if culture or serologic testing is performed, and the viral illness is attributed to the vaccine-strain measles virus, the presumption of causation will remain in effect. Bone marrow examination, if performed, must reveal a normal or an increased number of megakaryocytes in an otherwise normal marrow.

(8) *Vaccine-strain measles viral disease.* This term is defined as a measles illness that involves the skin and/or another organ (such as the brain or lungs). Measles virus must be isolated from the affected organ or histopathologic findings characteristic for the disease must be present. Measles viral strain determination may be performed by methods such as polymerase chain reaction test and vaccine-specific monoclonal antibody. If strain determination reveals wild-type measles virus or another, non-vaccine-strain virus, the disease shall not be considered to be a condition set forth in the Table. If strain determination is not done or if the strain cannot be identified, onset of illness in any organ must occur within 12 months after vaccination.

(9) *Vaccine-strain polio viral infection.* This term is defined as a disease caused by poliovirus that is isolated from the affected tissue and should be determined to be the vaccine-strain by oligonucleotide or polymerase chain reaction. Isolation of poliovirus from the stool is not sufficient to establish a tissue specific infection or disease caused by vaccine-strain poliovirus.

(10) *Shoulder injury related to vaccine administration (SIRVA).* SIRVA manifests as shoulder pain and limited range of motion occurring after the administration of a vaccine intended for intramuscular administration in the upper arm. These symptoms are thought to occur as a result of unintended injection of vaccine antigen or trauma from the needle into and around the underlying bursa of the shoulder resulting in an inflammatory reaction. SIRVA is caused by an injury to the musculoskeletal structures of the shoulder (*e.g.* tendons, ligaments, bursae, etc.). SIRVA is not a neurological injury and abnormalities on neurological examination or nerve conduction studies (NCS) and/or electromyographic (EMG) studies would not support SIRVA as a diagnosis (even if the condition causing the neurological abnormality is not known). A vaccine recipient shall be considered to have suffered SIRVA if such recipient manifests all of the following:

(i) No history of pain, inflammation or dysfunction of the affected shoulder prior to intramuscular vaccine administration that would explain the alleged signs, symptoms, examination findings, and/or diagnostic studies occurring after vaccine injection;

(ii) Pain occurs within the specified time-frame;

(iii) Pain and reduced range of motion are limited to the shoulder in which the intramuscular vaccine was administered; and

(iv) No other condition or abnormality is present that would explain the patient's symptoms (*e.g.* NCS/EMG or clinical evidence of radiculopathy, brachial neuritis, mononeuropathies, or any other neuropathy).

(11) *Disseminated varicella vaccine-strain viral disease.* Disseminated varicella vaccine-strain viral disease is defined as a varicella illness that involves the skin beyond the dermatome in which the vaccination was given and/or disease caused by vaccine-strain varicella in another organ. For organs other than the skin, the disease must be demonstrated in the involved organ and not just through mildly abnormal laboratory values. If there is involvement of an organ beyond the skin, and no virus was identified in that organ, the involvement of all organs must occur as part of the same, discrete illness. If strain determination reveals wild-type varicella virus or another, non-vaccine-strain virus, the viral disease shall not be considered to be a condition set forth in the Table. If strain determination is not done or if the strain cannot be identified, onset of illness in any organ must occur 7- 42 days after vaccination.

(12) *Varicella vaccine-strain viral reactivation disease.* Varicella vaccine-strain viral reactivation disease is defined as the presence of the rash of herpes zoster with or without concurrent disease in an organ other than the skin. Zoster, or shingles, is a painful, unilateral, pruritic rash appearing in one or more sensory dermatomes. For organs other than the skin, the disease must be demonstrated in the involved organ and not just through mildly abnormal laboratory values. There must be laboratory confirmation that the vaccine-strain of the varicella virus is present in the skin or in any other involved organ, for example by oligonucleotide or polymerase chain reaction. If strain determination reveals wild-type varicella virus or another, non-vaccine-strain virus, the viral disease shall not be considered to be a condition set forth in the Table.

(13) *Vasovagal syncope.* Vasovagal syncope (also sometimes called neurocardiogenic syncope) means loss of consciousness (fainting) and postural tone caused by a transient decrease in blood flow to the brain occurring after the administration of an injected vaccine. Vasovagal syncope is usually a benign condition but may result in falling and injury with significant sequela. Vasovagal syncope may be preceded by symptoms such as nausea, lightheadedness, diaphoresis, and/or pallor. Vasovagal syncope may be associated with transient seizure-like activity, but recovery of orientation and consciousness generally occurs simultaneously with vasovagal syncope. Loss of consciousness resulting from the following conditions will not be considered vasovagal syncope: organic heart disease, cardiac arrhythmias, transient ischemic attacks, hyperventilation, metabolic conditions, neurological conditions, and seizures. Episodes of recurrent syncope occurring after the applicable time period are not considered to be sequela of an episode of syncope meeting the Table requirements.

(14) *Immunodeficient recipient.* Immunodeficient recipient is defined as an individual with an identified defect in the immunological system which impairs the body's ability to fight infections. The identified defect may be due to an inherited disorder (such as severe combined immunodeficiency resulting in absent T lymphocytes), or an acquired disorder (such as acquired immunodeficiency syndrome resulting from decreased CD4 cell counts). The identified defect must be demonstrated in the medical records, either preceding or postdating vaccination.

(15) *Guillain-Barré Syndrome (GBS).* (i) GBS is an acute monophasic peripheral neuropathy that encompasses a spectrum of four clinicopathological subtypes described below. For each subtype of GBS, the interval between the first appearance of symptoms and the nadir of weakness is between 12 hours and 28 days. This is followed in all subtypes by a clinical plateau with stabilization at the nadir of symptoms, or subsequent improvement without significant relapse. Death may occur without a clinical plateau. Treatment related fluctuations in all subtypes of GBS can occur within 9 weeks of GBS symptom onset and recurrence of symptoms after this time-frame would not be consistent with GBS.

(ii) The most common subtype in North America and Europe, comprising more than 90 percent of cases, is acute inflammatory demyelinating polyneuropathy (AIDP), which has the pathologic and electrodiagnostic features of focal demyelination of motor and sensory peripheral nerves and nerve roots. Another subtype called acute motor axonal neuropathy (AMAN) is generally seen in other parts of the world and is predominated by axonal damage that primarily affects motor nerves. AMAN lacks features of demyelination. Another less common subtype of GBS includes acute motor and sensory neuropathy (AMSAN), which is an axonal form of GBS that is similar to AMAN, but also affects the sensory nerves and roots. AIDP, AMAN, and AMSAN are typically characterized by symmetric motor flaccid weakness, sensory abnormalities, and/or autonomic dysfunction caused by autoimmune damage to peripheral nerves and nerve roots. The diagnosis of AIDP, AMAN, and AMSAN requires:

(A) Bilateral flaccid limb weakness and decreased or absent deep tendon reflexes in weak limbs;

(B) A monophasic illness pattern;

(C) An interval between onset and nadir of weakness between 12 hours and 28 days;

(D) Subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse; however, death may occur without a clinical plateau); and,

(E) The absence of an identified more likely alternative diagnosis.

(iii) Fisher Syndrome (FS), also known as Miller Fisher Syndrome, is a subtype of GBS characterized by ataxia, areflexia, and ophthalmoplegia, and overlap between FS and AIDP may be seen with limb weakness. The diagnosis of FS requires:

(A) Bilateral ophthalmoparesis;

(B) Bilateral reduced or absent tendon reflexes;

(C) Ataxia;

(D) The absence of limb weakness (the presence of limb weakness suggests a diagnosis of AIDP, AMAN, or AMSAN);

(E) A monophasic illness pattern;

(F) An interval between onset and nadir of weakness between 12 hours and 28 days;

(G) Subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse; however, death may occur without a clinical plateau);

(H) No alteration in consciousness;

(I) No corticospinal track signs; and

(J) The absence of an identified more likely alternative diagnosis.

(iv) Evidence that is supportive, but not required, of a diagnosis of all subtypes of GBS includes electrophysiologic findings consistent with GBS or an elevation of cerebral spinal fluid (CSF) protein with

a total CSF white blood cell count below 50 cells per microliter. Both CSF and electrophysiologic studies are frequently normal in the first week of illness in otherwise typical cases of GBS.

(v) To qualify as any subtype of GBS, there must not be a more likely alternative diagnosis for the weakness.

(vi) Exclusionary criteria for the diagnosis of all subtypes of GBS include the ultimate diagnosis of any of the following conditions: chronic immune demyelinating polyradiculopathy (CIDP), carcinomatous meningitis, brain stem encephalitis (other than Bickerstaff brainstem encephalitis), myelitis, spinal cord infarct, spinal cord compression, anterior horn cell diseases such as polio or West Nile virus infection, subacute inflammatory demyelinating polyradiculoneuropathy, multiple sclerosis, cauda equina compression, metabolic conditions such as hypermagnesemia or hypophosphatemia, tick paralysis, heavy metal toxicity (such as arsenic, gold, or thallium), drug-induced neuropathy (such as vincristine, platinum compounds, or nitrofurantoin), porphyria, critical illness neuropathy, vasculitis, diphtheria, myasthenia gravis, organophosphate poisoning, botulism, critical illness myopathy, polymyositis, dermatomyositis, hypokalemia, or hyperkalemia. The above list is not exhaustive.

(d) *Glossary for purposes of paragraph (c) of this section*—(1) *Chronic encephalopathy.* (i) A chronic encephalopathy occurs when a change in mental or neurologic status, first manifested during the applicable Table time period as an acute encephalopathy or encephalitis, persists for at least 6 months from the first symptom or manifestation of onset or of significant aggravation of an acute encephalopathy or encephalitis.

(ii) Individuals who return to their baseline neurologic state, as confirmed by clinical findings, within less than 6 months from the first symptom or manifestation of onset or of significant aggravation of an acute encephalopathy or encephalitis shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequela of the acute encephalopathy or encephalitis.

(2) *Injected* refers to the intramuscular, intradermal, or subcutaneous needle administration of a vaccine.

(3) *Sequela* means a condition or event which was actually caused by a condition listed in the Vaccine Injury Table.

(4) *Significantly decreased level of consciousness* is indicated by the presence of one or more of the following clinical signs:

(i) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);

(ii) Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or

(iii) Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

(5) *Seizure* includes myoclonic, generalized tonic-clonic (grand mal), and simple and complex partial seizures, but not absence (petit mal), or pseudo seizures. Jerking movements or staring episodes alone are not necessarily an indication of seizure activity.

(e) *Coverage provisions.* (1) Except as provided in paragraph (e)(2), (3), (4), (5), (6), (7), or (8) of this section, this section applies only to petitions for compensation under the program filed with the United States Court of Federal Claims on or after February 21, 2017.

(2) Hepatitis B, Hib, and varicella vaccines (Items VIII, IX, and X of the Table) are included in the Table as of August 6, 1997.

(3) Rotavirus vaccines (Item XI of the Table) are included in the Table as of October 22, 1998.

(4) Pneumococcal conjugate vaccines (Item XII of the Table) are included in the Table as of December 18, 1999.

(5) Hepatitis A vaccines (Item XIII of the Table) are included on the Table as of December 1, 2004.

(6) Trivalent influenza vaccines (Included in item XIV of the Table) are included on the Table as of July 1, 2005. All other seasonal influenza vaccines (Item XIV of the Table) are included on the Table as of November 12, 2013.

(7) Meningococcal vaccines and human papillomavirus vaccines (Items XV and XVI of the Table) are included on the Table as of February 1, 2007.

(8) Other new vaccines (Item XVII of the Table) will be included in the Table as of the effective date of a tax enacted to provide funds for compensation paid with respect to such vaccines. An amendment to this section will be published in the FEDERAL REGISTER to announce the effective date of such a tax.

Vaccine Injury Compensation - Vaccines Covered in The Vaccine Injury Table

To bring a claim in the National Vaccine Injury Compensation Program, the injured party must have received one of the types of vaccines listed in the table below, such as the flu vaccine. The table covers almost every compensable vaccination. Certain less common or less available types of vaccinations are not included. For instance, the anthrax vaccination is not included in the Vaccine Injury Table largely because it is unavailable to the general public. It is only administered to certain members of the armed forces or research workers.

VACCINE TABLE INJURIES

As you will see in the Vaccine Injury Table below, there are two other columns to the right of the “Vaccine” column. The middle column is the “Illness, Disability, Injury or Condition Covered” column, followed by the third and final column "Time Period for First Symptom". The Vaccine Injury Compensation Program includes a provision that can be extremely beneficial to the injured parties. The provision states the court will 'presume that the vaccination caused the injury/condition,' if the injured party;

1. Received a vaccine listed in the "*Vaccine*" column, and

2. Developed an illness, disability, injury, or condition listed in the middle column, and

3. Within the time period listed in the far right column.

Presumption is a legal term that essentially means that if the injured party proves these three things, he or she does not need to prove anything else. The burden is on the defendant, the Department of Health and Human Services, to disprove the claim. It is extraordinarily difficult for HHS to do this. Therefore, table injury claims are generally resolved through settlement fairly quickly.

NON-TABLE INJURIES

That being said, it is not always necessary to have a "Table Injury." In fact, most vaccine injuries are not table injuries. If you receive one of the listed vaccines and suffer any injury, regardless of time period, you still may be entitled to compensation. When the injury is not a table injury, it simply means we must prove the injury was caused by the vaccination. For experienced vaccine injury lawyers like us, this is a regular occurrence. Click here for more information about how we prove your vaccine injury case.

LEARN MORE

- The Vaccine Injury Claim Process
- How We Can Help
- Types of Compensation
- The Vaccine Injury Table
- Notable Settlements

The Department of Health & Human Services (HHS) maintains a Vaccine Injury Table, which lists each vaccine, injuries known to be caused by that vaccine, and the time frames in which those injuries are known to occur. If your vaccine injury is found on the table, listed under the vaccine you received, and your injury occurred within the period of time listed, HHS typically will not challenge your claim for compensation from the Vaccine Injury Compensation Program (VICP). Even if your injury is listed, it can still help to have a VICP attorney work up your claim. The VICP program will pay your attorneys fees, whether or not your claim succeeds, as long as it is not frivolous.

Vaccine Injury Compensation Table

Vaccine	Illness or Injury (And Timeframe of Onset)
Tetanus (e.g. DTaP)	• Anaphylaxis (within 4 hours) • Brachial Neuritis (after 2-28 days) • Shoulder Injury (within 48 hours) • Vasovagal Syncope (within 1 hour)
Pertussis, or "whooping cough" (e.g. DTaP, DTP-Hib)	• Anaphylaxis (within 4 hours) • Encephalopathy or encephalitis (within 72 hours) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)

Measles, mumps, rubella (MMR)	• Anaphylaxis (within 4 hours) • Encephalopathy or encephalitis (after 5-15 days) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour) • Chronic arthritis (after 7-42 days)
Measles (MM)	• Thrombocytopenic purpura (after 7-30 days) • Vaccine-strain case of measles (no time limit, if lab testing confirms)
Live polio (OPV)	• Infection with paralytic polio (within 30 days for non-immunodeficient individuals, or within 6 months for immunodeficient individuals)
Inactivated polio (IPV)	• Anaphylaxis (within 4 hours) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)
Hepatitis B	• Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)
Haemophilus influenzae type b (Hib)	• Shoulder injury (within 48 hours) • Vasovagal syncope
Varicella	• Anaphylaxis (within 4 hours) • Vaccine-strain case of varicella (no time limit, if lab testing confirms or if it's a case of viral reactivation) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)

Rotavirus	• Intussusception (after 1-21 days)
Pneumococcacus (e.g. PCV13)	• Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)
Hepatitis A	• Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)
Seasonal influenza (flu vaccine)	• Anaphlaxis (within 4 hours) • Shoulder injury (48 hours) • Vasovagal syncope (within 1 hour) • Guillain-Barré Syndrome (after 3-42 days)
Meningococcus	• Anaphylaxis (within 4 hours) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)
Human papillomavirus (HPV)	• Anaphylaxis (within 4 hours) • Shoulder injury (within 48 hours) • Vasovagal syncope (within 1 hour)

Vaccine Injury Case Results in the Vaccine Injury Compensation Program

OUR VACCINE INJURY SETTLEMENTS TABLE IS UPDATED EVERY SIX MONTHS

Date	Vaccine	Injury Type	Amount	Case Link
2/23/17	Rotavirus	Intussusception	$250,000.00	14-1112V
8/26/16	Influenza	Parsonage-Turner Syndrome	$1,233,543.29	14-465V
3/2/16	Influenza	Guillain-Barre Syndrome	$271,544.00	14-481V
1/6/17	Influenza	Guillain-Barre Syndrome	$200,000.00	15-483V
6/7/16	Influenza	SIRVA	$182,194.04	15-1305V
6/1/16	Influenza	Guillain-Barre Syndrome	$175,000.00	14-987V
8/28/15	HPV / Influenza / Hepatitis A	Transverse Myelitis	$185,000.00	14-572V
5/31/18	Influenza	Guillain-Barre Syndrome	$120,000.00	17-1219V
12/6/17	Influenza	Guillain-Barre Syndrome	$68,394.18 annually	16-974V
8/5/16	TDaP / Influenza	Guillain-Barre Syndrome	$55,440.00 annually	15-052V
2/17/16	Influenza	SIRVA	$162,622.09	14-724V
3/1/18	Influenza	Guillain-Barre Syndrome / Death	$325,000.00	17-008V
12/29/17	Influenza	SIRVA	$175,000.00	17-157V
7/16/18	Influenza	Guillain-Barre Syndrome	$122,876.92	17-814V
12/6/17	Influenza	Guillain-Barre Syndrome	$270,000.00	16-1534V
10/16/17	Influenza	Guillain-Barre Syndrome	$165,000.00	16-993V
6/5/17	Influenza	Neuropathy	$125,000.00	15-1012V
4/24/18	TDaP	Encephalitis	$4,095,193.23	16-488V
2/25/19	Influenza	SIRVA	$185,000.00	17-12V
9/22/17	TDaP	SIRVA	$132,500.00	16-1480V
7/13/18	Influenza	SIRVA	$110,000.00	17-1067V
5/6/16	Influenza	Guillain-Barre Syndrome	$148,926.64	15-482V
6/21/18	TDaP	Bursitis	$143,100.00	17-880V
3/14/17	HPV	Transverse Myelitis	$142,899.54	14-1201V
1/11/17	Influenza	SIRVA	$141,357.13	15-1002V
4/25/17	Influenza	Guillain-Barre Syndrome	$140,000.00	15-1581V
8/2/16	TDaP	Transverse Myelitis	$140,000.00	15-221V
6/6/18	Influenza	SIRVA	$120,772.53	17-225V
5/2/16	Influenza	SIRVA	$135,000.00	15-682V

Vaccine Court Case Results by State

ALABAMA VACCINE INJURY CASE RESULTS

- **$106,160** for an Alabama woman who suffered various shoulder injuries after a flu shot. She was diagnosed with severe adhesive capsulitis (frozen shoulder) and treated with steroid medication and physical therapy. When the physical therapy only provided minimal relief, she was forced to undergo a shoulder manipulation under anesthesia, but continued to experience pain and limited range of motion months after the procedure.

CALIFORNIA VACCINE INJURY CASE RESULTS

- **$110,000** for a California woman who suffered adhesive capsulitis caused by improper administration of a flu shot. The client participated in physical therapy for several weeks. When she did not improve with therapy, her orthopedic surgeon recommended arthroscopic surgery.
- **$80,000** for a San Diego, California woman who suffered a shoulder injury caused by a flu shot.

COLORADO VACCINE INJURY CASE RESULTS

- **$115,000** for a Colorado woman who suffered a shoulder injury leading to surgery after a flu shot. Following a flu shot, the client developed severe pain and a bump at the site of the injection. She presented to the emergency room and was diagnosed with shoulder pain and cellulitis. When her symptoms failed to resolve on their own, she was later diagnosed with a severely torn rotator cuff by an MRI. She underwent an arthroscopic rotator cuff repair and post-op physical therapy, however, she continued to experience significant pain requiring subsequent cortisone injections.
- **$70,000** for a Colorado woman who suffered adhesive capsulitis from a tetanus shot.

DELAWARE VACCINE INJURY CASE RESULTS

- **$135,000** for a Delaware woman who suffered Guillain-Barre Syndrome after a flu shot at her local pharmacy. The client's initial symptoms, including numbness and tingling in her arms, started approximately three weeks post-vaccination. Her condition rapidly declined and eventually resulted in respiratory failure and quadriplegia. She was treated with IVIg. Fortunately, after an extended hospital stay and rehabilitation period, the client was able to regain her ability to walk.
- **$104,000** for a Delaware woman who suffered frozen shoulder, bursitis, and tendonitis from a flu shot she received at her workplace. The client participated in several weeks of physical therapy in order to strengthen her shoulder.

FLORIDA VACCINE INJURY CASE RESULTS

- **$80,000** for Florida man who suffered shoulder injury caused by a flu shot.

GEORGIA VACCINE INJURY CASE RESULTS

- **$120,000** for a Georgia woman who suffered subacromial bursitis and rotator cuff tendinitis following improper administration of a TDaP vaccination. The client received a cortisone injection and participated in a six week physical therapy course. When she did not improve, her orthopedic surgeon recommended a second six-week therapy course and another cortisone injection. Unfortunately all conservative treatment failed, leading to an arthroscopic surgery to repair the damage.

KENTUCKY VACCINE INJURY CASE RESULTS

- **$110,000** for a Kentucky man who developed a shoulder injury and had surgery after a flu shot. The client suffered a rotator cuff tear and bursitis following a flu shot. He was treated with physical therapy and a steroid injection but continued to experience pain and limited range of motion. He later underwent an arthroscopic rotator cuff repair and debridement.
- **$80,000** for a Kentucky man who developed various shoulder injuries after a flu shot.

LOUISIANA VACCINE INJURY CASE RESULTS

- **$111,390** for a Louisiana woman who suffered adhesive capsulitis (frozen shoulder) and tendinitis of the supraspinatus and subscapularis tendons as a result of improper administration of a flu shot. The client underwent an MRI which revealed a loose body within the subacromial space of the shoulder. The treating orthopedic surgeon recommended surgery to remove the loose body and repair the scar tissue and tearing.
- **$90,000** for a Louisiana woman who suffered a shoulder injury after a flu shot.

MISSISSIPPI VACCINE INJURY CASE RESULTS

- **$115,000** for a Mississippi woman who developed a shoulder injury and had surgery after a flu shot.

MISSOURI VACCINE INJURY CASE RESULTS

- **$80,000** for a Missouri woman who developed various shoulder injuries after a flu shot.

MONTANA VACCINE INJURY CASE RESULTS

- **$113,832** for a Montana woman that sustained shoulder injuries from a Tdap vaccine. The client developed severe pain and reduced range of motion immediately following a Tdap vaccine. She treated with a chiropractor and then an orthopedic surgeon and was diagnosed with bursitis secondary to a Tdap vaccine. She subsequently underwent left shoulder arthroscopy with thorough debridement of subacromial space and bursitis. Her compensation package included reimbursement for significant out of pocket medical expenses as she had to pay for the surgery out of pocket.

NEW HAMPSHIRE VACCINE INJURY CASE RESULTS

- **$120,000** for a New Hampshire woman who suffered a shoulder injury caused by a tetanus-diphtheria-pertussis (TDaP) vaccination. The client was diagnosed with subacromial bursitis. She participated in physical therapy for several weeks, and received a cortisone injection. However, conservative treatment failed and eventually it became necessary to undergo arthroscopic surgery.
- **$66,890** for a New Hampshire man who developed brachial neuritis after a TdaP vaccination.

NEW JERSEY VACCINE INJURY CASE RESULTS

- **$166,622** for a New Jersey woman who received a flu vaccine at work and suffered a shoulder injury that caused permanent symptoms.
- **$162,622** for a New Jersey woman who suffered a shoulder injury after a flu shot. The client suffered from edema, tendonitis and bursitis after a flu shot was injected too high on her shoulder. The injury caused her to lose her job as a nurse and take a lower paying job. Our vaccine injury lawyers recovered six figures for pain and suffering along with the projected difference in wages until she was 65 years old.
- **$160,465** for a New Jersey woman who suffered a shoulder injury after a flu shot.
- **$70,000** for a New Jersey man who suffered a shoulder injury caused by the tetanus shot.

NORTH CAROLINA VACCINE INJURY CASE RESULTS

- **$162,500** for a North Carolina man who suffered Guillain-Barre Syndrome after a flu shot. About three weeks after receiving the flu shot, the client began experiencing numbness and tingling in both feet. He was transferred to the hospital via ambulance and diagnosed with Guillian-Barre syndrome ("GBS"). He continued to experience neurological symptoms including weakness in his legs and feet for about a year after the vaccination. His treatment was complicated by chemotherapy for lung cancer.
- **$125,000** for a North Carolina man who suffered a torn rotator cuff requiring surgery after a meningococcal vaccination. The client was administered a meningitis vaccination while he was recovering from hip surgery in the hospital. By the time he was discharged, he couldn't move his arm. He was later diagnosed with a rotator cuff tear, subacromial impingement and bursitis by his orthopedic surgeon. He underwent a left shoulder arthroscopy with debridement, subacromial decompression and rotator cuff repair, which greatly improved his symptoms.

OKLAHOMA VACCINE INJURY CASE RESULTS

- **$140,000** for an Oklahoma child who suffered Transverse Myelitis following a Gardasil (HPV) vaccination. Approximately two weeks after receiving the second dose of the Gardasil vaccination, the client was admitted to the emergency room with severe weakness in his left leg. He was later diagnosed with transverse myelitis and treated with

steroid medication and physical therapy. Although his symptoms improved with treatment, the client continued to suffer from weakness in his left leg and difficulty walking.

OREGON VACCINE INJURY CASE RESULTS

- **$180,194** for an Oregon woman who suffered tendonitis, bursitis, and shoulder/deltoid edema following improper administration of a flu shot.
- **$80,000** for an Oregon man who suffered a shoulder injury after a flu shot.

PENNSYLVANIA VACCINE INJURY CASE RESULTS

- **$175,000** for a Pennsylvania woman who suffered a severe reaction after an HPV vaccine.
- **$150,203** for a Pennsylvania child who suffered an anaphylactic reaction to the chickenpox vaccination. The initial reaction occurred within only hours of the vaccination. The auto-immune response led to several food allergies. The client must now carry an Epipen at all times.
- **$135,000** for a Pennsylvania woman who suffered a shoulder injury after a flu shot. The client suffered from significant bursitis, tendonitis and adhesive capsulitis as the result of a flu shot. She was initially treated with physical therapy and a steroid injection. When conservative treatment failed to relieve her pain, she ultimately underwent a right shoulder arthroscopy, subacromial decompression and debridement.
- **$130,000** for a Pennsylvania woman who suffered a shoulder injury leading to surgery after a flu shot. The client received a flu shot at work and within 24 hours was unable to move her arm. She was diagnosed with bursitis, tendonitis and adhesive capsulitis and treated with physical therapy and a steroid injection. When the treatment failed to provide relief, she was forced to undergo an arthroscopic rotator cuff repair, but continued to experience pain and reduced range of motion.
- **$125,000** for a Pennsylvania man who developed the Miller Fisher variant of Guillain-Barre syndrome after a flu shot. Approximately three weeks after the flu shot, the client noticed left-sided facial paralysis and difficulty speaking. He was initially diagnosed with bell's palsy. He subsequently developed numbness and weakness in his lower extremities. He underwent a spinal tap which revealed elevated protein levels, prompting his treating neurologist to chang the diagnosis to the

Miller Fisher variant of GBS. Following treatment, his neurological symptoms mostly resolved but he continued to experience mild facial paralysis.

- **$109,000** for a Pennsylvania man who suffered a rotator cuff tear following a flu vaccination.
- **$108,000** for a Pennsylvania woman who suffered adhesive capsulitis and bursitis caused by improper administration of a flu shot. Her shoulder injuries would eventually require surgery followed by a lengthy physical therapy regimen.
- **$95,000** for a Pennsylvania woman who developed a shoulder injury after a flu shot. The client developed immediate pain, numbness and tingling following a flu shot. She was treated by both neurologists and orthopedic doctors with a variety of treatments including medications, injections and physical therapy. After more than a year of symptoms, she began to develop pain in her elbow as a result of overcompensating from the shoulder injury. She was subsequently diagnosed with Lateral Epicondylitis which her treating physicians opined was secondary to the shoulder injury.
- **$80,000** for Philadelphia, Pennsylvania woman who suffered adhesive capsulitis and tendinitis caused by flu shot.
- **$50,000** for a Pennsylvania man who developed various shoulder injuries after a flu shot.

RHODE ISLAND VACCINE INJURY CASE RESULTS

- **$140,000** for a Rhode Island woman who suffered Transverse Myelitis following a Tdap vaccine. About two months after the Tdap vaccination, the client began experiencing numbness and weakness in her feet. She was transported to the hospital and after multiple rounds of diagnostic testing, was diagnosed with transverse myelitis. She initially spent five weeks in the hospital. Following her discharge from the hospital, she spent weeks in outpatient physical therapy. Although she did not lose wages, the injury greatly affected her ability to perform her nursing job. The case was complicated by a two month onset, which is on the very fringe of acceptable onset in the court.

TENNESSEE VACCINE INJURY CASE RESULTS

- **$271,544** for a Tennessee man who suffered from chronic inflammatory demyelinating polyneuropathy (“CIDP”) after a flu vaccine.

- **$135,000** for a Tennessee woman who suffered a shoulder injury after improper administration of a flu shot at her local pharmacy. Following a shoulder MRI, the client was diagnosed with tendinitis, bursitis, and rotator cuff tear. The client received two cortisone injections to treat the pain. However, after conservative treatment failed she underwent arthroscopic surgery to repair the damage to her shoulder.

TEXAS VACCINE INJURY CASE RESULTS

- **$135,000** for a Texas woman who suffered a rotator cuff injury caused by a flu shot.
- **$135,000** for a Texas woman who suffered shoulder tendinitis, bursitis, impingement syndrome, and a rotator cuff tear caused by improper administration of a tetanus-diphtheria-pertussis (TDaP) vaccination. The shoulder injuries resulted in cortisone injections and a recommendation for arthroscopic surgery.
- **$50,000** for a Texas man who developed Guillain-Barre syndrome after a flu shot.

VIRGINIA VACCINE INJURY CASE RESULTS

- **$120,000** for a Virginia woman who suffered a rotator cuff tear requiring surgery caused by a flu shot.

WASHINGTON VACCINE INJURY CASE RESULTS

- **$95,000** for a Washington woman who suffered a shoulder injury after a flu shot.
- **$80,000** for a Washington man who suffered adhesive capsulitis after a flu shot.
- **$80,000** for a Washington woman who developed various shoulder injuries after a flu shot.

WISCONSIN VACCINE INJURY CASE RESULTS

- **$148,926.64** for a Wisconsin man who suffered from Guillain-Barre Syndrome (“GBS”) following a flu shot. About two weeks after the flu shot, the client was admitted to the hospital with extremity weakness and difficulty ambulating. Ove r the next three months, he underwent multiple rounds of intravenous immunoglobulin (“IVIG”) treatment and inpatient physical therapy. He ultimately made a good recovery with only mild ongoing lower extremity weakness.

- **$130,000** for a Wisconsin woman who suffered adhesive capsulitis (frozen shoulder) requiring surgery after a flu shot. The client suffered from significant bursitis, tendonitis, adhesive capsulitis and a fully torn rotator cuff as the result of a flu shot. She underwent more than 30 physical therapy sessions but her pain and range of motion issues failed to resolve. When conservative treatment failed to relieve her pain, she ultimately underwent a rotator cuff repair. Her settlement package included more than six months of wage loss.

HAVE YOU BEEN INJURED BY A VACCINE, DRUG OR MEDICAL DEVICE?
CONTACT US NOW. DO NOT DELAY.

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Maglio Christopher & Toale, P.A. | Complex Litigation Attorneys

GUILLAIN-BARRÉ SYNDROME TRIGGERED BY A VACCINE

A $3 Billion Dollar Federal Fund is Available for Vaccine Injury Compensation

Guillain-Barré Syndrome Triggered by Vaccine Reaction

Guillain-Barré Syndrome (GBS) is a disorder where a patient's immune system goes haywire and attacks the peripheral nervous system. The symptoms of Guillain-Barré Syndrome can begin anywhere from one day to several weeks after a vaccination but usually peak around one to two weeks after the shot is given. The chronic version of GBS is known as Chronic Inflammatory Demyelinating Polyneuropathy or CIDP.

What are the Symptoms of Guillain-Barré Syndrome (GBS)?

The first symptom of Guillain-Barré Syndrome is often weakness or tingling in the legs. Those sensations can spread to the arms and upper body until the victim becomes paralyzed. GBS can cause such severe muscle weakness that patients must be put on a ventilator to breathe. Some of the most common symptoms include:

- Pins and needles feeling in your extremities
- Weakness in your legs that spreads upwards
- Trouble walking or keeping your balance
- Difficulty chewing or swallowing
- Problems breathing

Vaccines That Can Trigger Guillain Barré Syndrome

Influenza Vaccine or Flu Shot

Tetanus Shot, Tdap, or DtaP

Hepatitis A or Hepatitis B Vaccines

Menactra (MCV4) Vaccine

Gardasil or HPV Vaccine

Other Common Vaccinations

The Influenza Vaccine (Flu Shot)

Your chances of getting Guillain Barré Syndrome after a flu shot are extremely low, but it does happen. Researchers who studied vaccine reaction rates found that "GBS is more strongly associated with vaccination for influenza" than for any other vaccine. The Journal of the American Medical Association cites Guillain Barré as the most frequent neurological condition reported after getting the flu shot. But the flu shot isn't the only vaccine that may lead to GBS.

Gardasil® (HPV) Vaccine

There is evidence that the Gardasil vaccine, also known as the HPV (human papillomavirus) vaccination, can trigger Guillain Barré Syndrome. This vaccine is commonly given to prevent cervical cancer. The Centers for Disease Control reports that "Guillain Barré has been reported after vaccination with Gardasil." Other studies show that 72% of patients who reported GBS symptoms after a Gardasil vaccine experienced those symptoms within 6 weeks after their shot.

What To Do if You Have GBS from a Vaccine Reaction?

Contact a lawyer who is experienced in representing patients in front of the United States Court of Federal Claims. Filing a vaccine injury claim is an extremely complex and litigious process.

There are **no legal costs** for an injured patient represented by Maglio Christopher & Toale, P.A. At the end of the case, our law firm asks the Court for reimbursement of the fees and costs incurred representing you.

This reimbursement is separate from any money you're awarded by the Court. You **never** have to share any portion of your money for damages with our law firm.

Click on this link to find out more about the legal process of vaccine injury compensation.

For more information, please fill out the online vaccine form at the bottom of this page or call our office at 855.703.5394 to speak directly with someone.

Review Our Guillain-Barré Case Results

Guillain-Barré Syndrome related vaccine cases are some of the most common that our Firm sees. Below is a listing of the more recent decisions of the United States Court of Federal Claims awarding compensation to our clients.

Client Compensation for Vaccine Injuries Related to Guillain-Barre Syndrome

Show 25 entries Search:

Date	Vaccine Name	Illness or Symptoms	Link to Court Decision	Amount Compensated
5/22/2018	Influenza	Guillain-Barre Syndrome, Myasthenia Grabis (MG), Death	Case 10-515V	$245,000
5/17/2018	Tetanus-Diptheria Acellular Pertussis (Tdap)	Guillain-Barre Syndrome	Case 16-15V	$130,000
2/5/2018	Influenza	Guillain-Barre Syndrome	Case 16-0574V	$115,000
2/5/2018	Influenza	Guillain-Barre Syndrome	Case 16-0574V	$115,000
1/2/2018	Tdap Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-752V	$235,000
11/13/2017	Tdap and Influenza Vaccines	Guillain-Barre Syndrome (GBS)	Case 16-1081V	$125,000
10/24/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 12-462V	$65,000
10/23/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-1476V	$328,638
10/19/2017	Flu Vaccine	Guillain-Barre Syndrome (GBS)	Case 15-22V	$683,309
9/27/2017	Influenza	Guillain_Barre Syndrome (GBS)	Case 16-1562V	$120,000
9/1/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-874V	$140,000
8/25/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-1679V	$180,720
8/23/2017	TDaP	Guillain-Barre Syndrome (GBS)	Case 12-124V	$850,000
8/11/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-132V	$125,000
8/8/2017	Flu Shot	Guillain-Barre Syndrome (GBS)	Case 16-564V	$355,000
8/7/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-1040V	$195,000

Date	Vaccine Name	Illness or Symptoms	Link to Court Decision	Amount Compensated
6/16/2017	Tetanus Diphtheria Acellular Pertussis (Tdap)	Guillain-Barre Syndrome	Case 16-902V	$325,000
6/16/2017	Tetanus Diphtheria Acellular Pertussis (Tdap)	Guillain-Barre Syndrome	Case 16-902V	$325,000
6/13/2017	Influenza	Guillain-Barre Syndrome	Case 16-153V	$193,000
6/13/2017	Influenza	Guillain-Barre Syndrome	Case 16-153V	$193,000
5/22/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-585V	$165,000
5/12/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 15-1481V	$20,000
5/11/2017	Influenza Vaccine	Guillain-Barre Syndrome (GBS)	Case 16-1389V	$150,000
5/10/2017	Tdap	Guillain-Barre Syndrome (GBS)	Case 16-74V	$150,000
5/9/2017	Flu Vaccine	Guillain-Barre Syndrome (GBS)	Case 15-1246V	$210,000

Showing 1 to 25 of 309 entries

Previous Next

Results depend upon a variety of factors unique to each case and do not guarantee or predict a similar result in any future case.

Types of Guillain-Barré Variations

A number of different Guillain-Barré Syndrome (GBS) variants have been identified. Some of the most common are listed below:

- Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
- Miller Fisher Syndrome (MFS)
- Acute Motor Axonal Neuropathy (AMAN)
- Acute Motor Sensory Axonal Neuropathy (AMSAN)
- Pharyngeal-Cervical-Brachial Variant
- Acute Panautonomic Neuropathy
- Bickerstaff's Brainstem Encephalitis (BBE)

Is It Possible To Completely Recover from GBS?

Complete recovery from Guillain-Barré Syndrome does occur, but often it is a long and painful road of therapy and treatment. Unfortunately, some GBS patients end up with severe disabilities that will last throughout their lives. In rare cases, patients can die from GBS.

Guillain-Barré Syndrome is considered an autoimmune disorder because the body's immune system attacks its own nervous system, damaging the coating around nerves.

Our Vaccine Attorneys Can Help

Maglio Christopher & Toale, P.A. currently represents hundreds of patients across the United States who are suffering from Guillain-Barre Syndrome triggered by a vaccine reaction.

Our law firm's vaccine attorneys obtain compensation for patients with vaccine injuries by filing a lawsuit in the United States Court of Federal Claims in Washington, D.C. The outcome of the lawsuit determines what kind of compensation a victim may receive.

Not all attorneys are able to practice law before the Federal Vaccine Court. That's why you should hire an attorney with extensive experience in this area of law. These are not simple personal injury cases. They are medically and scientifically complex.

VAERS Home
About VAERS
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Report an Adverse Event
VAERS Data +
Resources +
Submit Follow-Up Information
Frequently Asked Questions
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About VAERS

Background and Public Health Importance

Established in 1990, the Vaccine Adverse Event Reporting System (VAERS) is a national early warning system to detect possible safety problems in U.S.-licensed vaccines. VAERS is co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). VAERS accepts and analyzes reports of adverse events (possible side effects) after a person has received a vaccination. Anyone can report an adverse event to VAERS. Healthcare professionals are required to report certain adverse events and vaccine manufacturers are required to report all adverse events that come to their attention.

VAERS is a passive reporting system, meaning it relies on individuals to send in reports of their experiences to CDC and FDA. VAERS is not designed to determine if a vaccine caused a health problem, but is especially useful for detecting unusual or unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine. This way, VAERS can provide CDC and FDA with valuable information that additional work and evaluation is necessary to further assess a possible safety concern.

Objectives of VAERS

The primary objectives of VAERS are to:

- Detect new, unusual, or rare vaccine adverse events;
- Monitor increases in known adverse events;
- Identify potential patient risk factors for particular types of adverse events;
- Assess the safety of newly licensed vaccines;
- Determine and address possible reporting clusters (*e.g., suspected localized [temporally or geographically] or product-/batch-/lot-specific adverse event reporting*);
- Recognize persistent safe-use problems and administration errors;
- Provide a national safety monitoring system that extends to the entire general population for response to public health emergencies, such as a large-scale pandemic influenza vaccination program.

Grant Final Report

Grant ID: R18 HS 017045

Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)

Inclusive dates: 12/01/07 - 09/30/10

Principal Investigator:
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Submitted to:
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U.S. Department of Health and Human Services
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Abstract

Purpose: To develop and disseminate HIT evidence and evidence-based tools to improve healthcare decision making through the use of integrated data and knowledge management.

Scope: To create a generalizable system to facilitate detection and clinician reporting of vaccine adverse events, in order to improve the safety of national vaccination programs.

Methods: Electronic medical records available from all ambulatory care encounters in a large multi-specialty practice were used. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions were evaluated for values suggestive of an adverse event.

Results: Restructuring at CDC and consequent delays in terms of decision making have made it challenging despite best efforts to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial and comparison of ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. However, Preliminary data were collected and analyzed and this initiative has been presented at a number of national symposia.

Key Words: electronic health records, vaccinations, adverse event reporting

Final Report

Purpose

This research project was funded to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS), via the following aims:

Aim 1. Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration.

Aim 2. Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS).

Aim 3. Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.

Aim 4. Distribute documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems.

Scope

Public and professional confidence in vaccination depends on reliable postmarketing surveillance systems to ensure that rare and unexpected adverse effects are rapidly identified. The goal of this project is to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS). This project is serving as an extension of the Electronic Support for Public Health (ESP) project, an automated system using electronic health record (EHR) data to detect and securely report cases of certain diseases to a local public health authority. ESP provides a ready-made platform for automatically converting clinical, laboratory, prescription, and demographic data from almost any EHR system into database tables on a completely independent server, physically located and secured by the same logical and physical security as the EHR data itself. The ESP:VAERS project developed criteria and algorithms to identify important adverse events related to vaccinations in ambulatory care EHR data, and made attempts at formatting and securely sending electronic VAERS reports directly to the Centers for Disease Control and Prevention (CDC).

Patient data were available from Epic System's Certification Commission for Health Information Technology-certified EpicCare system at all ambulatory care encounters within Atrius Health, a large multispecialty group practice with over 35 facilities. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions are evaluated for values

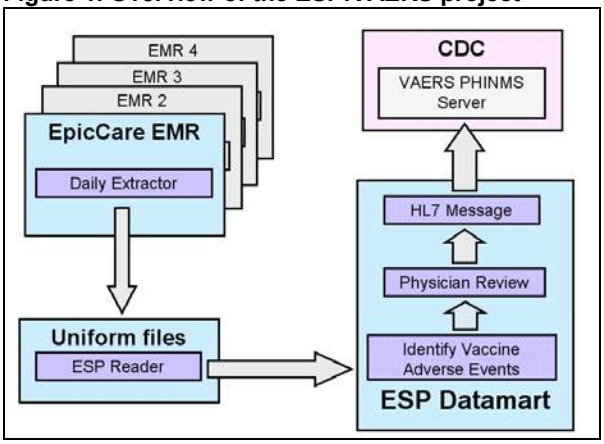
suggestive of an adverse vaccine event. When a possible adverse event was detected, it was recorded, and the appropriate clinician was to be notified electronically.

Clinicians in-basket messaging was designed to provide a preview a pre-populated report with information from the EHR about the patient, including vaccine type, lot number, and possible adverse effect, to inform their clinical judgment regarding whether they wish to send a report to VAERS. Clinicians would then have the option of adding free-text comments to pre-populated VAERS reports or to document their decision not to send a report. The CDC's Public Health Information Network Messaging System (PHIN-MS) software was installed within the facilities so that the approved reports could be securely transferred to VAERS as electronic messages in an interoperable health data exchange format using Health Level 7 (HL7).

Methods

The goal of Aim 1: *Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration*, and Aim 2: *Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS)*, was to construct the below flow of data in order to support the first two Aims:

Figure 1. Overview of the ESP:VAERS project



Existing and functioning ESP components are shown on the left, and Aims 1 and 2 on the right. ESP:VAERS flags every vaccinated patient, and prospectively accumulate that patient's diagnostic codes, laboratory tests, allergy lists, vital signs, and medication prescriptions. A main component of Aim 1 was to *Develop AE criteria to assess these parameters for new or abnormal values that might be suggestive of an adverse effect.* A reporting protocol & corresponding algorithms were developed to detect potential adverse event cases using diagnostic codes, and methods were tested to identify prescriptions or abnormal laboratory values that might be suggestive of an adverse effect. These algorithms were designed to seek both expected and unexpected adverse effects.

This reporting protocol was approved by both internal & external partners. We initially prepared a draft document describing the elements, algorithms, interval of interest after vaccination, and actions for broad classes of post-vaccination events, including those to be reported immediately without delay (such as acute anaphylactic reaction following vaccination), those never to be reported (such as routine check-ups following vaccination) and those to be reported at the discretion and with additional information from the attending physician through a feedback mechanism. The draft was then widely circulated as an initial / working draft for comment by relevant staff in the CDC and among our clinical colleagues at Atrius. In addition to review by the internal CDC Brighton Collaboration liaison, this protocol has also received review & comment via the CDC's Clinical Immunization Safety Assessment (CISA) Network.

The goal of Aim 2 was the *Development of HL7 messages code for ESP:VAERS to ensure secure transmission to CDC via PHIN-MS*. The HL7 specification describing the elements for an electronic message to be submitted to Constella, the consultants engaged by CDC for this project was implemented. Synthetic and real test data was been generated and transmitted between Harvard and Constella. However, real data transmissions of non-physician approved reports to the CDC was unable to commence, as by the end of this project, the CDC had yet to respond to multiple requests to partner for this activity.

The goal of Aim 3 was to *Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.*

We had initially planned to evaluate the system by comparing adverse event findings to those in the Vaccine Safety Datalink project—a collaborative effort between CDC's Immunization Safety Office and eight large managed care organizations. Through a randomized trial, we would also test the hypothesis that the combination of secure, computer-assisted, clinician-approved, adverse event detection, and automated electronic reporting will substantially increase the number, completeness, validity, and timeliness of physician-approved case reports to VAERS compared to the existing spontaneous reporting system; however, due to restructuring at CDC and consequent delays in terms of decision making, it became impossible to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial, and compare ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. Therefore, the components under this particular Aim were not achieved.

Aim 4 *Distribution of documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems* has been successfully completed. Functioning source code is available to share under an approved open source license. ESP:VAERS source code is available as part of the ESP source code distribution. It is licensed under the LGPL, an open source license compatible with commercial use. We have added the ESP:VAERS code, HL7 and other specifications and documentation to the existing ESP web documentation and distribution resource center http://esphealth.org, specifically, the Subversion repository available at:
http://esphealth.org/trac/ESP/wiki/ESPVAERS.

Results

Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month. These data were presented at the 2009 AMIA conference.

In addition, ESP:VAERS investigators participated on a panel to explore the perspective of clinicians, electronic health record (EHR) vendors, the pharmaceutical industry, and the FDA towards systems that use proactive, automated adverse event reporting.

Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health. New surveillance methods for drug and vaccine adverse effects are needed. Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting: reporting is not part of clinicians' usual workflow, takes time, and is duplicative. Proactive, spontaneous, automated adverse event reporting imbedded within EHRs and other information systems has the potential to speed the identification of problems with new drugs and more careful quantification of the risks of older drugs.

Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.

Inclusion of AHRQ Priority Populations

The focus of our project was the Atrius Health (formerly HealthOne) provider & patient community. This community serves several AHRQ inclusion populations, specifically low-income and minority populations in primarily urban settings.

Atruis currently employs approximately 700 physicians to serve 500,000 patients at more than 18 office sites spread throughout the greater Metropolitan Boston area. The majority of Atruis physicians are primary care internal medicine physicians or pediatricians but the network also includes physicians from every major specialty.

The entire adult and pediatric population served by Atruis was included in our adverse event surveillance system (ESP:VAERS). Atruis serves a full spectrum of patients that reflects the broad diversity of Eastern Massachusetts. A recent analysis suggests that the population served by Atruis is 56% female, 16.6% African American, 4% Hispanic. The prevalence of type 2 diabetes in the adult population is 5.7%. About a quarter of the Atruis population is under age 18.

List of Publications and Products

ESP:VAERS [source code available as part of the ESP source code distribution]. Licensed under the GNU Lesser General Public License (LGPL), an open source license compatible with commercial use. Freely available under an approved open source license at: http://esphealth.org.

Lazarus, R, Klompas M, Hou X, Campion FX, Dunn J, Platt R. Automated Electronic Detection & Reporting of Adverse Events Following Vaccination: ESP:VAERS. The CDC Vaccine Safety Datalink (VSD) Annual Meeting. Atlanta, GA; April, 2008.

Lazarus R, Klompas M Automated vaccine adverse event detection and reporting from electronic medical records. CDC Public Health Informatics Network (PHIN) Conference August 27, 2008.

Klompas M, Lazarus R ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 17th.

Lazarus R, Klompas M, Kruskal B, Platt R Temporal patterns of fever following immunization in ambulatory care data identified by ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Linder J, Klompas M, Cass B, et al. Spontaneous Electronic Adverse Event Reporting: Perspectives from Clinicians, EHR Vendors, Biopharma, and the FDA. Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

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- Guide to immunize.org -

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PEDIARIX safely and effectively. See full prescribing information for PEDIARIX.

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine]
Suspension for Intramuscular Injection
Initial U.S. Approval: 2002

---------- INDICATIONS AND USAGE----------
PEDIARIX is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------
Three doses (0.5-mL each) by intramuscular injection at 2, 4, and 6 months of age. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Single-dose prefilled syringes containing a 0.5-mL suspension for injection. (3)

---------- CONTRAINDICATIONS ----------
- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or poliovirus-containing vaccine, or to any component of PEDIARIX. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussis-containing vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

---------- WARNINGS AND PRECAUTIONS----------
- In clinical trials, PEDIARIX was associated with higher rates of fever, relative to separately administered vaccines. (5.1)
- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX should be based on potential benefits and risks. (5.2)
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.3)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.4)
- If specified adverse events (i.e., temperature ≥105°F, collapse or shock-like state, or inconsolable crying lasting ≥3 hours, within 48 hours after vaccination; seizures within 3 days after vaccination) have occurred following a pertussis-containing vaccine, the decision to give PEDIARIX should be based on potential benefits and risks. (5.5)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX. (5.6)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.7)

---------- ADVERSE REACTIONS ----------
Common solicited adverse events following any dose (≥25%) included local injection site reactions (pain, redness, and swelling), fever (≥100.4°F), drowsiness, irritability/fussiness, and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- DRUG INTERACTIONS----------
Do not mix PEDIARIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEDIARIX® is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle and administer intramuscularly.

The preferred administration site is the anterolateral aspect of the thigh for children younger than 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular injection. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Recommended Dose and Schedule

Immunization with PEDIARIX consists of 3 doses of 0.5 mL each, by intramuscular injection, at 2, 4, and 6 months of age (at intervals of 6 to 8 weeks, preferably 8 weeks). The first dose may be given as early as 6 weeks of age. Three doses of PEDIARIX constitute a primary immunization course for diphtheria, tetanus, pertussis, and poliomyelitis and the complete vaccination course for hepatitis B.

2.3 Modified Schedules in Previously Vaccinated Children

Children Previously Vaccinated with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP)

PEDIARIX may be used to complete the first 3 doses of the DTaP series in children who have received 1 or 2 doses of INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), manufactured by GlaxoSmithKline, identical to the DTaP component of PEDIARIX *[see Description (11)]* and are also scheduled to receive the other vaccine

components of PEDIARIX. Data are not available on the safety and effectiveness of using PEDIARIX following one or more doses of a DTaP vaccine from a different manufacturer.

Children Previously Vaccinated with Hepatitis B Vaccine

PEDIARIX may be used to complete the hepatitis B vaccination series following 1 or 2 doses of another hepatitis B vaccine (monovalent or as part of a combination vaccine), including vaccines from other manufacturers, in children born of HBsAg-negative mothers who are also scheduled to receive the other vaccine components of PEDIARIX.

A 3-dose series of PEDIARIX may be administered to infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth. However, data are limited regarding the safety of PEDIARIX in such infants *[see Adverse Reactions (6.1)]*. There are no data to support the use of a 3-dose series of PEDIARIX in infants who have previously received more than one dose of hepatitis B vaccine.

Children Previously Vaccinated with Inactivated Poliovirus Vaccine (IPV)

PEDIARIX may be used to complete the first 3 doses of the IPV series in children who have received 1 or 2 doses of IPV from a different manufacturer and are also scheduled to receive the other vaccine components of PEDIARIX.

2.4 Booster Immunization following PEDIARIX

Children who have received a 3-dose series with PEDIARIX should complete the DTaP and IPV series according to the recommended schedule.[1] Because the pertussis antigens contained in INFANRIX and KINRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine), manufactured by GlaxoSmithKline, are the same as those in PEDIARIX, these children should receive INFANRIX as their fourth dose of DTaP and either INFANRIX or KINRIX as their fifth dose of DTaP, according to the respective prescribing information for these vaccines. KINRIX or another manufacturer's IPV may be used to complete the 4-dose IPV series according to the respective prescribing information.

3 DOSAGE FORMS AND STRENGTHS

PEDIARIX is a suspension for injection available in 0.5-mL single-dose prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis antigen-, hepatitis B-, or poliovirus-containing vaccine or any component of this vaccine, including yeast, neomycin, and polymyxin B, is a contraindication to administration of PEDIARIX *[see Description (11)]*.

4.2 Encephalopathy

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX. PEDIARIX should not be administered to individuals with such conditions until the neurologic status is clarified and stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Fever

In clinical trials, administration of PEDIARIX in infants was associated with higher rates of fever, relative to separately administered vaccines *[see Adverse Reactions (6.1)]*.

5.2 Guillain-Barré Syndrome

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.4 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.5 Adverse Events following Prior Pertussis Vaccination

If any of the following events occur in temporal relation to receipt of a vaccine containing a pertussis component, the decision to give any pertussis-containing vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:

- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

5.6 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a vaccine containing a pertussis component, including PEDIARIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

5.8 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice.

A total of 23,849 doses of PEDIARIX have been administered to 8,088 infants who received one or more doses as part of the 3-dose series during 14 clinical studies. Common adverse events that occurred in ≥25% of subjects following any dose of PEDIARIX included local injection site reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of appetite. In comparative studies (including the German and U.S. studies described below), administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines *[see Warnings and Precautions (5.1)]*. The prevalence of fever was highest on the day of vaccination and the day following vaccination. More than 96% of episodes of fever resolved within the 4-day period following vaccination (i.e., the period including the day of vaccination and the next 3 days).

In the largest of the 14 studies, conducted in Germany, safety data were available for 4,666 infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4 *Haemophilus influenzae* type b (Hib) conjugate vaccines (GlaxoSmithKline [licensed in the U.S. only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in the U.S.], Sanofi Pasteur SA [U.S.-licensed], or Merck & Co, Inc. [U.S.-licensed]) at 3, 4, and 5 months of

age and for 768 infants in the control group that received separate U.S.-licensed vaccines (INFANRIX, Hib conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus vaccine [OPV] [Wyeth Pharmaceuticals, Inc.; no longer licensed in the U.S.]). In this study, information on adverse events that occurred within 30 days following vaccination was collected. More than 95% of study participants were white.

In a U.S. study, the safety of PEDIARIX administered to 673 infants was compared with the safety of separately administered INFANRIX, ENGERIX-B® [Hepatitis B Vaccine (Recombinant)], and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse events were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days). Telephone follow-up was conducted 1 month and 6 months after the third vaccination to inquire about serious adverse events. At the 6-month follow-up, information also was collected on new onset of chronic illnesses. A total of 638 subjects who received PEDIARIX and 313 subjects who received INFANRIX, ENGERIX-B, and IPV completed the 6-month follow-up. Among subjects in both study groups combined, 69% were white, 18% were Hispanic, 7% were black, 3% were Oriental, and 3% were of other racial/ethnic groups.

Solicited Adverse Events

Data on solicited local reactions and general adverse events from the U.S. safety study are presented in Table 1. This study was powered to evaluate fever >101.3°F following Dose 1. The rate of fever ≥100.4°F following each dose was significantly higher in the group that received PEDIARIX compared with separately administered vaccines. Other statistically significant differences between groups in rates of fever, as well as other solicited adverse events, are noted in Table 1. Medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought in the group who received PEDIARIX for 8 infants after the first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third dose (0.8%) (Table 1). Following Dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 1). Among infants who had a medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX and 1 of 2 who received separately administered vaccines, had one or more diagnostic studies performed to evaluate the cause of fever.

Table 1. Percentage of Infants with Solicited Local Reactions or General Adverse Events within 4 Days of Vaccination[a] at 2, 4, and 6 Months of Age with PEDIARIX Administered Concomitantly with Hib Conjugate Vaccine and 7-Valent Pneumococcal Conjugate Vaccine (PCV7) or with Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Hib Conjugate Vaccine, and PCV7 (Modified Intent-to-Treat Cohort)

	PEDIARIX, Hib Vaccine, & PCV7			INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7		
	Dose 1	**Dose 2**	**Dose 3**	**Dose 1**	**Dose 2**	**Dose 3**
Local[b]						
N	**671**	**653**	**648**	**335**	**323**	**315**
Pain, any	36.1	36.1	31.2	31.9	30.0	29.8
Pain, Grade 2 or 3	11.5	10.9	10.6	9.0	8.7	8.9
Pain, Grade 3	2.4	2.5	1.7	2.7	1.5	1.3
Redness, any	24.9[c]	37.2	40.1	18.2	32.8	39.0
Redness, >5 mm	6.0[c]	9.6[c]	12.7[c]	1.8	5.9	7.3
Redness, >20 mm	0.9	1.2[c]	2.8	0.3	0.0	1.9
Swelling, any	17.3[c]	26.5[c]	28.7	9.6	20.4	24.8
Swelling, >5 mm	5.8[c]	9.6[c]	9.3[c]	1.8	5.0	4.1
Swelling, >20 mm	1.9	2.5[c]	3.1	0.6	0.0	1.3
General						
N	**667**	**644**	**645**	**333**	**321**	**311**
Fever[d], ≥100.4°F	27.9[c]	38.8[c]	33.5[c]	19.8	30.2	23.8
Fever[d], >101.3°F	7.0	14.1[c]	8.8	4.5	9.7	5.8
Fever[d], >102.2°F	2.2[c]	3.6	3.4	0.3	3.1	2.3
Fever[d], >103.1°F	0.4	1.4	1.1	0.0	0.3	0.3
Fever[d], M.A.	1.2[c]	0.2	0.8	0.0	0.6	0.0
N	**671**	**653**	**648**	**335**	**323**	**315**
Drowsiness, any	57.2	51.6	40.9	54.0	48.3	38.4
Drowsiness, Grade 2 or 3	15.8	13.8	11.4	17.6	12.4	11.1
Drowsiness, Grade 3	2.5	1.2	0.9	3.6	0.6	1.9
Irritability/Fussiness, any	60.5	64.9	61.1	61.5	61.6	56.5
Irritability/Fussiness, Grade 2 or 3	19.8	27.9[c]	25.2[c]	19.4	21.1	19.4
Irritability/Fussiness, Grade 3	3.4	4.4	3.5	3.9	3.4	3.2
Loss of appetite, any	30.4	30.6	26.2	27.8	26.6	23.8
Loss of appetite, Grade 2 or 3	6.6	7.8[c]	5.9	5.1	3.4	5.4
Loss of appetite, Grade 3	0.7	0.3	0.2	0.6	0.3	0.0

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were available.

N = Number of infants for whom at least one symptom sheet was completed; for fever, numbers exclude missing temperature recordings or tympanic measurements.

M.A. = Medically attended (a visit to or from medical personnel).
Grade 2 defined as sufficiently discomforting to interfere with daily activities.
Grade 3 defined as preventing normal daily activities.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] Local reactions at the injection site for PEDIARIX or INFANRIX.

[c] Rate significantly higher in the group that received PEDIARIX compared with separately administered vaccines (*P* value <0.05 [2-sided Fisher Exact test] or the 95% CI on the difference between groups [Separate minus PEDIARIX] does not include 0).

[d] Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive equivalent rectal temperature.

Serious Adverse Events

Within 30 days following any dose of vaccine in the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 7 serious adverse events were reported in 7 subjects (1% [7/673]) who received PEDIARIX (1 case each of pyrexia, gastroenteritis, and culture-negative clinical sepsis and 4 cases of bronchiolitis) and 5 serious adverse events were reported in 4 subjects (1% [4/335]) who received INFANRIX, ENGERIX-B, and IPV (uteropelvic junction obstruction and testicular atrophy in one subject and 3 cases of bronchiolitis).

Deaths

In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1 death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of Sudden Infant Death Syndrome (SIDS) and one case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of SIDS among all recipients of PEDIARIX across the 14 trials was 0.25/1,000. The rate of SIDS observed for recipients of PEDIARIX in the German safety study was 0.2/1,000 infants (reported rate of SIDS in Germany in the latter part of the 1990s was 0.7/1,000 newborns). The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.

Onset of Chronic Illnesses

In the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 21 subjects (3%) who received PEDIARIX and 14 subjects (4%) who received INFANRIX, ENGERIX-B, and IPV reported new onset of a chronic illness during the period from 1 to 6 months following the last dose of study vaccines. Among the chronic illnesses reported in the subjects who received PEDIARIX, there were 4 cases of asthma and 1 case each of diabetes mellitus and chronic neutropenia. There were 4 cases of asthma in subjects who received INFANRIX, ENGERIX-B, and IPV.

Seizures

In the German safety study over the entire study period, 6 subjects in the group that received PEDIARIX (N = 4,666) reported seizures. Two of these subjects had a febrile seizure, 1 of whom also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with infantile spasms. Two subjects reported seizures within 7 days following vaccination (1 subject had both febrile and afebrile seizures, and 1 subject had afebrile seizures), corresponding to a rate of 0.22 seizures per 1,000 doses (febrile seizures 0.07 per 1,000 doses, afebrile seizures 0.14 per 1,000 doses). No subject who received concomitant INFANRIX, Hib vaccine, and OPV (N = 768) reported seizures. In a separate German study that evaluated the safety of INFANRIX in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000 doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).

Over the entire study period in the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 4 subjects in the group that received PEDIARIX (N = 673) reported seizures. Three of these subjects had a febrile seizure and 1 had an afebrile seizure. Over the entire study period, 2 subjects in the group that received INFANRIX, ENGERIX-B, and IPV (N = 335) reported febrile seizures. There were no afebrile seizures in this group. No subject in either study group had seizures within 7 days following vaccination.

Other Neurological Events of Interest

No cases of hypotonic-hyporesponsiveness or encephalopathy were reported in either the German or U.S. safety studies.

Safety of PEDIARIX after a Previous Dose of Hepatitis B Vaccine

Limited data are available on the safety of administering PEDIARIX after a previous dose of hepatitis B vaccine. In 2 separate studies, 160 Moldovan infants and 96 U.S. infants, respectively, received 3 doses of PEDIARIX following 1 previous dose of hepatitis B vaccine. Neither study was designed to detect significant differences in rates of adverse events associated with PEDIARIX administered after a previous dose of hepatitis B vaccine compared with PEDIARIX administered without a previous dose of hepatitis B vaccine.

6.2 Postmarketing Safety Surveillance Study

In a safety surveillance study conducted at a health maintenance organization in the U.S., infants who received one or more doses of PEDIARIX from approximately mid-2003 through mid-2005 were compared with age-, gender-, and area-matched historical controls who received one or more doses of separately administered U.S.-licensed DTaP vaccine from 2002 through approximately mid-2003. Only infants who received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with PEDIARIX or DTaP vaccine were included in the cohorts. Other U.S.-licensed vaccines were administered according to routine practices at the study sites, but concomitant administration with PEDIARIX or DTaP was not a criterion for

inclusion in the cohorts. A birth dose of hepatitis B vaccine had been administered routinely to infants in the historical DTaP control cohort, but not to infants who received PEDIARIX. For each of Doses 1-3, a random sample of 40,000 infants who received PEDIARIX was compared with the historical DTaP control cohort for the incidence of seizures (with or without fever) during the 8-day period following vaccination. For each dose, random samples of 7,500 infants in each cohort were also compared for the incidence of medically-attended fever (fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit) during the 4-day period following vaccination. Possible seizures and medical visits plausibly related to fever were identified by searching automated inpatient and outpatient data files. Medical record reviews of identified events were conducted to verify the occurrence of seizures or medically-attended fever. The incidence of verified seizures and medically-attended fever from this study are presented in Table 2.

Table 2. Percentage of Infants with Seizures (with or without Fever) within 8 Days of Vaccination and Medically-attended Fever within 4 Days of Vaccination with PEDIARIX Compared with Historical Controls

	PEDIARIX			Historical DTaP Controls			Difference (PEDIARIX–DTaP Controls)
	N	n	% (95% CI)	N	n	% (95% CI)	% (95% CI)
All Seizures (with or without fever)							
Dose 1, Days 0-7	40,000	7	0.02 (0.01, 0.04)	39,232	6	0.02 (0.01, 0.03)	0.00 (-0.02, 0.02)
Dose 2, Days 0-7	40,000	3	0.01 (0.00, 0.02)	37,405	4	0.01 (0.00, 0.03)	0.00 (-0.02, 0.01)
Dose 3, Days 0-7	40,000	6	0.02 (0.01, 0.03)	40,000	5	0.01 (0.00, 0.03)	0.00 (-0.01, 0.02)
Total doses	120,000	16	0.01 (0.01, 0.02)	116,637	15	0.01 (0.01, 0.02)	0.00 (-0.01, 0.01)
Medically-attended Fever[a]							
Dose 1, Days 0-3	7,500	14	0.19 (0.11, 0.30)	7,500	14	0.19 (0.11, 0.30)	0.00 (-0.14, 0.14)
Dose 2, Days 0-3	7,500	25	0.33 (0.22, 0.48)	7,500	15	0.20 (0.11, 0.33)	0.13 (-0.03, 0.30)
Dose 3, Days 0-3	7,500	21	0.28 (0.17, 0.43)	7,500	19	0.25 (0.15, 0.39)	0.03 (-0.14, 0.19)
Total doses	22,500	60	0.27 (0.20, 0.34)	22,500	48	0.21 (0.16, 0.28)	0.05 (-0.01, 0.14)

DTaP – any U.S.-licensed DTaP vaccine. Infants received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with each dose of PEDIARIX or DTaP. Other U.S.-licensed vaccines were administered according to routine practices at the study sites.
N = Number of subjects in the given cohort.
n = Number of subjects with events reported in the given cohort.
[a] Medically-attended fever defined as fever ≥100.4°F that resulted in hospitalization, an

emergency department visit, or an outpatient visit.

6.3 Postmarketing Spontaneous Reports for PEDIARIX

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for PEDIARIX since market introduction of this vaccine are listed below. This list includes serious adverse events or events that have a suspected causal connection to components of PEDIARIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders

Cyanosis.

Gastrointestinal Disorders

Diarrhea, vomiting.

General Disorders and Administration Site Conditions

Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site nodule/lump, injection site reaction, injection site vesicles, injection site warmth, limb pain, limb swelling.

Immune System Disorders

Anaphylactic reaction, anaphylactoid reaction, hypersensitivity.

Infections and Infestations

Upper respiratory tract infection.

Investigations

Abnormal liver function tests.

Nervous System Disorders

Bulging fontanelle, depressed level of consciousness, encephalitis, hypotonia, hypotonic-hyporesponsive episode, lethargy, somnolence, syncope.

Psychiatric Disorders

Crying, insomnia, nervousness, restlessness, screaming, unusual crying.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, cough, dyspnea.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema, rash, urticaria.

Vascular Disorders

Pallor, petechiae.

6.4 Postmarketing Spontaneous Reports for INFANRIX and/or ENGERIX-B

Worldwide voluntary reports of adverse events received for INFANRIX and/or ENGERIX-B in children younger than 7 years of age but not already reported for PEDIARIX are listed below. This list includes serious adverse events or events that have a suspected causal connection to components of INFANRIX and/or ENGERIX-B. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders

Idiopathic thrombocytopenic purpura,[a,b] lymphadenopathy,[a] thrombocytopenia.[a,b]

Gastrointestinal Disorders

Abdominal pain,[b] intussusception,[a,b] nausea.[b]

General Disorders and Administration Site Conditions

Asthenia,[b] malaise.[b]

Hepatobiliary Disorders

Jaundice.[b]

Immune System Disorders

Anaphylactic shock,[a] serum sickness–like disease.[b]

Musculoskeletal and Connective Tissue Disorders

Arthralgia,[b] arthritis,[b] muscular weakness,[b] myalgia.[b]

Nervous System Disorders

Encephalopathy,[a] headache,[a] meningitis,[b] neuritis,[b] neuropathy,[b] paralysis.[b]

Skin and Subcutaneous Tissue Disorders

Alopecia,[b] erythema multiforme,[b] lichen planus,[b] pruritus,[a,b] Stevens Johnson syndrome.[a]

Vascular Disorders

Vasculitis.[b]

[a] Following INFANRIX (licensed in the United States in 1997).

[b] Following ENGERIX-B (licensed in the United States in 1989).

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

Immune responses following concomitant administration of PEDIARIX, Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.), and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) were evaluated in a clinical trial *[see Clinical Studies (14.3)]*.

When PEDIARIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. PEDIARIX should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to PEDIARIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with PEDIARIX. It is not known whether PEDIARIX can cause fetal harm when administered to a pregnant woman or if PEDIARIX can affect reproduction capacity.

8.4 Pediatric Use

Safety and effectiveness of PEDIARIX were established in the age group 6 weeks through 6 months on the basis of clinical studies *[see Adverse Reactions (6.1), Clinical Studies (14.1, 14.2)]*. Safety and effectiveness of PEDIARIX in the age group 7 months through 6 years are supported by evidence in infants 6 weeks through 6 months of age. Safety and effectiveness of PEDIARIX in infants younger than 6 weeks of age and children 7 to 16 years of age have not been evaluated.

11 DESCRIPTION

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] is a noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), 8 mcg of pertactin (69 kiloDalton outer membrane protein), 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The diphtheria, tetanus, and

pertussis components are the same as those in INFANRIX and KINRIX. The hepatitis B surface antigen is the same as that in ENGERIX-B.

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor present an undue risk for bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

The hepatitis B surface antigen is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic medium. The surface antigen expressed in the *S. cerevisiae* cells is purified by several physiochemical steps, which include precipitation, ion exchange chromatography, and ultrafiltration.

The inactivated poliovirus component is an enhanced potency component. Each of the 3 strains of poliovirus is individually grown in VERO cells, a continuous line of monkey kidney cells, cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during VERO cell culture and/or virus culture. Calf serum is sourced from countries the USDA has determined neither have nor present an undue risk for BSE. After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.

Diphtheria and tetanus toxoids and pertussis antigens (inactivated PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide. The hepatitis B component is adsorbed onto aluminum phosphate.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis component (inactivated PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. Potency of the hepatitis B component is established by HBsAg ELISA. The potency of the inactivated poliovirus component is determined by using the D-antigen ELISA and by a poliovirus neutralizing cell culture assay on sera from previously immunized rats.

Each 0.5-mL dose contains aluminum salts as adjuvant (not more than 0.85 mg aluminum by

assay) and 4.5 mg of sodium chloride. Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). Neomycin sulfate and polymyxin B are used in the poliovirus vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B per dose. The procedures used to manufacture the HBsAg antigen result in a product that contains ≤5% yeast protein.

The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex.

PEDIARIX is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection; a level of 0.1 IU/mL is regarded as protective.[2]

Tetanus

Tetanus is an acute toxin-mediated disease caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.[3,4] A level ≥0.1 IU/mL is considered protective.[5]

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. There is no established serological correlate of protection for pertussis.

Hepatitis B

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[6]

Poliomyelitis

Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Poliovirus neutralizing antibodies confer protection

against poliomyelitis disease.[7]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PEDIARIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

The efficacy of PEDIARIX is based on the immunogenicity of the individual antigens compared with licensed vaccines. Serological correlates of protection exist for the diphtheria, tetanus, hepatitis B, and poliovirus components. The efficacy of the pertussis component, which does not have a well established correlate of protection, was determined in clinical trials of INFANRIX.

14.1 Efficacy of INFANRIX

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.

A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute protective efficacy of INFANRIX when administered at 2, 4, and 6 months of age. The population used in the primary analysis of the efficacy of INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76%, 89%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was 71% (95% CI: 60%, 78%) against >7 days of any cough and 73% (95% CI: 63%, 80%) against ≥14 days of any cough. A longer unblinded follow-up period showed that after 3 doses and with no booster dose in the second year of life, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79%, 91%) among children followed to 6 years of age. For details see INFANRIX prescribing information.

A prospective efficacy trial was also conducted in Germany employing a household contact study design. In this study, the protective efficacy of INFANRIX administered to infants at 3, 4, and 5 months of age, against WHO-defined pertussis was 89% (95% CI: 77%, 95%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52%, 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68%, 89%). For details see INFANRIX prescribing information.

14.2 Immunological Evaluation of PEDIARIX

In a U.S. multicenter study, infants were randomized to 1 of 3 groups: (1) a combination vaccine

group that received PEDIARIX concomitantly with Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.) and U.S.-licensed 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.); (2) a separate vaccine group that received U.S.-licensed INFANRIX, ENGERIX-B, and IPV (Sanofi Pasteur SA) concomitantly with the same Hib and pneumococcal conjugate vaccines; and (3) a staggered vaccine group that received PEDIARIX concomitantly with the same Hib conjugate vaccine but with the same pneumococcal conjugate vaccine administered 2 weeks later. The schedule of administration was 2, 4, and 6 months of age. Infants either did not receive a dose of hepatitis B vaccine prior to enrollment or were permitted to receive one dose of hepatitis B vaccine administered at least 30 days prior to enrollment. For the separate vaccine group, ENGERIX-B was not administered at 4 months of age to subjects who received a dose of hepatitis B vaccine prior to enrollment. Among subjects in all 3 vaccine groups combined, 84% were white, 7% were Hispanic, 6% were black, 0.7% were Oriental, and 2.4% were of other racial/ethnic groups.

The immune responses to the pertussis (PT, FHA, and pertactin), diphtheria, tetanus, poliovirus, and hepatitis B antigens were evaluated in sera obtained one month (range: 20 to 60 days) after the third dose of PEDIARIX or INFANRIX. Geometric mean antibody concentrations (GMCs) adjusted for pre-vaccination values for PT, FHA, and pertactin and the seroprotection rates for diphtheria, tetanus, and the polioviruses among subjects who received PEDIARIX in the combination vaccine group were shown to be non-inferior to those achieved following separately administered vaccines (Table 3).

Because of differences in the hepatitis B vaccination schedule among subjects in the study, no clinical limit for non-inferiority was pre-defined for the hepatitis B immune response. However, in a previous U.S. study, non-inferiority of PEDIARIX relative to separately administered INFANRIX, ENGERIX-B, and an oral poliovirus vaccine, with respect to the hepatitis B immune response was demonstrated.

Table 3. Antibody Responses following PEDIARIX as Compared with Separate Concomitant Administration of INFANRIX, ENGERIX-B, and IPV (One Month[a] after Administration of Dose 3) in Infants Vaccinated at 2, 4, and 6 Months of Age When Administered Concomitantly with Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7)

	PEDIARIX, Hib Vaccine, & PCV7	INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7
	(N = 154-168)	**(N = 141-155)**
Anti-diphtheria Toxoid % ≥0.1 IU/mL[b]	99.4	98.7
Anti-tetanus Toxoid % ≥0.1 IU/mL[b]	100	98.1
Anti-PT % VR[c] GMC[b]	98.7 48.1	95.1 28.6
Anti-FHA % VR[c] GMC[b]	98.7 111.9	96.5 97.6
Anti-pertactin % VR[c] GMC[b]	91.7 95.3	95.1 80.6
Anti-polio 1 % ≥1:8[b,d]	100	100
Anti-polio 2 % ≥1:8[b,d]	100	100
Anti-polio 3 % ≥1:8[b,d]	100	100
	(N = 114-128)	**(N = 111-121)**
Anti-HBsAg[e] % ≥10 mIU/mL[f] GMC (mIU/mL)[f]	97.7 1032.1	99.2 614.5

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay methods used: ELISA for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-pertactin, and anti-HBsAg; micro-neutralization for anti-polio (1, 2, and 3).

VR = Vaccine response: In initially seronegative infants, appearance of antibodies (concentration ≥5 EL.U./mL); in initially seropositive infants, at least maintenance of pre-vaccination concentration.

GMC = Geometric mean antibody concentration. GMCs are adjusted for pre-vaccination levels.

[a] One month blood sampling, range: 20 to 60 days.

[b] Seroprotection rate or GMC for PEDIARIX not inferior to separately administered vaccines (upper limit of 90% CI on GMC ratio [separate vaccine group/combination vaccine group] <1.5 for anti-PT, anti-FHA, and anti-pertactin, and upper limit of 95% CI for the difference in

seroprotection rates [separate vaccine group minus combination vaccine group] <10% for diphtheria and tetanus and <5% for the 3 polioviruses). GMCs are adjusted for pre-vaccination levels.

[c] The upper limit of 95% CI for differences in vaccine response rates (separate vaccine group minus combination group) was 0.31, 1.52, and 9.46 for PT, FHA, and pertactin, respectively. No clinical limit defined for non-inferiority.

[d] Poliovirus neutralizing antibody titer.

[e] Subjects who received a previous dose of hepatitis B vaccine were excluded from the analysis of hepatitis B seroprotection rates and GMCs presented in the table.

[f] No clinical limit defined for non-inferiority.

14.3 Concomitant Vaccine Administration

In a U.S. multicenter study *[see Clinical Studies (14.2)]*, there was no evidence for interference with the immune responses to PEDIARIX when administered concomitantly with 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) relative to 2 weeks prior.

Anti-PRP (Hib polyribosyl-ribitol-phosphate) seroprotection rates and GMCs of pneumococcal antibodies one month (range: 20 to 60 days) after the third dose of vaccines for the combination vaccine group and the separate vaccine group from the U.S. multicenter study *[see Clinical Studies (14.2)]*, are presented in Table 4.

Table 4. Anti-PRP Seroprotection Rates and GMCs (mcg/mL) of Pneumococcal Antibodies One Month[a] following the Third Dose of Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7) Administered Concomitantly with PEDIARIX or with INFANRIX, ENGERIX-B, and IPV

	PEDIARIX, Hib Vaccine, & PCV7	**INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7**
	(N = 161-168)	**(N = 146-156)**
	% (95% CI)	**% (95% CI)**
Anti-PRP ≥0.15 mcg/mL	100 (97.8, 100)	99.4 (96.5, 100)
Anti-PRP ≥1.0 mcg/mL	95.8 (91.6, 98.3)	91.0 (85.3, 95.0)
	GMC (95% CI)	**GMC (95% CI)**
Pneumococcal Serotype		
4	1.7 (1.5, 2.0)	2.1 (1.8, 2.4)
6B	0.8 (0.7, 1.0)	0.7 (0.5, 0.9)
9V	1.6 (1.4, 1.8)	1.6 (1.4, 1.9)
14	4.7 (4.0, 5.4)	6.3 (5.4, 7.4)
18C	2.6 (2.3, 3.0)	3.0 (2.5, 3.5)
19F	1.1 (1.0, 1.3)	1.1 (0.9, 1.2)
23F	1.5 (1.2, 1.8)	1.8 (1.5, 2.3)

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay method used: ELISA for anti-PRP and 7 pneumococcal serotypes.

GMC = Geometric mean antibody concentration.

[a] One month blood sampling, range: 20 to 60 days.

15 REFERENCES

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2. Vitek CR and Wharton M. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, and Offit PA, eds. *Vaccines*. 5th ed. Saunders;2008:139-156.
3. Wassilak SGF, Roper MH, Kretsinger K, and Orenstein WA. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, and Offit PA, eds. *Vaccines*. 5th ed. Saunders;2008:805-839.
4. Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117.
5. Centers for Disease Control and Prevention. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-15):1-48.

6. Ambrosch F, Frisch-Niggemeyer W, Kremsner P, et al. Persistence of vaccine-induced antibodies to hepatitis B surface antigen and the need for booster vaccination in adult subjects. *Postgrad Med J* 1987;63(Suppl. 2):129-135.
7. Sutter RW, Pallansch MA, Sawyer LA, et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. In: Williams JC, Goldenthal KL, Burns DL, Lewis Jr BP, eds. Combined vaccines and simultaneous administration. Current issues and perspectives. New York, NY: The New York Academy of Sciences; 1995:289-299.

16 HOW SUPPLIED/STORAGE AND HANDLING

PEDIARIX is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-811-43 Syringe in Package of 10: NDC 58160-811-52

Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

The parent or guardian should be:

- informed of the potential benefits and risks of immunization with PEDIARIX, and of the importance of completing the immunization series.
- informed about the potential for adverse reactions that have been temporally associated with administration of PEDIARIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider.
- given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/nip).

Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, U.S. License 1617, and

GSK Vaccines GmbH

Marburg, Germany, U.S. License 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

PDX:24PI

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Pentacel safely and effectively. See full prescribing information for Pentacel.

Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine
Suspension for Intramuscular Injection
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------

- Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------

- The four dose immunization series consists of a 0.5-mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)
- Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration.(2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Suspension for injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. (3)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Carefully consider benefits and risks before administering Pentacel to persons with a history of:
  - fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
  - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with Pentacel and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)

----------ADVERSE REACTIONS----------

- Rates of adverse reactions varied by dose number. Systemic reactions that occurred in >50% of participants following any dose included fussiness/irritability and inconsolable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in >30% of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

----------DRUG INTERACTIONS----------

- Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)
- Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)
- Urine antigen detection may not have definitive diagnostic value in suspected *H. influenzae* type b disease within one week following Pentacel. (7.3)

See **17 for PATIENT COUNSELING INFORMATION**
Revised: [09/2016]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Pentacel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to fifth birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

Pentacel is to be administered as a 4 dose series at 2, 4, 6 and 15-18 months of age. The first dose may be given as early as 6 weeks of age. Four doses of Pentacel constitute a primary immunization course against pertussis. Three doses of Pentacel constitute a primary immunization course against diphtheria, tetanus, *H. influenzae* type b invasive disease, and poliomyelitis; the fourth dose is a booster for diphtheria, tetanus, *H. influenzae* type b invasive disease, and poliomyelitis immunizations. [See *14 Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)*.]

Mixed Sequences of Pentacel and DTaP Vaccine

While Pentacel and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed [DTaP], Sanofi Pasteur Limited) vaccines contain the same pertussis antigens, manufactured by the same process, Pentacel contains twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL. Pentacel may be used to complete the first 4 doses of the 5-dose DTaP series in infants and children who have received 1 or more doses of DAPTACEL and are also scheduled to receive the other antigens of Pentacel. However, data are not available on the safety and immunogenicity of such mixed sequences of Pentacel and DAPTACEL for successive doses of the primary DTaP series. Children who have completed a 4-dose series with Pentacel should receive a fifth dose of DTaP vaccine using DAPTACEL at 4-6 years of age. (1)

Data are not available on the safety and effectiveness of using mixed sequences of Pentacel and DTaP vaccine from different manufacturers.

Mixed Sequences of Pentacel and IPV Vaccine

Pentacel may be used in infants and children who have received 1 or more doses of another licensed IPV vaccine and are scheduled to receive the antigens of Pentacel. However, data are not available on the safety and immunogenicity of Pentacel in such infants and children.

The Advisory Committee on Immunization Practices (ACIP) recommends that the final dose in the 4-dose IPV series be administered at age ≥4 years. (2) When Pentacel is administered at ages 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at age 4-6 years, resulting in a 5-dose IPV series. (2)

Mixed Sequences of Pentacel and Haemophilus b Conjugate Vaccine

Pentacel may be used to complete the vaccination series in infants and children previously vaccinated with one or more doses of Haemophilus b Conjugate Vaccine (either separately administered or as part of another combination vaccine), who are also scheduled to receive the other antigens of Pentacel. However, data are not available on the safety and immunogenicity of Pentacel in such infants and children. If different brands of Haemophilus b Conjugate Vaccines are administered to complete the series, three primary immunizing doses are needed, followed by a booster dose.

2.2 Administration

The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB vaccine component.

After removing the "flip-off" caps, cleanse the DTaP-IPV and ActHIB vial stoppers with a suitable germicide. Do not remove the vial stoppers or metal seals holding them in place. Just before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Gently swirl the vial now containing Pentacel until a cloudy, uniform, white to off-white (yellow tinge) suspension results.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, Pentacel should not be administered.

Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL dose of Pentacel intramuscularly. Use a separate sterile needle and syringe for each injection.

Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Pentacel should be used immediately after reconstitution. Refer to Figures 1, 2, 3, 4 and 5.

Pentacel: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV Component

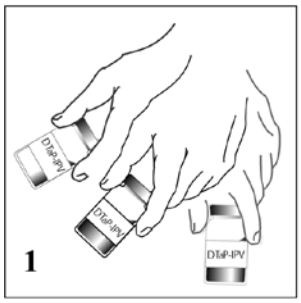

Figure 1
Gently shake the vial of DTaP-IPV component.

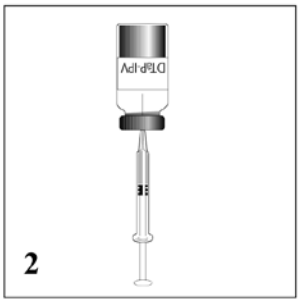

Figure 2
Withdraw the entire liquid content.

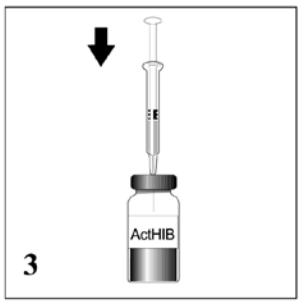

Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

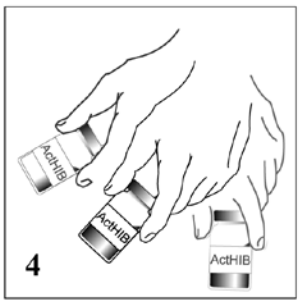

Figure 4
Swirl vial gently.

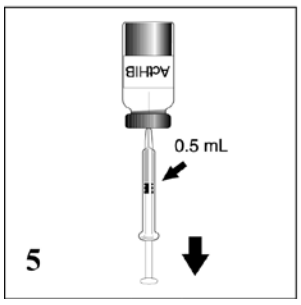

Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly.
Pentacel vaccine should be used immediately after reconstitution.

In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously or subcutaneously.

Pentacel should not be mixed in the same syringe with other parenteral products.

3 DOSAGE FORMS AND STRENGTHS

Pentacel is a suspension for injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. [See *Dosage and Administration (2.2)* and *How Supplied/Storage and Handling (16)*.]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel or any other diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine, or any ingredient of this vaccine is a contraindication to administration of Pentacel. [See *Description (11)*.]

4.2 Encephalopathy

Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including Pentacel.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine including Pentacel. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Adverse Reactions Following Prior Pertussis Vaccination

If any of the following events occur within the specified period after administration of a pertussis vaccine, the decision to administer Pentacel should be based on careful consideration of potential benefits and possible risks.

- Temperature of ≥40.5°C (≥105°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode (HHE)) within 48 hours.
- Persistent, inconsolable crying lasting ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

5.3 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (3) If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel.

5.4 Infants and Children with a History of Previous Seizures

For infants or children with a history of previous seizures, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing acellular pertussis antigens (including Pentacel) and for the following 24 hours, to reduce the possibility of post-vaccination fever.

5.5 Limitations of Vaccine Effectiveness

Vaccination with Pentacel may not protect all individuals.

5.6 Altered Immunocompetence

If Pentacel is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See *Drug Interactions (7.2)*.]

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

Rates of adverse reactions varied by dose number. The most frequent (>50% of participants) systemic reactions following any dose were fussiness/irritability and inconsolable crying. The most frequent (>30% of participants) injection site reactions following any dose were tenderness and increased circumference of the injected arm.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of Pentacel was evaluated in four clinical studies in which a total of 5,980 participants received at least one dose of Pentacel. In three of the studies, conducted in the US, a total of 4,198 participants were enrolled to receive four consecutive doses of Pentacel. In the fourth study, conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel received a fourth dose. The vaccination schedules of Pentacel, Control vaccines, and concomitantly administered vaccines used in these studies are provided in Table 1.

Across the four studies, 50.8% of participants were female. Among participants in the three US studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and

9.5% were of other racial/ethnic groups. In the two controlled studies, the racial/ethnic distribution of participants who received Pentacel and Control vaccines was similar. In the Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.8% were Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of other racial/ethnic groups.

Table 1: Clinical Safety Studies of Pentacel: Vaccination Schedules

Study	Pentacel	Control Vaccines	Concomitantly Administered Vaccines
494-01	2, 4, 6 and 15 months	HCPDT + POLIOVAX + ActHIB at 2, 4, 6, and 15 months	7-valent pneumococcal conjugate vaccine* (PCV7) at 2, 4, and 6 months in a subset of participants† Hepatitis B vaccine at 2 and 6 months‡
P3T06	2, 4, 6, and 15-16 months	DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months	PCV7* at 2, 4, and 6 months Hepatitis B vaccine at 2 and 6 months‡
494-03	2, 4, 6, and 15-16 months	None	PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered)‡ or at 2, 4, and 6 months (if no previous dose) Measles, mumps, rubella vaccine§ (MMR) and varicella vaccine at 12 or 15 months in random subsets of participants
5A9908	15-18 months**	None	None

HCPDT: non-US licensed DTaP vaccine that is identical to the DTaP component of Pentacel.
POLIOVAX: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited.
IPOL: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur SA.

* PCV7 manufactured by Wyeth Laboratories.

† PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine in a subset of participants.

‡ The first dose of hepatitis B vaccine (manufacturer not specified) was administered prior to study initiation, from birth to 21 days of age. Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co.

§ MMR and varicella vaccines were both manufactured by Merck and Co.

** Study participants previously had received three doses of Pentacel vaccine by 8 months of age.

Solicited Adverse Reactions

The incidence and severity of selected solicited injection site and systemic adverse reactions that occurred within 3 days following each dose of Pentacel or Control vaccines in Study P3T06 is shown in Table 2. Information on these reactions was recorded daily by parents or guardians on diary cards. In Table 2, injection site reactions are reported for the Pentacel and DAPTACEL injection sites.

Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days of Pentacel or Control Vaccines in Study P3T06

Injection Site Reactions	Pentacel				DAPTACEL			
	Dose 1 N = 465-467 %	**Dose 2** N = 451 %	**Dose 3** N = 438-440 %	**Dose 4** N = 387-396 %	**Dose 1** N = 1,400-1,404 %	**Dose 2** N = 1,358-1,359 %	**Dose 3** N = 1,311-1,312 %	**Dose 4** N = 376-380 %
Redness								
>5 mm	7.1	8.4	8.7	17.3	6.2	7.1	9.6	16.4
>25 mm	2.8	1.8	1.8	9.2	1.0	0.6	1.9	7.9
>50 mm	0.6	0.2	0.0	2.3	0.4	0.1	0.0	2.4
Swelling								
>5 mm	7.5	7.3	5.0	9.7	4.0	4.0	6.5	10.3
>25 mm	3.0	2.0	1.6	3.8	1.6	0.7	1.1	4.0
>50 mm	0.9	0.0	0.0	0.8	0.4	0.1	0.1	1.3
Tenderness*								
Any	47.5	39.2	42.7	56.1	48.8	38.2	40.9	51.1
Moderate or Severe	19.6	10.6	11.6	16.7	20.7	12.2	12.3	15.8
Severe	5.4	1.6	1.4	3.3	4.1	2.3	1.7	2.4
Increase in Arm Circumference								
>5 mm	–	–	–	33.6	–	–	–	30.6
>20 mm				4.7				6.9
>40 mm				0.5				0.8
Systemic Reactions	**Pentacel**				**DAPTACEL + IPOL + ActHIB**			**DAPTACEL + ActHIB**
	Dose 1 N = 466-467 %	**Dose 2** N = 451-452 %	**Dose 3** N = 435-440 %	**Dose 4** N = 389-398 %	**Dose 1** N = 1,390-1,406 %	**Dose 2** N = 1,346-1,360 %	**Dose 3** N = 1,301-1,312 %	**Dose 4** N = 379-381 %
Fever†‡								
≥38.0°C	5.8	10.9	16.3	13.4	9.3	16.1	15.8	8.7
>38.5°C	1.3	2.4	4.4	5.1	1.6	4.3	5.1	3.2
>39.5°C	0.4	0.0	0.7	0.3	0.1	0.4	0.3	0.8

Decreased Activity/Lethargy§								
Any	45.8	32.7	32.5	24.1	51.1	37.4	33.2	24.1
Moderate or Severe	22.9	12.4	12.7	9.8	24.3	15.8	12.7	9.2
Severe	2.1	0.7	0.2	2.5	1.2	1.4	0.6	0.3
Inconsolable Crying								
Any	59.3	49.8	47.3	35.9	58.5	51.4	47.9	36.2
≥1 hour	19.7	10.6	13.6	11.8	16.4	16.0	12.2	10.5
>3 hours	1.9	0.9	1.1	2.3	2.2	3.4	1.4	1.8
Fussiness/Irritability								
Any	76.9	71.2	68.0	53.5	75.8	70.7	67.1	53.8
≥1 hour	34.5	27.0	26.4	23.6	33.3	30.5	26.2	19.4
>3 hours	4.3	4.0	5.0	5.3	5.6	5.5	4.3	4.5

* Any: Mild, Moderate or Severe; Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.

† Fever is based upon actual temperatures recorded with no adjustments to the measurement route.

‡ Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 46.0%, 53.0%, 1.0%, and 0% respectively, for Pentacel vaccine and 44.8%, 54.0%, 1.0%, and 0.1%, respectively, for DAPTACEL + IPOL + ActHIB. Following Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 62.7%, 34.4%, 2.4% and 0.5%, respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB.

§ Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

Hypotonic Hyporesponsive Episodes

In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01, 494-03, and 5A9908, a question about the occurrence of fainting or change in mental status was asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report of a US Public Health Service workshop (4) were reported among participants who received Pentacel (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB (N = 1,032) or separately administered DAPTACEL + IPOL + ActHIB (N = 1,455). Hypotonia not fulfilling HHE criteria within 7 days following vaccination was reported in 4 participants after the administration of Pentacel (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose) and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB (4 days following the 1st dose).

Seizures

Across Studies 494-01, 494-03, 5A9908 and P3T06, a total of 8 participants experienced a seizure within 7 days following either Pentacel (4 participants; N = 4,197 for at least one of Doses 1-3; N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB (3 participants; N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered DAPTACEL + IPOL + ActHIB (1 participant; N = 1,455 for at least one of Doses 1-3), or separately administered DAPTACEL + ActHIB (0 participants; N = 418 for Dose 4). Among the four participants who experienced a seizure within 7 days following Pentacel, one participant in Study 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01 had a possible seizure the same day as the third dose, and two participants in Study 5A9908 had a febrile seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who experienced a seizure within 7 days following Control vaccines, one participant had an afebrile seizure the same day as the first dose of DAPTACEL + IPOL + ActHIB, one participant had an afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB, and two participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT + POLIOVAX + ActHIB.

Serious Adverse Events

In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of 484 (3.9%) participants who received Pentacel and 50 of 1,455 (3.4%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4 of 418 (1.0%) participants who received DAPTACEL + ActHIB experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 23 of 2,506 (0.9%) participants who received Pentacel and 11 of 1,032 (1.1%) participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants who received Pentacel and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event.

Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03, 5A9908 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

Across Studies 494-01, 494-03, 5A9908 and P3T06, two cases of encephalopathy were reported, both in participants who had received Pentacel (N = 5,979). One case occurred 30 days post-vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural cerebral abnormalities and was diagnosed with congenital encephalopathy.

A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children who had received Pentacel (N = 5,979) and one in a participant who had received DAPTACEL + IPOL + ActHIB (N = 1,455). There were no deaths reported in children who received HCPDT + POLIOVAX + ActHIB (N = 1,032). Causes of death among children who received Pentacel were asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8,

23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB.

6.2 Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of Pentacel worldwide, since 1997. Between 1997 and 2007, Pentacel was primarily used in Canada. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Pentacel.

- ***Cardiac disorders***
  Cyanosis
- ***Gastrointestinal disorders***
  Vomiting, diarrhea
- ***General disorders and administration site conditions***
  Injection site reactions (including inflammation, mass, abscess and sterile abscess), extensive swelling of the injected limb (including swelling that involved adjacent joints), vaccination failure/therapeutic response decreased (invasive *H. influenzae* type b disease)
- ***Immune system disorders***
  Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria)
- ***Infections and infestations***
  Meningitis, rhinitis, viral infection

- ***Metabolism and nutrition disorders***
  Decreased appetite
- ***Nervous system disorders***
  Somnolence, HHE, depressed level of consciousness
- ***Psychiatric disorders***
  Screaming
- ***Respiratory, thoracic and mediastinal disorders***
  Apnea, cough
- ***Skin and subcutaneous tissue disorders***
  Erythema, skin discoloration
- ***Vascular disorders***
  Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In clinical trials, Pentacel was administered concomitantly with one or more of the following US licensed vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and varicella vaccines. [See *Adverse Reactions (6)* and *Clinical Studies (14)*.] When Pentacel is given at the same time as another injectable vaccine(s), the vaccine(s) should be administered with different syringes and at different injection sites.

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to Pentacel. [See *Warnings and Precautions (5.6)*.]

7.3 Drug/Laboratory Test Interactions

Antigenuria has been detected in some instances following receipt of ActHIB. Urine antigen detection may not have definite diagnostic value in suspected *H. influenzae* type b disease within one week following receipt of Pentacel. (5)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Pentacel. It is also not known whether Pentacel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

8.4 Pediatric Use

The safety and effectiveness of Pentacel was established in the age group 6 weeks through 18 months on the basis of clinical studies. [See *Adverse Reactions (6.1)* and *Clinical Studies (14)*.] The safety and effectiveness of Pentacel in the age group 19 months through 4 years is supported by evidence in children 6 weeks through 18 months. The safety and effectiveness of Pentacel in infants less than 6 weeks of age and in children 5 to 16 years of age have not been established.

11 DESCRIPTION

Pentacel consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® component combined through reconstitution for intramuscular injection. ActHIB (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), consists of *H. influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T). The DTaP-IPV component is supplied as a sterile liquid used to reconstitute the lyophilized ActHIB component to form Pentacel. Pentacel is a uniform, cloudy, white to off-white (yellow tinge) suspension.

Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses [40 D-antigen units (DU) Type 1 (Mahoney), 8 DU Type 2 (MEF-1), 32 DU Type 3 (Saukett)] and 10 mcg PRP of *H. influenzae* type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).

Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), 42.5 mg sucrose, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), <4 pg of neomycin and <4 pg polymyxin B sulfate.

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (6) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered.

Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (7) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (8) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

Poliovirus Type 1, Type 2 and Type 3 are each grown in separate cultures of MRC-5 cells, a line of normal human diploid cells, by the microcarrier method. (9) (10) The cells are grown in CMRL (Connaught Medical Research Laboratories) 1969 medium, supplemented with calf serum. For viral growth, the culture medium is replaced by Medium 199, without calf serum. After clarification and filtration, the viral suspensions are concentrated by ultrafiltration, and purified by liquid chromatography steps. The monovalent viral suspensions are inactivated with formaldehyde. Monovalent concentrates of each inactivated poliovirus are combined to produce a trivalent poliovirus concentrate.

The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the DTaP-IPV component is diluted to its final concentration. The DTaP-IPV component does not contain a preservative.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig potency test. The potency of the acellular pertussis antigens is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). The potency of inactivated poliovirus antigens is determined by measuring antibody-mediated neutralization of poliovirus in sera from immunized rats.

PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b strain 1482 grown in a semi-synthetic medium. (11) The tetanus toxoid for conjugation to PRP is prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (12) The toxoid is filter sterilized prior to the conjugation process. The ActHIB component does not contain a preservative. Potency of the ActHIB component is specified on each lot by limits on the content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and protein that is characterized as high molecular weight conjugate.

The vial stoppers for the DTaP-IPV and ActHIB components of Pentacel are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (13) Levels of 1.0 IU/mL have been associated with long-term protection. (14)

Tetanus

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (13) (15) A tetanus antitoxoid level ≥0.1 IU/mL as measured by the ELISA used in clinical studies of Pentacel is considered protective.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

Poliomyelitis

Polioviruses, of which there are three serotypes (Types 1, 2, and 3) are enteroviruses. The presence of poliovirus type-specific neutralizing antibodies has been correlated with protection against poliomyelitis. (16)

Invasive Disease Due to *H. influenzae* Type b

H. influenzae type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody has been shown to correlate with protection against invasive disease due to *H. influenzae* type b.

Based on data from passive antibody studies (17) and an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland, (18) a post-vaccination anti-PRP level of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination predicts protection through a subsequent one-year period. (19) (20) These levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB component of Pentacel.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Pentacel has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

The efficacy of Pentacel is based on the immunogenicity of the individual antigens compared to separately administered vaccines. Serological correlates of protection exist for diphtheria, tetanus, poliomyelitis, and invasive disease due to *H. influenzae* type b. [See *Clinical Pharmacology (12.1)*.] The efficacy against pertussis, for which there is no well established serological correlate of protection, was based, in part, on a comparison of pertussis immune responses following Pentacel in US children to responses following DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) manufactured by Sanofi Pasteur Limited) in an efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by the same process, Pentacel contains twice as much detoxified PT and four times as much FHA as DAPTACEL.

Immune responses to Pentacel were evaluated in four US studies: Studies 494-01, P3T06, 494-03, and M5A10. The vaccination schedules of Pentacel, Control vaccines, and concomitantly administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1. [See *Adverse Reactions (6.1)*.] In Study M5A10, participants were randomized to receive Pentacel or separately administered DAPTACEL, IPOL, and ActHIB at 2, 4, and 6 months of age. 7-valent pneumococcal conjugate (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age, and Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2 and 6 months of age, were administered concomitantly with Pentacel or Control vaccines.

14.1 Diphtheria

The proportions of participants achieving diphtheria antitoxin seroprotective levels one month following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table 3.

14.2 Tetanus

The proportions of participants achieving tetanus antitoxoid seroprotective levels one month following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table 3.

Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month Following Dose 3 and Dose 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Children Vaccinated at 2, 4, 6, and 15-16 Months of Age

	Pentacel	**DAPTACEL + IPOL + ActHIB**
Post-Dose 3	**N = 331-345**	**N = 1,037-1,099**
Diphtheria Antitoxin		
% ≥0.01 IU/mL*	100.0%	100.0%
% ≥0.10 IU/mL†	98.8%	98.5%
Tetanus Antitoxoid		
% ≥0.10 IU/mL†	99.7%	100.0%
Post-Dose 4	**N = 341-352**	**N = 328-334**
Diphtheria Antitoxin		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†	96.5%	95.7%
Tetanus Antitoxoid		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†‡	92.9%	99.4%

Per Protocol Immunogenicity population.

* Seroprotection rate following Pentacel vaccine is not inferior to DAPTACEL vaccine (upper limit of 90% CI of the difference DAPTACEL – Pentacel is <10%).

† Non-inferiority criteria were not pre-specified.

‡ With the ELISA used in this study, a tetanus antitoxoid level of 1.0 IU/mL is 10 times the protective level.

14.3 Pertussis

In a clinical pertussis vaccine efficacy study conducted in Sweden during 1992-1995 (Sweden I Efficacy Trial), 2,587 infants received DAPTACEL and 2,574 infants received a non-US licensed DT vaccine as placebo at 2, 4, and 6 months of age. (1) The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL against pertussis after 3 doses of vaccine using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1%, 88.6%). The protective efficacy of DAPTACEL against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by DAPTACEL was sustained for the 2-year follow-up period.

Based on comparisons of the immune responses to DAPTACEL in US infants (Post-Dose 3) and Canadian children (Post-Dose 4) relative to infants who participated in the Sweden I Efficacy Trial, it was concluded that 4 doses of DAPTACEL were needed for primary immunization against pertussis in US children. (1)

In a serology bridging analysis, immune responses to FHA, PRN and FIM in a subset of infants who received three doses of DAPTACEL in the Sweden I Efficacy Trial were compared to the Post-Dose 3 and Post-Dose 4 responses in a subset of US children from Study 494-01 who received Pentacel (Table 4). Available stored sera from infants who received DAPTACEL in the Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first three doses of Pentacel in Study 494-01 (Table 1) were assayed in parallel. Data on levels of antibody to PT using an adequately specific assay were not available for this serology bridging analysis.

Geometric mean antibody concentrations (GMCs) and seroconversion rates for antibodies to FHA, PRN and FIM one month following Dose 3 of DAPTACEL in the subset of infants from the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset of infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and anti-FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-PRN,

and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL. The non-inferiority criterion for anti-PRN seroconversion following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL was not met [upper limit of 95% CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%]. Whether the lower anti-PRN seroconversion rate following Dose 4 of Pentacel in US children relative to Dose 3 of DAPTACEL in Swedish infants correlates with diminished efficacy of Pentacel against pertussis is unknown.

Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of DAPTACEL in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel in a Subset of Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in US Study 494-01

	Post-Dose 3 DAPTACEL Sweden I Efficacy Trial N = 80	Post-Dose 3 Pentacel * US Study 494-01 N = 730-995	Post-Dose 4 Pentacel† US Study 494-01 N = 507-554
Anti-FHA			
% achieving 4-fold rise‡	68.8	79.8	91.7§
GMC (EU/mL)	40.70	71.46	129.85§
Anti-PRN			
% achieving 4-fold rise‡	98.8	74.4	89.2**
GMC (EU/mL)	111.26	38.11	90.82§
Anti-FIM			
% achieving 4-fold rise‡	86.3	86.5	91.5§
GMC (EU/mL)-	339.31	265.02	506.57§

Analyzed sera were from subsets of the Per Protocol Immunogenicity populations in each study.
Data on anti-PT levels using an adequately specific assay were not available.

* Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.

† Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs. DAPTACEL vaccine Post-Dose 3.

‡ Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

§ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].

** Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis immune responses (GMCs and seroconversion rates) one month following the third and fourth doses were compared between the two groups (Table 5). Seroconversion was defined as a 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). Data on anti-PT responses obtained from an adequately specific assay were available on only a non-random subset of study participants. The subset of study participants was representative of all study participants with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to FHA, PRN and FIM. For each of the pertussis antigens, non-inferiority criteria were met for seroconversion rates and GMCs following Dose 3 of Pentacel relative to Dose 3 of DAPTACEL. Following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL, non-inferiority criteria were met for all comparisons except for anti-PRN GMCs [upper limit of 90% CI for ratio of GMCs (DAPTACEL/Pentacel) = 2.25]. Whether the lower anti-PRN GMC following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL in US children correlates with diminished efficacy of Pentacel against pertussis is unknown.

Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in Study P3T06

	Post-Dose 3 Pentacel	Post-Dose 3 DAPTACEL + IPOL + ActHIB	Post-Dose 4 Pentacel	Post-Dose 4 DAPTACEL + ActHIB
	N = 143	**N = 481-485**	**N = 113**	**N = 127-128**
Anti-PT **% achieving 4-fold rise*** **GMC (EU/mL)**	95.8† 102.62†	87.3 61.88	93.8‡ 107.89‡	91.3 100.29
	N = 218-318	**N = 714-1,016**	**N = 230-367**	**N = 237-347**
Anti-FHA **% achieving 4-fold rise*** **GMC (EU/mL)**	81.9§ 73.68§	60.9 29.22	88.4** 107.94**	79.3 64.02
Anti-PRN **% achieving 4-fold rise*** **GMC (EU/mL)**	74.2§ 36.05§	75.4 43.25	92.7** 93.59††	98.3 186.07
Anti-FIM **% achieving 4-fold rise*** **GMC (EU/mL)**	91.7§ 268.15§	86.3 267.18	93.5** 553.39**	91.6 513.54

Per Protocol Immunogenicity population for anti-FHA, anti-PRN, and anti-FIM.
Non-random subset of per Protocol Immunogenicity population for anti-PT. See text for further information on the subset evaluated.

* Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

† Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

‡ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

§ Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

** Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

†† Non-inferiority criterion is not met for GMC Post-Dose 4 Pentacel vaccine relative to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) = 2.25, which exceeds the non-inferiority criterion of <1.5].

14.4 Poliomyelitis

In Study P3T06 (Table 1), in which infants were randomized to receive the first three doses of Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months of age, one month following the third dose of study vaccines, ≥99.4% of participants in both groups (Pentacel: N = 338-350), (DAPTACEL + IPOL + ActHIB: N = 1,050-1,097) achieved neutralizing antibody levels of ≥1:8 for Poliovirus types 1, 2, and 3.

In Study 494-01 (Table 1), in which infants were randomized to receive Pentacel or HCPDT + POLIOVAX + ActHIB, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month following Dose 4 of Pentacel (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one month following Dose 4 of POLIOVAX (N = 284-287) were 2,330, 2,840, and 3,300, respectively.

14.5 Invasive Disease due to *H. Influenzae* Type b

Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel-or separately administered ActHIB in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL and for anti-PRP GMCs following Pentacel compared with separately administered ActHIB. In each of Studies P3T06 and M5A10, the non-inferiority criterion was met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL following Pentacel compared with separately administered ActHIB. In Study M5A10, the non-inferiority criterion was met for anti-PRP GMCs following Pentacel compared with separately administered ActHIB.

Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel or Separate DTaP + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and M5A10

	Study 494-01	
	Pentacel N = 1,127	**HCPDT + POLIOVAX + ActHIB N = 401**
% achieving anti-PRP ≥0.15 mcg/mL	95.4*	98.3
% achieving anti-PRP ≥1.0 mcg/mL	79.1†	88.8
Anti-PRP GMC (mcg/mL)	3.19‡	6.23
	Study P3T06	
	Pentacel N = 365	**DAPTACEL + IPOL + ActHIB N = 1,128**
% achieving anti-PRP ≥0.15 mcg/mL	92.3*	93.3
% achieving anti-PRP ≥1.0 mcg/mL	72.1*	70.8
Anti-PRP GMC (mcg/mL)	2.31§	2.29
	Study M5A10	
	Pentacel N = 826	**DAPTACEL + IPOL + ActHIB N = 421**
% achieving anti-PRP ≥0.15 mcg/mL	93.8**	90.3
% achieving anti-PRP ≥1.0 mcg/mL	75.1**	74.8
Anti-PRP GMC (mcg/mL)	2.52††	2.38

Per Protocol Immunogenicity population for all studies.

IPV indicates Poliovirus Vaccine Inactivated.

* Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel) <10%].

† Non-inferiority criterion not met for percent achieving anti-PRP ≥1.0 mcg/mL following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%, exceeds the non-inferiority criterion <10%].

‡ Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel), 2.26, exceeds the non-inferiority criterion <1.5].

§ Non-inferiority criterion not pre-specified.

** Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 95% CI for difference in rates (ActHIB minus Pentacel) <10%].

†† GMC following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel) <1.5].

In Study 494-01, at 15 months of age prior to receipt of Dose 4 of study vaccines, 68.6% of Pentacel recipients (N = 829) and 80.8% of separately administered ActHIB recipients (N = 276) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel recipients (N = 874) and 99.0% of separately administered ActHIB recipients (N = 291) had an anti-PRP level ≥1.0 mcg/mL.

In Study P3T06, at 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an anti-PRP level ≥1.0 mcg/mL.

14.6 Concomitantly Administered Vaccines

In Study P3T06, (Table 1) there was no evidence for reduced antibody responses to hepatitis B vaccine (percent of participants with anti-HBsAg ≥10 mIU/mL and GMCs) or PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL and GMCs to each serotype) administered concomitantly with Pentacel (N = 321-325) relative to these vaccines administered concomitantly with DAPTACEL + IPOL + ActHIB (N = 998-1,029). The immune responses to hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

In Study 494-03, (Table 1) there was no evidence for interference in the immune response to the fourth dose of PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL and GMCs to each serotype) administered at 15 months of age concomitantly with Pentacel (N = 155) relative to this vaccine administered concomitantly with MMR and varicella vaccines (N = 158). There was no evidence for interference in the immune response to MMR and varicella vaccines (percent of participants with pre-specified seroresponse level) administered at 15 months of age concomitantly with Pentacel (N = 154) relative to these vaccines administered concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the fourth dose of PCV7 were evaluated one month post-vaccination.

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16 HOW SUPPLIED/STORAGE AND HANDLING

The vial stoppers for the DTaP-IPV and ActHIB vaccine components of Pentacel are not made with natural rubber latex.

5 Dose Package (NDC No. 49281-510-05) containing 5 vials of DTaP-IPV component (NDC No. 49281-560-05) to be used to reconstitute 5 single dose vials of lyophilized ActHIB vaccine component (NDC No. 49281-545-15).

Pentacel should be stored at 2° to 8°C (35° to 46°F). Do not freeze. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

Pentacel should be used immediately after reconstitution.

17 PATIENT COUNSELING INFORMATION

Before administration of Pentacel, health-care personnel should inform the parent or guardian of the benefits and risks of the vaccine and the importance of completing the immunization series unless a contraindication to further immunization exists.

The health-care provider should inform the parent or guardian about the potential for adverse reactions that have been temporally associated with Pentacel or other vaccines containing similar ingredients. The health-care provider should provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The parent or guardian should be instructed to report adverse reactions to their health-care provider.

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada

and **Sanofi Pasteur SA**
Lyon France

Distributed by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

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R5-0916 USA

Liquid PedvaxHIB®
[Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

DESCRIPTION

PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] is a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) that is covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. The covalent bonding of the PRP to the OMPC which is necessary for enhanced immunogenicity of the PRP is confirmed by quantitative analysis of the conjugate's components following chemical treatment which yields a unique amino acid. The potency of PedvaxHIB is determined by assay of PRP.

Haemophilus influenzae type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

Liquid PedvaxHIB is ready to use and does not require a diluent. Each 0.5 mL dose of Liquid PedvaxHIB is a sterile product formulated to contain: 7.5 mcg of Haemophilus b PRP, 125 mcg of *Neisseria meningitidis* OMPC and 225 mcg of aluminum as amorphous aluminum hydroxyphosphate sulfate (previously referred to as aluminum hydroxide), in 0.9% sodium chloride, but does not contain lactose or thimerosal. Liquid PedvaxHIB is a slightly opaque white suspension.

This vaccine is for intramuscular administration and not for intravenous injection. (See DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY

Prior to the introduction of Haemophilus b Conjugate Vaccines, *Haemophilus influenzae* type b (Hib) was the most frequent cause of bacterial meningitis and a leading cause of serious, systemic bacterial disease in young children worldwide.[1,2,3,4]

Hib disease occurred primarily in children under 5 years of age in the United States prior to the initiation of a vaccine program and was estimated to account for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which were meningitis. The mortality rate from Hib meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation.[5,6] Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis.

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Hib disease occurred in infants less than 6 months of age.[7] The peak incidence of Hib meningitis occurs between 6 to 11 months of age. Forty-seven percent of all cases occur by one year of age with the remaining 53% of cases occurring over the next four years.[2,20]

Among children under 5 years of age, the risk of invasive Hib disease is increased in certain populations including the following:

- Daycare attendees[8,9]
- Lower socio-economic groups[10]
- Blacks[11] (especially those who lack the Km(1) immunoglobulin allotype)[12]
- Caucasians who lack the G2m(n or 23) immunoglobulin allotype[13]
- Native Americans[14,15,16]
- Household contacts of cases[17]
- Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes[18,19]

An important virulence factor of the Hib bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Hib disease.[3,21] While the anti-PRP level associated with protection using conjugated vaccines has not yet been

determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from >0.15 to >1.0 mcg/mL.[22-28]

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier[29] producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen resulting in both an enhanced antibody response and immunologic memory.

Clinical Evaluation of PedvaxHIB

PedvaxHIB, in a lyophilized formulation (lyophilized PedvaxHIB), was initially evaluated in 3,486 Native American (Navajo) infants, who completed the primary two-dose regimen in a randomized, double-blind, placebo-controlled study (The Protective Efficacy Study). At the time of the study, this population had a much higher incidence of Hib disease than the United States population as a whole and also had a lower antibody response to Haemophilus b Conjugate Vaccines, including PedvaxHIB.[14,15,16,30,33]

Each infant in this study received two doses of either placebo or lyophilized PedvaxHIB with the first dose administered at a mean of 8 weeks of age and the second administered approximately two months later; DTP and OPV were administered concomitantly. Antibody levels were measured in a subset of each group (TABLE 1).

TABLE 1
Antibody Responses in Navajo Infants

Vaccine	No. of Subjects	Time	% Subjects with >0.15 mcg/mL	% Subjects with >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Lyophilized PedvaxHIB*	416**	Pre-Vaccination	44	10	0.16
	416	Post-Dose 1	88	52	0.95
	416	Post-Dose 2	91	60	1.43
Placebo*	461**	Pre-Vaccination	44	9	0.16
	461	Post-Dose 1	21	2	0.09
	461	Post-Dose 2	14	1	0.08
Lyophilized PedvaxHIB	27†	Prebooster	70	33	0.51
	27	Postbooster††	100	89	8.39

* Post-Vaccination values obtained approximately 1–3 months after each dose.
** The Protective Efficacy Study
† Immunogenicity Trial[34]
†† Booster given at 12 months of age; Post-Vaccination values obtained 1 month after administration of booster dose.

Most subjects were initially followed until 15 to 18 months of age. During this time, 22 cases of invasive Hib disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the primary two-dose regimen, the protective efficacy of lyophilized PedvaxHIB was calculated to be 93% with a 95% confidence interval of 57%-98% (p=0.001, two-tailed). In the two months between the first and second doses, the difference in number of cases of disease between placebo and vaccine recipients (8 vs. 0 cases, respectively) was statistically significant (p=0.008, two-tailed); however, a primary two-dose regimen is required for infants 2-14 months of age.

At termination of the study, placebo recipients were offered vaccine. All original participants were then followed two years and nine months from termination of the study. During this extended follow-up, invasive Hib disease occurred in an additional seven of the original placebo recipients prior to receiving vaccine and in one of the original vaccine recipients (who had received only one dose of vaccine). No cases of invasive Hib disease were observed in placebo recipients after they received at least one dose of vaccine. Efficacy for this follow-up period, estimated from person-days at risk, was 96.6% (95 C.I., 72.2-99.9%) in children under 18 months of age and 100% (95 C.I., 23.5-100%) in children over 18 months of age.[33]

Since protective efficacy with lyophilized PedvaxHIB was demonstrated in such a high risk population, it would be expected to be predictive of efficacy in other populations.

The safety and immunogenicity of lyophilized PedvaxHIB were evaluated in infants and children in other clinical studies that were conducted in various locations throughout the United States. PedvaxHIB was highly immunogenic in all age groups studied.[31,32]

Lyophilized PedvaxHIB induced antibody levels greater than 1.0 mcg/mL in children who were poor responders to nonconjugated PRP vaccines. In a study involving such a subpopulation,[33,34] 34 children ranging in age from 27 to 61 months who developed invasive Hib disease despite previous vaccination with nonconjugated PRP vaccines were randomly assigned to 2 groups. One group (n=14) was vaccinated with lyophilized PedvaxHIB and the other group (n=20) with a nonconjugated PRP vaccine at a mean interval of approximately 12 months after recovery from disease. All 14 children vaccinated with lyophilized PedvaxHIB but only 6 of 20 children re-vaccinated with a nonconjugated PRP vaccine achieved an antibody level of >1.0 mcg/mL. The 14 children who had not responded to revaccination with the nonconjugated PRP vaccine were then vaccinated with a single dose of lyophilized PedvaxHIB; following this vaccination, all achieved antibody levels of >1.0 mcg/mL.

In addition, lyophilized PedvaxHIB has been studied in children at high risk of Hib disease because of genetically-related deficiencies [Blacks who were Km(1) allotype negative and Caucasians who were G2m(23) allotype negative] and are considered hyporesponsive to nonconjugated PRP vaccines on this basis.[35] The hyporesponsive children had anti-PRP responses comparable to those of allotype positive children of similar age range when vaccinated with lyophilized PedvaxHIB. All children achieved anti-PRP levels of >1.0 mcg/mL.

The safety and immunogenicity of Liquid PedvaxHIB were compared with those of lyophilized PedvaxHIB in a randomized clinical study involving 903 infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. The antibody responses induced by each formulation of PedvaxHIB were similar. TABLE 2 shows antibody responses from this clinical study in subjects who received their first dose at 2 to 3 months of age.

TABLE 2
Antibody Responses to Liquid and Lyophilized PedvaxHIB in Infants From the General U.S. Population

Formulation	Age (Months)	Time	No. of Subjects	% Subjects with anti-PRP >0.15 mcg/mL	% Subjects with anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Liquid PedvaxHIB (7.5 mcg PRP)		Pre-Vaccination	487	32	7	0.12
	2-3	Post-Dose 1*	480	94	64	1.55
		Post-Dose 2**	393	97	80	3.22
	12-15	Prebooster	284	80	30	0.49
		Postbooster**	284	99	95	10.23
	24†	Persistence	94	97	55	1.29
Lyophilized PedvaxHIB (15 mcg PRP)		Pre-Vaccination	171	37	6	0.13
	2-3	Post-Dose 1*	169	97	72	1.88
		Post-Dose 2**	133	99	81	2.69
	12-15	Prebooster	87	71	28	0.39
		Postbooster**	87	99	91	7.64
	24†	Persistence	37	97	54	1.10

* Approximately two months Post-Vaccination
** Approximately one month Post-Vaccination
† Approximately

A booster dose of PedvaxHIB is required in infants who complete the primary two-dose regimen before 12 months of age. This booster dose will help maintain antibody levels during the first two years of life when children are at highest risk for invasive Hib disease. (See TABLE 2 and DOSAGE AND ADMINISTRATION.)

In four United States studies, antibody responses to lyophilized PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 3.)

TABLE 3
Antibody Responses*
After Two Doses of Lyophilized PedvaxHIB Among Infants Initially Vaccinated at 2–3 Months of Age By Racial/Ethnic Group

		LYOPHILIZED		
Racial/Ethnic Groups	No. of Subjects	% Subjects With Anti-PRP >0.15 mcg/mL	% Subjects With Anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Native American†	54	96	70	2.47
Caucasian	201	99	82	3.52
Hispanic	76	99	88	3.54
Black	23	100	96	5.40

* One month after the second dose
† Apache and Navajo

In two United States studies, antibody responses to Liquid PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 4.)

TABLE 4
Antibody Responses*
After Two Doses of Liquid PedvaxHIB Among Infants Initially Vaccinated at 2–3 Months of Age By Racial/Ethnic Group

		LIQUID		
Racial/Ethnic Groups	No. of Subjects	% Subjects With Anti-PRP >0.15 mcg/mL	% Subjects With Anti-PRP >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)
Native American**	90	97	78	2.76
Caucasian	143	94	72	2.16
Hispanic	184	98	85	4.34
Black	18	100	94	7.58

* One month after the second dose
** Apache and Navajo

Antibodies to the OMPC of *N. meningitidis* have been demonstrated in vaccinee sera, but the clinical relevance of these antibodies has not been established.[33]

Interchangeability of Licensed Haemophilus b Conjugate Vaccines and PedvaxHIB

Published studies have examined the interchangeability of other licensed Haemophilus b Conjugate Vaccines and PedvaxHIB.[42,43,44,45,52] According to the American Academy of Pediatrics, excellent immune responses have been achieved when different vaccines have been interchanged in the primary series. If PedvaxHIB is given in a series with one of the other products licensed for infants, the recommended number of doses to complete the series is determined by the other product and not by PedvaxHIB. PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the booster dose.[52]

Use with Other Vaccines

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)].[33] No impairment of immune response to individual tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

In addition, a PRP-OMPC-containing product, COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.[33]

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS.)

Revaccination

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine[36] and another Haemophilus b Conjugate Vaccine[37], cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence that Liquid PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.[46]

If PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.[47]

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB;[38] in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Liquid PedvaxHIB has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen).[49-51] Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB with those of lyophilized PedvaxHIB, 1,699 doses of Liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both formulations of PedvaxHIB were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in TABLE 5, in decreasing order of frequency, were: irritability, sleepiness, injection site pain/soreness, injection site erythema (≤2.5 cm diameter, see also TABLE 5), injection site swelling/induration (≤2.5 cm diameter, see also TABLE 5), unusual high-pitched crying, prolonged crying (>4 hr), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB are summarized in TABLE 5.

TABLE 5
Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB*

Reaction	Post-Dose 1 (hr) No. of Subjects Evaluated	6	24	48	Post-Dose 2 (hr) No. of Subjects Evaluated	6	24	48
		Percentage				Percentage		
Fever** >38.3°C (≥101°F) Rectal	222	18.1	4.4	0.5	206	14.1	9.4	2.8
Erythema >2.5 cm diameter	674	2.2	1.0	0.5	562	1.6	1.1	0.4
Swelling >2.5 cm diameter	674	2.5	1.9	0.9	562	0.9	0.9	1.3

* DTP and OPV were administered concomitantly to most subjects.
** Fever was also measured by another method or reported as normal for an additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.[36,37,39,40,41,49]

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skin

Sterile injection site abscess

DOSAGE AND ADMINISTRATION

Liquid PedvaxHIB

FOR INTRAMUSCULAR ADMINISTRATION

DO NOT INJECT INTRAVENOUSLY

If there is an interruption or delay between doses in the primary series, there is no need to repeat the series, but dosing should be continued at the next clinic visit. (See CONTRAINDICATIONS and PRECAUTIONS.)

2 to 14 Months of Age

Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see below and TABLE 6). Infants born prematurely, regardless of birth weight, should be vaccinated at the same chronological age and according to the same schedule and precautions as full-term infants and children.[46]

15 Months of Age and Older

Children 15 months of age and older previously unvaccinated against Hib disease should receive a single 0.5 mL dose of vaccine.

Booster Dose

In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months of age, but not earlier than 2 months after the second dose.

Vaccination regimens for Liquid PedvaxHIB by age group are outlined in TABLE 6.

TABLE 6
Vaccination Regimens for Liquid PedvaxHIB
By Age Groups

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2–10	2 doses, 2 mo. apart	12–15
11–14	2 doses, 2 mo. apart	—
15–71	1 dose	—

Interchangeability

PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the primary and booster doses.[52] (See CLINICAL PHARMACOLOGY.)

Use with Other Vaccines

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)]. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen with the other vaccines when given alone. (See CLINICAL PHARMACOLOGY.)

In addition, a PRP-OMPC-containing product, COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.[33]

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit.

Liquid PedvaxHIB is a slightly opaque white suspension. (See DESCRIPTION.)

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Inject 0.5 mL intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm. The buttocks should not be used for active vaccination of infants and children, because of the potential risk of injury to the sciatic nerve.

HOW SUPPLIED

Liquid PedvaxHIB is supplied as follows:

No. 4897 — A box of 10 single-dose vials of liquid vaccine, **NDC** 0006-4897-00.

Storage

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE.

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Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENGERIX-B safely and effectively. See full prescribing information for ENGERIX-B.

ENGERIX-B [Hepatitis B Vaccine (Recombinant)]
Suspension for Intramuscular Injection
Initial U.S. Approval: 1989

----------INDICATIONS AND USAGE----------

ENGERIX-B is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus. (1)

---------- DOSAGE AND ADMINISTRATION ----------

For intramuscular administration. (2, 2.2)

- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Persons 20 years of age and older: A series of 3 doses (1 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule. (2.3)

----------DOSAGE FORMS AND STRENGTHS ----------

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled syringes (3)
- 1-mL (20 mcg) single-dose vials and prefilled syringes (3)

---------- CONTRAINDICATIONS ----------

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)
- Temporarily defer vaccination of infants with a birth weight less than 2,000 g born to HBsAg-negative mothers. (5.3)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. (5.4)

----------ADVERSE REACTIONS----------

The most common solicited adverse events were injection-site soreness (22%) and fatigue (14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS ----------

Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial. (7.1)

---------- USE IN SPECIFIC POPULATIONS----------

- Safety and effectiveness of ENGERIX-B have not been established in pregnant women and nursing mothers. ENGERIX-B should only be given to a pregnant woman if clearly needed. (8.1, 8.3)
- Antibody responses are lower in persons older than 60 years of age than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENGERIX-B® is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons at risk of hemorrhage.

2.1 Preparation for Administration

Shake well before use. With thorough agitation, ENGERIX-B is a homogeneous, turbid white suspension. Do not administer if it appears otherwise. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

2.2 Administration

ENGERIX-B should be administered by intramuscular injection. The preferred administration site is the anterolateral aspect of the thigh for infants younger than 1 year and the deltoid muscle in older children (whose deltoid is large enough for an intramuscular injection) and adults. ENGERIX-B should not be administered in the gluteal region; such injections may result in suboptimal response.

ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g., hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in a lower antibody response. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

Do not administer this product intravenously or intradermally.

2.3 Recommended Dose and Schedule

Persons from Birth through 19 Years

Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or HBsAg-positive mothers), children (birth through 10 years), and adolescents (aged 11 through 19 years) consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

Persons Aged 20 Years and Older

Primary immunization for persons aged 20 years and older consists of a series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule.

Adults on Hemodialysis

Primary immunization consists of a series of 4 doses (2-mL each) given as a single 2-mL dose or two 1-mL doses on a 0-, 1-, 2-, and 6-month schedule. In hemodialysis patients, antibody response is lower than in healthy persons and protection may persist only as long as antibody levels remain above 10 mIU/mL. Therefore, the need for booster doses should be assessed by annual antibody testing. A 2-mL booster dose (as a single 2-mL dose or two 1-mL doses) should be given when antibody levels decline below 10 mIU/mL.[1] *[See Clinical Studies (14.2).]*

Table 1. Recommended Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of:		
HBsAg-negative mothers	0.5 mL	0, 1, 6 months
HBsAg-positive mothers[b]	0.5 mL	0, 1, 6 months
Children:		
Birth through 10 years	0.5 mL	0, 1, 6 months
Adolescents:		
Aged 11 through 19 years	0.5 mL	0, 1, 6 months
Adults:		
Aged 20 years and older	1 mL	0, 1, 6 months
Adults on hemodialysis	2 mL[c]	0, 1, 2, 6 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] Given as a single 2-mL dose or as two 1-mL doses.

2.4 Alternate Dosing Schedules

There are alternate dosing and administration schedules which may be used for specific populations (e.g., neonates born of hepatitis B–infected mothers, persons who have or might have been recently exposed to the virus, and travelers to high-risk areas) (Table 2). For some of these alternate schedules, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

Table 2. Alternate Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of:		
HBsAg-positive mothers[b]	0.5 mL	0, 1, 2, 12 months
Children:		
Birth through 10 years	0.5 mL	0, 1, 2, 12 months
Aged 5 through 10 years	0.5 mL	0, 12, 24 months[c]
Adolescents:		
Aged 11 through 16 years	0.5 mL	0, 12, 24 months[c]
Aged 11 through 19 years	1 mL	0, 1, 6 months
Aged 11 through 19 years	1 mL	0, 1, 2, 12 months
Adults:		
Aged 20 years and older	1 mL	0, 1, 2, 12 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

2.5 Booster Vaccinations

Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 0.5 mL for children aged 10 years and younger and 1 mL for persons aged 11 years and older. Studies have demonstrated a substantial increase in antibody titers after booster vaccination with ENGERIX-B. See Section 2.3 for information on booster vaccination for adults on hemodialysis.

2.6 Known or Presumed Exposure to Hepatitis B Virus

Persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers, persons who experienced percutaneous or permucosal exposure to the virus) should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance with Advisory Committee on Immunization Practices recommendations and with the package

insert for HBIG. ENGERIX-B can be given on either dosing schedule (0, 1, and 6 months or 0, 1, 2, and 12 months).

3 DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK® syringes
- 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes

[See Description (11), How Supplied/Storage and Handling (16).]

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast, is a contraindication to administration of ENGERIX-B *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Infants Weighing Less than 2,000 g at Birth

Hepatitis B vaccine should be deferred for infants with a birth weight <2,000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or hospital discharge. Infants born weighing <2,000 g to HBsAg-positive mothers should receive vaccine and HBIG within 12 hours after birth. Infants born weighing <2,000 g to mothers of unknown HBsAg status should receive vaccine and HBIG within 12 hours after birth if the mother's HBsAg status cannot be determined within the first 12 hours of life. The birth dose in infants born weighing <2,000 g should not be counted as the first dose in the vaccine series and it should be followed with a full 3-dose standard regimen (total of 4 doses).[2] *[See Dosage and Administration (2).]*

5.4 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants

born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. For ENGERIX-B, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if vaccination is delayed.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to immunization, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur. *[See Contraindications (4).]*

5.6 Moderate or Severe Acute Illness

To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine adverse effects, vaccination with ENGERIX-B should be postponed in persons with moderate or severe acute febrile illness unless they are at immediate risk of hepatitis B infection (e.g., infants born of HBsAg-positive mothers).

5.7 Altered Immunocompetence

Immunocompromised persons may have a diminished immune response to ENGERIX-B, including individuals receiving immunosuppressant therapy.

5.8 Multiple Sclerosis

Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,[3] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[4]

5.9 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. ENGERIX-B may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most common solicited adverse events were injection site soreness (22%) and fatigue (14%).

In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse events tended to decrease with successive doses of ENGERIX-B.

Using a symptom checklist, the most frequently reported adverse events were injection site soreness (22%) and fatigue (14%). Other events are listed below. Parent or guardian completed forms for children and neonates. Neonatal checklist did not include headache, fatigue, or dizziness.

Incidence 1% to 10% of Injections

Nervous System Disorders: Dizziness, headache.

General Disorders and Administration Site Conditions: Fever (>37.5°C), injection site erythema, injection site induration, injection site swelling.

Incidence <1% of Injections

Infections and Infestations: Upper respiratory tract illnesses.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Agitation, insomnia.

Nervous System Disorders: Somnolence, tingling.

Vascular Disorders: Flushing, hypotension.

Gastrointestinal Disorders: Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

Skin and Subcutaneous Tissue Disorders: Erythema, petechiae, pruritus, rash, sweating, urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia, pain/stiffness in arm, shoulder, or neck.

General Disorders and Administration Site Conditions: Chills, influenza-like symptoms, injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise, weakness.

In a clinical trial, 416 adults with type 2 diabetes and 258 control subjects without type 2 diabetes who were seronegative for hepatitis B markers received at least 1 dose of ENGERIX-B. Subjects were monitored for solicited adverse events for 4 days following each vaccination. The most frequently reported solicited adverse events in the entire study population were injection site pain (reported in 39% of diabetic subjects and 45% of control subjects) and fatigue (reported in 29% of diabetic subjects and 27% of control subjects). Serious adverse events were monitored

through 30 days following the last vaccination. Serious adverse events (SAEs) occurred in 3.8% of diabetic subjects and 1.6% of controls. No SAEs were deemed related to ENGERIX-B.

6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for ENGERIX-B since market introduction (1990) are listed below. This list includes SAEs or events that have a suspected causal connection to components of ENGERIX-B.

Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Infections and Infestations

Herpes zoster, meningitis.

Blood and Lymphatic System Disorders

Thrombocytopenia.

Immune System Disorders

Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

Nervous System Disorders

Encephalitis; encephalopathy; migraine; multiple sclerosis; neuritis; neuropathy including hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy; optic neuritis; paralysis; paresis; seizures; syncope; transverse myelitis.

Eye Disorders

Conjunctivitis, keratitis, visual disturbances.

Ear and Labyrinth Disorders

Earache, tinnitus, vertigo.

Cardiac Disorders

Palpitations, tachycardia.

Vascular Disorders

Vasculitis.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, bronchospasm including asthma-like symptoms.

Gastrointestinal Disorders

Dyspepsia.

Skin and Subcutaneous Tissue Disorders

Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome, erythema nodosum, lichen planus, purpura.

Musculoskeletal and Connective Tissue Disorders

Arthritis, muscular weakness.

General Disorders and Administration Site Conditions

Injection site reaction.

Investigations

Abnormal liver function tests.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Vaccines and Immune Globulin

ENGERIX-B may be administered concomitantly with immune globulin.

When concomitant administration of other vaccines or immune globulin is required, they should be given with different syringes and at different injection sites. Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial.

7.2 Interference with Laboratory Tests

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including ENGERIX-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with ENGERIX-B. It is also not known whether ENGERIX-B can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ENGERIX-B should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ENGERIX-B is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENGERIX-B is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ENGERIX-B have been established in all pediatric age-groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. *[See Adverse Reactions (6), Clinical Studies (14.1, 14.3, 14.4).]*

The timing of the first dose in infants weighing less than 2,000 g at birth depends on the HBsAg status of the mother. *[See Warnings and Precautions (5.3).]*

8.5 Geriatric Use

Clinical studies of ENGERIX-B used for licensure did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response and seroprotective levels can be expected in persons older than 60 years.[5] *[See Clinical Studies (14.2).]*

11 DESCRIPTION

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a sterile suspension of noninfectious hepatitis B virus surface antigen (HBsAg) for intramuscular administration. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The HBsAg expressed in the cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture ENGERIX-B result in a product that contains no more than 5% yeast protein.

Each 0.5-mL pediatric/adolescent dose contains 10 mcg of HBsAg adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Each 1-mL adult dose contains 20 mcg of HBsAg adsorbed on 0.5 mg aluminum as aluminum hydroxide.

ENGERIX-B contains the following excipients: Sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

ENGERIX-B is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

ENGERIX-B is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[1] Seroconversion is defined as antibody titers ≥1 mIU/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Efficacy in Neonates

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.[6,7] Fifty-eight neonates born of mothers who were both HBsAg-positive and hepatitis B "e" antigen (HBeAg)-positive were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 2 months, without concomitant hepatitis B immune globulin (HBIG). Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

14.2 Efficacy and Immunogenicity in Specific Populations

Homosexual Men

ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months was evaluated in homosexual men aged 16 to 59 years. Four of 244 subjects became infected with hepatitis B during the period prior to completion of the 3-dose immunization schedule. No additional subjects became infected during the 18-month follow-up period after completion of the immunization course.

Adults with Chronic Hepatitis C

In a clinical trial of 67 adults aged 25 to 67 years with chronic hepatitis C, ENGERIX-B (20 mcg/1 mL) was given at 0, 1, and 6 months. Of the subjects assessed at Month 7 (n = 31), 100% responded with seroprotective titers. The geometric mean antibody titer (GMT) was 1,260 mIU/mL (95% Confidence Interval [CI]: 709, 2,237).

Adults on Hemodialysis

Hemodialysis patients given hepatitis B vaccines respond with lower titers, which remain at protective levels for shorter durations than in normal subjects. In a clinical trial of 56 adults who had been on hemodialysis for a mean period of 56 months, ENGERIX-B (40 mcg/2 mL given as two 1-mL doses) was given at 0, 1, 2, and 6 months. Two months after the fourth dose, 67% (29/43) of patients had seroprotective antibody levels (≥10 mIU/mL) and the GMT among seroconverters was 93 mIU/mL.

Adults with Type 2 Diabetes Mellitus

In a descriptive study, 674 adult subjects with type 2 diabetes (diagnosed within the preceding 5 years) or without type 2 diabetes were enrolled and stratified by age and body mass index (BMI). The per-protocol immunogenicity cohort included 378 diabetic subjects and 189 matched control subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects, the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m^2 (range: 17 to 64 kg/m^2); 51% were male; 88% were white, 3% were American Indian or Alaskan Native, 3% were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino.

The overall seroprotection rates (1 month after the third dose) were 75% (95% CI: 71, 80) in patients with diabetes and 82% (95% CI: 76, 87) in control subjects. The seroprotection rates in those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in these same age-groups were 100%, 86%, 82%, and 70%, respectively. Subjects with diabetes and a BMI of at least 30 kg/m^2 had a seroprotection rate of 72% compared with 80% in diabetic subjects with lower BMIs. In control subjects, seroprotection rates were 82% in those with a BMI of at least 30 kg/m^2 and 83% in those with lower BMIs.

14.3 Immunogenicity in Neonates

In clinical studies, neonates were given ENGERIX-B (10 mcg/0.5 mL) at age 0, 1, and 6 months or at age 0, 1, and 2 months. The immune response to vaccination was evaluated in sera obtained 1 month after the third dose of ENGERIX-B.

Among infants administered ENGERIX-B at age 0, 1, and 6 months, 100% of evaluable subjects (n = 52) seroconverted by Month 7. The GMT was 713 mIU/mL. Of these, 97% had seroprotective levels (≥10 mIU/mL).

Among infants enrolled (n = 381) to receive ENGERIX-B at age 0, 1, and 2 months, 96% had seroprotective levels (≥10 mIU/mL) by Month 4. The GMT among seroconverters (n = 311) (antibody titer ≥1 mIU/mL) was 210 mIU/mL. A subset of these children received a fourth dose of ENGERIX-B at age 12 months. One month following this dose, seroconverters (n = 126) had a GMT of 2,941 mIU/mL.

14.4 Immunogenicity in Children and Adults

Persons Aged 6 Months through 10 Years

In clinical trials, children (N = 242) aged 6 months through 10 years were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 6 months. One to 2 months after the third dose, the seroprotection rate was 98% and the GMT of seroconverters was 4,023 mIU/mL.

Persons Aged 5 through 16 Years

In a separate clinical trial including both children and adolescents aged 5 through 16 years, ENGERIX-B (10 mcg/0.5 mL) was administered at 0, 1, and 6 months (n = 181) or 0, 12, and 24 months (n = 161). Immediately before the third dose of vaccine, seroprotection was achieved in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the 0-, 12-, and 24-month schedule (GMT: 118 mIU/mL versus 162 mIU/mL, respectively, $P = 0.18$). One month following the third dose, seroprotection was achieved in 99.5% of children vaccinated on the 0-, 1-, and 6-month schedule compared with 98.1% of those on the 0-, 12-, and 24-month schedule. GMTs were higher ($P = 0.02$) for children receiving vaccine on the 0-, 1-, and 6-month schedule compared with those on the 0-, 12-, and 24-month schedule (5,687 mIU/mL versus 3,159 mIU/mL, respectively).

Persons Aged 11 through 19 Years

In clinical trials with healthy adolescent subjects aged 11 through 19 years, ENGERIX-B (10 mcg/0.5 mL) given at 0, 1, and 6 months produced a seroprotection rate of 97% at Month 8 (n = 119) with a GMT of 1,989 mIU/mL (n = 118, 95% CI: 1,318, 3,020). Immunization with ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months produced a seroprotection rate of 99% at Month 8 (n = 122) with a GMT of 7,672 mIU/mL (n = 122, 95% CI: 5,248, 10,965).

Persons Aged 16 through 65 Years

Clinical trials in healthy adult and adolescent subjects (aged 16 through 65 years) have shown that following a course of 3 doses of ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months, the seroprotection (antibody titers ≥10 mIU/mL) rate for all individuals was 79% at Month 6 (5 months after second dose) and 96% at Month 7 (1 month after third dose); the GMT for seroconverters was 2,204 mIU/mL at Month 7 (n = 110).

An alternate 3-dose schedule (20 mcg/1 mL given at 0, 1, and 2 months) designed for certain populations (e.g., individuals who have or might have been recently exposed to the virus and travelers to high-risk areas) was also evaluated. At Month 3 (1 month after third dose), 99% of all individuals were seroprotected and remained protected through Month 12. On the alternate schedule, a fourth dose of ENGERIX-B (20 mcg/1 mL) at 12 months produced a GMT of 9,163 mIU/mL at Month 13 (1 month after fourth dose) (n = 373).

Persons Aged 40 Years and Older

Among subjects aged 40 years and older given ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months, the seroprotection rate 1 month after the third dose was 88% and the GMT for seroconverters was 610 mIU/mL (n = 50). In adults aged older than 40 years, ENGERIX-B produced anti-HBsAg antibody titers that were lower than those in younger adults.

14.5 Interchangeability with Other Hepatitis B Vaccines

A controlled study (N = 48) demonstrated that completion of a course of immunization with 1 dose of ENGERIX-B (20 mcg/1 mL) at Month 6 following 2 doses of RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)] (10 mcg) at Months 0 and 1 produced a similar GMT (4,077 mIU/mL) to immunization with 3 doses of RECOMBIVAX HB (10 mcg) at Months 0, 1, and 6 (GMT: 2,654 mIU/mL). Thus, ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.[8]

15 REFERENCES

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6. André FE, Safary A. Clinical experience with a yeast-derived hepatitis B vaccine. In: Zuckerman AJ, ed. *Viral Hepatitis and Liver Disease*. New York, NY: Alan R Liss, Inc.; 1988:1025-1030.
7. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *JAMA*. 1989;261(22):3278-3281.

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16 HOW SUPPLIED/STORAGE AND HANDLING

ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged without needles) (Preservative-Free Formulation):

10 mcg/0.5 mL Pediatric/Adolescent Dose

NDC 58160-820-01 Vial in Package of 10: NDC 58160-820-11

NDC 58160-820-43 Syringe in Package of 10: NDC 58160-820-52

20 mcg/mL Adult Dose

NDC 58160-821-01 Vial in Package of 10: NDC 58160-821-11

NDC 58160-821-05 Syringe in Package of 1: NDC 58160-821-34

NDC 58160-821-43 Syringe in Package of 10: NDC 58160-821-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen. Do not dilute to administer.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of immunization with ENGERIX-B.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential side effects, that ENGERIX-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their healthcare provider.
- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, US License No. 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

ENG:56PI

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GARDASIL 9 safely and effectively. See full prescribing information for GARDASIL 9.

GARDASIL®9
(Human Papillomavirus 9-valent Vaccine, Recombinant)
Suspension for intramuscular injection
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.1)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS). (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1. (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.1)

GARDASIL 9 is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.2)

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

Limitations of Use and Effectiveness:

- GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3, 17)
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider. (1.3, 17)
- GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity. (1.3)
- GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN. (1.3)
- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 does not protect against genital diseases not caused by HPV. (1.3)
- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients. (1.3)
- Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age. (1.3)

----------DOSAGE AND ADMINISTRATION----------

For intramuscular administration only. (2)

Each dose of GARDASIL 9 is 0.5-mL
Administer GARDASIL 9 as follows: (2.1)

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 26 years	3-dose	0, 2, 6 months

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. (14.2 and 14.5)

----------DOSAGE FORMS AND STRENGTHS----------

0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

----------CONTRAINDICATIONS----------

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL®. (4, 11)

---------- WARNINGS AND PRECAUTIONS ----------

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

---------- ADVERSE REACTIONS ----------

The most common (≥10%) local and systemic adverse reactions reported:

- In girls and women 16 through 26 years of age: injection-site pain (89.9%), injection-site swelling (40.0%), injection-site erythema (34.0%) and headache (14.6%). (6.1)
- In girls 9 through 15 years of age: injection-site pain (89.3%), injection-site swelling (47.8%), injection-site erythema (34.1%) and headache (11.4%). (6.1)
- In boys and men 16 through 26 years of age: injection-site pain (63.4%), injection-site swelling (20.2%) and injection-site erythema (20.7%). (6.1)
- In boys 9 through 15 years of age: injection-site pain (71.5%), injection-site swelling (26.9%), and injection-site erythema (24.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy registry: available at 1-800-986-8999. (8.1)

Safety and effectiveness of GARDASIL 9 have not been established in the following populations:

- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL 9 may be diminished. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Girls and Women

GARDASIL®9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.2 Boys and Men

GARDASIL 9 is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

1.3 Limitations of Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care. *[See Patient Counseling Information (17).]*

Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider *[see Patient Counseling Information (17)].*

GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Each dose of GARDASIL 9 is 0.5-mL.
Administer GARDASIL 9 as follows:

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months*
	3-dose	0, 2, 6 months
15 through 26 years	3-dose	0, 2, 6 months

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose. *[See Clinical Studies (14.2 and 14.5).]*

2.2 Method of Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL 9 should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL 9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

Administer GARDASIL 9 intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Observe patients for 15 minutes after administration *[see Warnings and Precautions (5)].*

Single-Dose Vial Use

Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

Prefilled Syringe Use

This package does not contain a needle. Shake well before use. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

2.3 Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL®

Safety and immunogenicity were assessed in individuals who completed a three-dose vaccination series with GARDASIL 9 and had previously completed a three-dose vaccination series with GARDASIL *[see Adverse Reactions (6.1) and Clinical Studies (14.4)].* Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.

3 DOSAGE FORMS AND STRENGTHS

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL *[see Description (11)].*

5 WARNINGS AND PRECAUTIONS

5.1 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL 9.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of GARDASIL 9 was evaluated in seven clinical studies that included 15,703 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also included 7,378 individuals who received at least one dose of GARDASIL as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 9,097 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age, and 5,212 girls and boys 9 through 15 years of age (3,436 girls and 1,776 boys) at enrollment who received GARDASIL 9; and 7,078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL. The race distribution of the integrated safety population for GARDASIL 9 was similar between girls and women 16 through 26 years of age (56.8% White; 25.2% Other Races or Multiracial; 14.1% Asian; 3.9% Black), girls and boys 9 through 15 years of age (62.0% White; 19.2% Other Races or Multiracial; 13.5% Asian; 5.4% Black), and boys and men 16 through 26 years of age (62.1% White; 22.6% Other Races or Multiracial; 9.8% Asian; 5.5% Black). The safety of GARDASIL 9 was compared directly to the safety of GARDASIL in two studies (Study 1 and Study 3) for which the overall race distribution of the GARDASIL cohorts (57.0% White; 26.3% Other Races or Multiracial; 13.6% Asian; 3.2% Black) was similar to that of the GARDASIL 9 cohorts.

Injection-Site and Systemic Adverse Reactions

Injection-site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for five days after each injection of GARDASIL 9 during the clinical studies. The rates and severity of these solicited adverse reactions that occurred within five days following each dose of GARDASIL 9 compared with GARDASIL in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL 9. Recipients of GARDASIL 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL.

Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	**N=7069**	**N=6997**	**N=6909**	**N=7071**	**N=7076**	**N=6992**	**N=6909**	**N=7078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
Systemic Adverse Reactions	**n=6995**	**n=6913**	**n=6743**	**n=7022**	**n=7003**	**n=6914**	**n=6725**	**n=7024**
Temperature ≥100°F	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥102°F	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	**N=300**	**N=297**	**N=296**	**N=299**	**N=299**	**N=299**	**N=294**	**N=300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	**n=300**	**n=294**	**n=295**	**n=299**	**n=299**	**n=297**	**n=291**	**n=300**
Temperature ≥100°F	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥102°F	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).
N=number of subjects vaccinated with safety follow-up
n=number of subjects with temperature data
Pain, Any=mild, moderate, severe or unknown intensity
Pain, Severe=incapacitating with inability to work or do usual activity
Swelling, Any=any size or size unknown
Swelling, Severe=maximum size greater than 2 inches
Erythema, Any=any size or size unknown
Erythema, Severe=maximum size greater than 2 inches

Unsolicited injection-site and systemic adverse reactions (assessed as vaccine-related by the investigator) observed among recipients of either GARDASIL 9 or GARDASIL in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%).

Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among ≥1.0% of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	Girls and Women 16 through 26 Years of Age		Girls 9 through 15 Years of Age	
	GARDASIL 9 N=7071	**GARDASIL N=7078**	**GARDASIL 9 N=299**	**GARDASIL N=300**
Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	0.7
Abdominal pain, upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).
N=number of subjects vaccinated with safety follow-up

In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL 9 were similar between boys and girls. Rates of solicited and unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3.

In another uncontrolled clinical trial with 1,394 boys and men and 1,075 girls and women 16 through 26 years of age (Study 7), the rates of solicited and unsolicited adverse reactions following each dose of GARDASIL 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of solicited and unsolicited adverse reactions reported by boys and men 16 through 26 years of age in this study are shown in Table 3.

Table 3: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 Years of Age Who Received GARDASIL 9 (Studies 2 and 7)

	GARDASIL 9
Boys and Men 16 through 26 Years of Age	**N=1394**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain, Any	63.4
Injection-Site Pain, Severe	0.6
Injection-Site Erythema, Any	20.7
Injection-Site Erythema, Severe	0.4
Injection-Site Swelling, Any	20.2
Injection-Site Swelling, Severe	1.1
Oral Temperature ≥100.0°F[†]	4.4
Oral Temperature ≥102°F	0.6
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hypersensitivity	1.0
Injection-Site Pruritus	1.0
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	7.3
Pyrexia	2.4
Fatigue	1.4
Dizziness	1.1
Nausea	1.0
Boys 9 through 15 Years of Age	**N=639**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain, Any	71.5
Injection-Site Pain, Severe	0.5
Injection-Site Erythema, Any	24.9
Injection-Site Erythema, Severe	1.9
Injection-Site Swelling, Any	26.9
Injection-Site Swelling, Severe	5.2
Oral Temperature ≥100.0°F[†]	10.4
Oral Temperature ≥102°F	1.4
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hematoma	1.3
Injection-Site Induration	1.1
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	9.4
Pyrexia	8.9
Nausea	1.3

The data for GARDASIL 9 boys 9 through 15 years of age are from Study 2 (NCT00943722). The data for boys and men 16 through 26 years of age for GARDASIL 9 are from Study 7 (NCT01651949).
*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjects vaccinated with safety follow-up
[†]For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N=637; for boys and men 16 through 26 years of age N=1,386
Pain, Any=mild, moderate, severe or unknown intensity
Pain, Severe=incapacitating with inability to work or do usual activity
Swelling, Any=any size or size unknown
Swelling, Severe=maximum size greater than 2 inches
Erythema, Any=any size or size unknown
Erythema, Severe=maximum size greater than 2 inches

Serious Adverse Events in Clinical Studies

Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the seven clinical studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 354 reported a serious adverse event; representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing 2.5% of the population. Four GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, and headache.

Deaths in the Entire Study Population

Across the clinical studies, ten deaths occurred (five each in the GARDASIL 9 and GARDASIL groups); none were assessed as vaccine-related. Causes of death in the GARDASIL 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypovolemic septic shock, and one unexplained sudden death 678 days following the last dose of GARDASIL 9. Causes of death in the GARDASIL control group included one automobile accident, one airplane crash, one cerebral hemorrhage, one gunshot wound, and one stomach adenocarcinoma.

Systemic Autoimmune Disorders

In all of the clinical trials with GARDASIL 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of GARDASIL 9 recipients and 3.3% (240/7,378) of GARDASIL recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL, AAHS control, or saline placebo in historical clinical trials.

Clinical Trials Experience for GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

A clinical study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with three doses of GARDASIL. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL (Tables 1 and 4).

Table 4: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age) (Study 4)

	GARDASIL 9 N=608	Saline Placebo N=305
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature ≥100.0°F†	6.5	3.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

The data for GARDASIL 9 and saline placebo are from Study 4 (NCT01047345).
*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjects vaccinated with safety follow-up
†For oral temperature: number of subjects with temperature data GARDASIL 9 N=604; Saline Placebo N=304

Safety in Concomitant Use with Menactra and Adacel

In Study 5, the safety of GARDASIL 9 when administered concomitantly with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years *[see Clinical Studies (14.6)]*.

Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection-site adverse reactions. The rates of injection-site adverse reactions were similar between the concomitant group and non-concomitant group (vaccination with GARDASIL 9 separated from vaccination with Menactra and Adacel by 1 month) with the exception of an increased rate of swelling reported at the injection site for GARDASIL 9 in the concomitant group (14.4%) compared to the non-concomitant group (9.4%). The majority of injection-site swelling adverse reactions were reported as being mild to moderate in intensity.

6.2 Post-Marketing Experience

There is limited post-marketing experience following administration of GARDASIL 9. However, the post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain the same antigens from HPV types 6, 11, 16, and 18. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure. The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL and may also be seen in post-marketing experience with GARDASIL 9:

Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.

Gastrointestinal disorders: Nausea, pancreatitis, vomiting.

General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise.

Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-

clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Infections and infestations: Cellulitis.

Vascular disorders: Deep venous thrombosis.

7 DRUG INTERACTIONS

7.1 Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines *[see Use in Specific Populations (8.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to GARDASIL 9 during pregnancy. To enroll in or obtain information about the registry, call Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-800-986-8999.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of GARDASIL 9 in pregnant women. Available human data do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when GARDASIL 9 is administered during pregnancy.

In one developmental toxicity study, 0.5 mL of a vaccine formulation containing between 1 and 1.5 – fold of each of the 9 HPV antigen types was administered to female rats prior to mating and during gestation. In another study, animals were administered a single human dose (0.5 mL) of GARDASIL 9 prior to mating, during gestation and during lactation. These animal studies revealed no evidence of harm to the fetus due to GARDASIL 9 *[see Data]*.

Data

Human Data

In pre-licensure clinical studies of GARDASIL 9, women underwent pregnancy testing immediately prior to administration of each dose of GARDASIL 9 or control vaccine (GARDASIL). (Data from GARDASIL are relevant to GARDASIL 9 because both vaccines are manufactured using the same process and have overlapping compositions.) Subjects who were determined to be pregnant were instructed to defer vaccination until the end of their pregnancy. Despite this pregnancy screening regimen, some subjects were vaccinated very early in pregnancy before human chorionic gonadotropin (HCG) was detectable. An analysis was conducted to evaluate pregnancy outcomes for pregnancies with onset within 30 days before or after vaccination with GARDASIL 9 or GARDASIL. Among such pregnancies, there were 62 and 55 with known outcomes (excluding ectopic pregnancies and elective terminations) for GARDASIL 9 and GARDASIL, respectively, including 44 and 48 live births, respectively. The rates of pregnancies that resulted in a miscarriage were 27.4% (17/62) and 12.7% (7/55) in subjects who received GARDASIL 9 or GARDASIL, respectively. The rates of live births with major birth defects were 0% (0/44) and 2.1% (1/48) in subjects who received GARDASIL 9 or GARDASIL, respectively.

A five-year pregnancy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 2,566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates.

In two post-marketing studies of GARDASIL (one conducted in the U.S., and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL during pregnancy were evaluated retrospectively. Among the 1,740 pregnancies included in the U.S. study database, outcomes

were available to assess the rates of major birth defects and miscarriage. Among the 499 pregnancies included in the Nordic study database, outcomes were available to assess the rates of major birth defects. In both studies, rates of assessed outcomes did not suggest an increased risk with the administration of GARDASIL during pregnancy.

Animal Data

Developmental toxicity studies were conducted in female rats. In one study, animals were administered 0.5 mL of a vaccine formulation containing between 1 and 1.5 –fold of each of the 9 HPV antigen types 5 and 2 weeks prior to mating, and on gestation day 6. In a second study, animals were administered a single human dose (0.5 mL of GARDASIL 9) 5 and 2 weeks prior to mating, on gestation day 6, and on lactation day 7. No adverse effects on pre- and post-weaning development were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

Available data are not sufficient to assess the effects of GARDASIL 9 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GARDASIL 9 and any potential adverse effects on the breastfed child from GARDASIL 9 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

8.5 Geriatric Use

The safety and effectiveness of GARDASIL 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

8.6 Immunocompromised Individuals

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals *[see Drug Interactions (7.1)]*.

11 DESCRIPTION

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL 9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein.

Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL 9 has not been evaluated for the potential to cause carcinogenicity, genotoxicity or impairment of male fertility. GARDASIL 9 administered to female rats had no effects on fertility *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre-specified serostatus cutoff for a given HPV type. The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of competitive Luminex Immunoassay (cLIA). The lower limits of quantification and serostatus cutoffs for each of the 9 vaccine HPV types are shown in Table 5 below. PCR positive is defined as DNA detected for a given HPV type. PCR negative is defined as DNA not detected for a given HPV type. The lower limit of detection for the multiplexed HPV PCR assays ranged from 5 to 34 copies per test across the 9 vaccine HPV types.

Table 5: Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL 9 HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/mL)	cLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

*mMU=milli-Merck Units

14.1 Efficacy and Effectiveness Data for GARDASIL

Efficacy and effectiveness of GARDASIL are relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain four of the same HPV L1 VLPs.

Individuals 16 through 26 Years of Age

Efficacy of GARDASIL was assessed in five AAHS-controlled, double-blind, randomized clinical trials evaluating 24,596 individuals 16 through 26 years of age (20,541 girls and women and 4,055 boys and men). The results of these trials are shown in Table 6 below.

Table 6: Analysis of Efficacy of GARDASIL in the PPE* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

*The PPE population consisted of individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7).
†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N=Number of individuals with at least one follow-up visit after Month 7
CI=Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: Table 6 does not include cases due to HPV types not covered by the vaccine.
AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate, CIN = Cervical Intraepithelial Neoplasia, VIN = Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, PIN=Penile Intraepithelial Neoplasia, AIN=Anal Intraepithelial Neoplasia, AIS=Adenocarcinoma *In Situ*

In an extension study in females 16 through 26 years of age at enrollment, prophylactic efficacy of GARDASIL through Month 60 against overall cervical and genital disease related to HPV 6, 11, 16, and 18 was 100% (95% CI: 12.3%, 100%) compared to AAHS control.

An extension study in girls and women 16 through 23 years of age used national healthcare registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaccination with GARDASIL. An interim analysis of the per-protocol effectiveness population included 1,902 subjects who completed the GARDASIL vaccination series within one year, were naïve to the relevant HPV type through 1 month post-dose 3, had no protocol violations, and had follow-up data available. The median follow-up from the first dose of vaccine was 6.7 years with a range of 2.8 to 8.4 years. At the time of interim analysis, no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed over a total of 5,765 person-years at risk.

Girls and Boys 9 through 15 Years of Age

An extension study of 614 girls and 565 boys 9 through 15 years of age at enrollment who were randomized to vaccination with GARDASIL actively followed subjects for endpoint cases of HPV 6-, 11-, 16-, or 18-related persistent infection, CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, and external genital lesions from the initiation of sexual activity or age 16 onwards. An interim analysis of the per-protocol effectiveness population included 246 girls and 168 boys who completed the GARDASIL vaccination series within one year, were seronegative to the relevant HPV type at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of GARDASIL. The median follow-up from the first dose of vaccine was 7.2 years with a range of

0.5 to 8.5 years. At the time of interim analysis, no cases of persistent infection of at least 12 months' duration and no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, or external genital lesions were observed over a total 1,105 person-years at risk. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of which persisted to 12 months' duration.

Women 27 through 45 Years of Age

A clinical trial evaluated efficacy of GARDASIL in 3,253 women 27 through 45 years of age, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy estimate for the combined endpoint was driven primarily by prevention of persistent infection. No statistically significant efficacy was demonstrated for GARDASIL in prevention of cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3), adenocarcinoma *in situ* (AIS) or cervical cancer related to HPV types 16 and 18.

14.2 Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL 9 were assessed in six clinical trials. Study 1 evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

The analysis of efficacy for GARDASIL 9 was evaluated in the per-protocol efficacy (PPE) population of 16- through 26-year-old girls and women, who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR negative for the relevant HPV type(s) through one month post-dose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma *in situ* (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar and vaginal disease of any grade, persistent infection, cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated compared with GARDASIL. Efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine.

Effectiveness against disease caused by HPV Types 6, 11, 16, and 18 was assessed by comparison of geometric mean titers (GMTs) of type-specific antibodies following vaccination with GARDASIL 9 with those following vaccination with GARDASIL (Study 1 and Study 3). The effectiveness of GARDASIL 9 in girls and boys 9 through 15 years old and in boys and men 16 through 26 years old was inferred based on a comparison of type-specific antibody GMTs to those of 16 through 26-year-old girls and women following vaccination with GARDASIL 9. Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met pre-defined day range for serum collection for assessment of antibody response and were naïve [PCR negative (in girls and women 16 through 26 years of age; Studies 1 and 2) and seronegative (Studies 1, 2, 3, 5, 7 and 8)] to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women (Studies 1 and 2) remained PCR negative to the relevant HPV type(s) through Month 7. Pre-defined day ranges for vaccinations were relative to Day 1 (dose 1). For the 3-dose schedule, dose 2 was at 2 months (± 3 weeks) and dose 3 was at 6 months (± 4 weeks). For the 2-dose schedule, dose 2 was at 6 or 12 months (± 4 weeks). Pre-defined day range for serum collection for assessment of antibody response was 21 to 49 days after the last dose.

Study 1 evaluated immunogenicity of GARDASIL 9 and efficacy to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women.

Study 2 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogenicity of GARDASIL 9 compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL. Study 5 evaluated GARDASIL 9 concomitantly administered with Menactra and Adacel in girls and boys 11 through 15 years of age. Together, these five clinical trials evaluated 12,233 individuals who received GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years. Study 7 evaluated immunogenicity of GARDASIL 9 in boys and men, including 1,106 self-identified as heterosexual men (HM) and 313 self-identified as men having sex with men (MSM), 16 through 26 years of age at enrollment (mean ages 20.8 years and 22.2 years, respectively) and 1,101 girls and women 16 through 26 years of age at enrollment (mean age 21.3 years).

The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.8% White; 25.2% Other; 14.1% Asian; and 3.9% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% Black. The race distribution of the 16- through 26-year-old boys and men in the clinical trials was as follows: 62.1% White; 22.6% Other; 9.8% Asian; and 5.5% Black.

One clinical trial (Study 8) assessed the 2-dose regimen of GARDASIL 9. Study 8 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and women 16 through 26 years of age; (N=1,518; 753 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years. In Study 8, the race distribution was as follows: 61.1% White; 16.3% Asian; 13.3% Other; and 8.9% Black.

14.3 Efficacy – HPV Types 31, 33, 45, 52 and 58 in Girls and Women 16 through 26 Years of Age

Studies Supporting the Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58

The efficacy of GARDASIL 9 in 16- through 26-year-old girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105) who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaccination.

The primary efficacy evaluation was conducted in the PPE population based on a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58-related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. Efficacy was further evaluated with the clinical endpoints of HPV 31-, 33-, 45-, 52-, and 58-related CIN 1, vulvar and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58-related abnormal Papanicolaou (Pap) tests, cervical and external genital biopsy, and definitive therapy [including loop electrosurgical excision procedure (LEEP) and conization]. Efficacy for all endpoints was measured starting after the Month 7 visit.

GARDASIL 9 prevented HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease and also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital biopsy, and definitive therapy (Table 7).

Table 7: Analysis of Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population of 16- through 26-Year-old Girls and Women (Study 1)

Disease Endpoint	GARDASIL 9 N†=7099		GARDASIL N†=7105		GARDASIL 9 Efficacy % (95% CI)
	n‡	Number of cases	n‡	Number of cases	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6016	1	6017	30	96.7 (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5948	1	5943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5948	1	5943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6009	1	6012	16	93.8 (61.5, 99.7)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months§	5939	26	5953	642	96.2 (94.4, 97.5)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months¶	5939	15	5953	375	96.1 (93.7, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap# Abnormality	5881	35	5882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6016	7	6017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapyᵖ	6012	4	6014	32	87.5 (65.7, 96.0)

*The PPE population consisted of individuals who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7); data from Study 1 (NCT00543543).
†N=Number of individuals randomized to the respective vaccination group who received at least one injection
‡n=Number of individuals contributing to the analysis
§Persistent infection detected in samples from two or more consecutive visits at least six months apart
¶Persistent infection detected in samples from two or more consecutive visits over 12 months or longer
#Papanicolaou test
ᵖIncluding loop electrosurgical excision procedure (LEEP) and conization
CI=Confidence Interval
CIN=Cervical Intraepithelial Neoplasia, VIN=Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, AIS=Adenocarcinoma *In Situ*, ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk

14.4 Immunogenicity of a 3-Dose Regimen

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Type-specific immunoassays (i.e., cLIA) with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate. Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18

Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaccination with GARDASIL 9 with those following vaccination with GARDASIL. A low number of efficacy endpoint cases related to HPV types 6, 11, 16 and 18 in both vaccination groups precluded a meaningful assessment of efficacy using disease endpoints associated with these HPV types. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7.

Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 through 26 years of age were non-inferior to those among the corresponding populations for GARDASIL (Table 8). At least 99.7% of individuals included in the analyses for each HPV type became seropositive by Month 7.

Table 8: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the PPI* Population of 9- through 26-Year-Old Girls and Women (Studies 1 and 3)

Population	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N† (n‡)	GMT mMU§/mL	N† (n‡)	GMT mMU§/mL	GMT Ratio	(95% CI)¶
Anti-HPV 6						
9- through 15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	893.1	6795 (3975)	875.2	1.02	(0.99, 1.06)
Anti-HPV 11						
9- through 15-year-old girls	300 (273)	1315.6	300 (261)	1417.3	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	666.3	6795 (3982)	830.0	0.80	(0.77, 0.83)
Anti-HPV 16						
9- through 15-year-old girls	300 (276)	6739.5	300 (270)	6887.4	0.97	(0.85, 1.11)
16- through 26-year-old girls and women	6792 (4032)	3131.1	6795 (4062)	3156.6	0.99	(0.96, 1.03)
Anti-HPV 18						
9- through 15-year-old girls	300 (276)	1956.6	300 (269)	1795.6	1.08	(0.91, 1.29)
16- through 26-year-old girls and women	6792 (4539)	804.6	6795 (4541)	678.7	1.19	(1.14, 1.23)

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Study 1 (NCT00543543), and the data for 9- through 15-year-old girls are from Study 3 (NCT01304498).
†N=Number of individuals randomized to the respective vaccination group who received at least one injection
‡n=Number of individuals contributing to the analysis
§mMU=milli-Merck Units
¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
CI=Confidence Interval
GMT=Geometric Mean Titer
cLIA=competitive Luminex Immunoassay

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison conducted in the PPI population in Study 2 of GMTs following vaccination with GARDASIL 9 among 9- through 15-year-old girls and boys with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 9).

Table 9: Comparison of Immune Responses (Based on cLIA) between the PPI* Populations of 16- through 26-Year-Old Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL 9 Vaccine HPV Types (Study 2)

Population	N†	n‡	GMT mMU§/mL	GMT Ratio relative to 16- through 26-year-old girls and women (95% CI)¶
Anti-HPV 6				
9- through 15-year-old girls	630	503	1703.1	1.89 (1.68, 2.12)
9- through 15-year-old boys	641	537	2083.4	2.31 (2.06, 2.60)

16- through 26-year-old girls and women	463	328	900.8	1
Anti-HPV 11				
9- through 15-year-old girls	630	503	1291.5	1.83 (1.63, 2.05)
9- through 15-year-old boys	641	537	1486.3	2.10 (1.88, 2.36)
16- through 26-year-old girls and women	463	332	706.6	1
Anti-HPV 16				
9- through 15-year-old girls	630	513	6933.9	1.97 (1.75, 2.21)
9- through 15-year-old boys	641	546	8683.0	2.46 (2.20, 2.76)
16- through 26-year-old girls and women	463	329	3522.6	1
Anti-HPV 18				
9- through 15-year-old girls	630	516	2148.3	2.43 (2.12, 2.79)
9- through 15-year-old boys	641	544	2855.4	3.23 (2.83, 3.70)
16- through 26-year-old girls and women	463	345	882.7	1
Anti-HPV 31				
9- through 15-year-old girls	630	506	1894.7	2.51 (2.21, 2.86)
9- through 15-year-old boys	641	543	2255.3	2.99 (2.63, 3.40)
16- through 26-year-old girls and women	463	340	753.9	1
Anti-HPV 33				
9- through 15-year-old girls	630	518	985.8	2.11 (1.88, 2.37)
9- through 15-year-old boys	641	544	1207.4	2.59 (2.31, 2.90)
16- through 26-year-old girls and women	463	354	466.8	1
Anti-HPV 45				
9- through 15-year-old girls	630	518	707.7	2.60 (2.25, 3.00)
9- through 15-year-old boys	641	547	912.1	3.35 (2.90, 3.87)
16- through 26-year-old girls and women	463	368	272.2	1
Anti-HPV 52				
9- through 15-year-old girls	630	517	962.2	2.21 (1.96, 2.49)
9- through 15-year-old boys	641	545	1055.5	2.52 (2.22, 2.84)
16- through 26-year-old girls and women	463	337	419.6	1
Anti-HPV 58				
9- through 15-year-old girls	630	516	1288.0	2.18 (1.94, 2.46)
9- through 15-year-old boys	641	544	1593.3	2.70 (2.40, 3.03)
16- through 26-year-old girls and women	463	332	590.5	1

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative [among 16- through 26-year old girls and women] and seronegative) to the relevant HPV type(s) prior to dose 1 and among 16- through 26-year-old girls and women remained PCR negative to the relevant HPV types through one month post-dose 3 (Month 7). The data are from Study 2 (NCT00943722).

†N=Number of individuals randomized to the respective vaccination group who received at least one injection

‡n=Number of individuals contributing to the analysis

§mMU=milli-Merck Units

¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titer

Study Supporting the Effectiveness of GARDASIL 9 against Vaccine HPV Types in 16- through 26-Year-Old Boys and Men

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority comparison conducted in the PPI population in Study 7 of GMTs following vaccination with GARDASIL 9 among 16- through 26-year-old HM with those among 16- through 26-year-old girls and women. Anti-HPV GMTs at Month 7 among 16- through 26-year-old HM were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 10). Study 7 also enrolled 313 16- through 26-year-old HIV-negative MSM. At Month 7, anti-HPV GMT ratios for MSM relative to HM ranged from 0.6 to 0.8, depending on HPV type. The GMT ratios for MSM relative to HM were generally similar to those previously observed in clinical trials with GARDASIL.

Table 10: Comparison of Immune Responses (Based on cLIA) between the PPI* Populations of 16- through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men Self-Identified as Heterosexual (HM) for All GARDASIL 9 Vaccine HPV Types (Study 7)

Population	N[†]	n[‡]	GMT mMU[§]/mL	GMT Ratio relative to 16- through 26-year-old girls and women (95% CI)[¶]
Anti-HPV 6				
16- through 26-year-old HM	1103	847	782.0	1.11 (1.02, 1.21)
16- through 26-year-old girls and women	1099	708	703.9	1
Anti-HPV 11				
16- through 26-year-old HM	1103	851	616.7	1.09 (1.00, 1.19)
16- through 26-year-old girls and women	1099	712	564.9	1
Anti-HPV 16				
16- through 26-year-old HM	1103	899	3346.0	1.20 (1.10, 1.30)
16- through 26-year-old girls and women	1099	781	2788.3	1
Anti-HPV 18				
16- through 26-year-old HM	1103	906	808.2	1.19 (1.08, 1.31)
16- through 26-year-old girls and women	1099	831	679.8	1
Anti-HPV 31				
16- through 26-year-old HM	1103	908	708.5	1.24 (1.13, 1.37)
16- through 26-year-old girls and women	1099	826	570.1	1
Anti-HPV 33				
16- through 26-year-old HM	1103	901	384.8	1.19 (1.10, 1.30)
16- through 26-year-old girls and women	1099	853	322.0	1
Anti-HPV 45				
16- through 26-year-old HM	1103	909	235.6	1.27 (1.14, 1.41)
16- through 26-year-old girls and women	1099	871	185.7	1
Anti-HPV 52				
16- through 26-year-old HM	1103	907	386.8	1.15 (1.05, 1.26)
16- through 26-year-old girls and women	1099	849	335.2	1
Anti-HPV 58				
16- through 26-year-old HM	1103	897	509.8	1.25 (1.14, 1.36)
16- through 26-year-old girls and women	1099	839	409.3	1

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Study 7 (NCT01651949).

[†]Number of individuals randomized to the respective vaccination group who received at least one injection

[‡]Number of individuals contributing to the analysis

[§]mMU=milli-Merck Units

[¶]Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

cLIA=competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titer

Immune Response to GARDASIL 9 across All Clinical Trials

Across all clinical trials, at least 99.5% of individuals included in the analyses for each of the nine vaccine HPV types became seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys and 16- through 26-year-old boys and men were comparable to anti-HPV responses among 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL 9.

Persistence of Immune Response to GARDASIL 9

The duration of immunity following a 3-dose schedule of vaccination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for each vaccine HPV type occurred at Month 7. Proportions of individuals who remained seropositive to each vaccine HPV type at Month 24 were similar to the corresponding seropositive proportions at Month 7.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Study 4 evaluated the immunogenicity of 3 doses of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with 3 doses of GARDASIL. Prior to enrollment in the study, over 99% of subjects had received three injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaccinated with GARDASIL were 25-63% of the GMTs in the combined populations from Studies 1, 2, 3, and 5, who had not previously received GARDASIL, although the clinical relevance of these differences is unknown. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

Concomitant Use of Hormonal Contraceptives

Among 7,269 female recipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of clinical studies 1 and 2. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

14.5 Immune Responses to GARDASIL 9 Using a 2-Dose Regimen in Individuals 9 through 14 Years of Age

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 14-year-old girls and boys who received a 2-dose regimen was inferred from non-inferiority comparison conducted in the PPI population in Study 8 of GMTs following vaccination with GARDASIL 9 among 9- through 14-year-old girls and boys who received a 2-dose regimen (at 0, 6 months or 0, 12 months) with those among 16- through 26-year-old girls and women who received a 3-dose regimen (at 0, 2, 6 months). Anti-HPV GMTs at one month after the last dose among 9- through 14-year-old girls and boys who received 2 doses of GARDASIL 9 were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women who received 3 doses of GARDASIL 9 (Table 11).

One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types (Table 11).

In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 11). The clinical relevance of these findings is unknown.

Duration of immunity of a 2-dose schedule of GARDASIL 9 has not been established.

Table 11: Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population at One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses† or 3 Doses† of GARDASIL 9 (Study 8)

Population (Regimen)	N	n	GMT mMU‡/mL	GMT Ratio relative to 3-dose regimen in 16- through 26-year-old girls and women (95% CI)
Anti-HPV 6				
9- to 14-year-old girls (0, 6)†	301	258	1657.9	2.15 (1.83, 2.53)§
9- to 14-year-old boys (0, 6)†	301	263	1557.4	2.02 (1.73, 2.36)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2678.8	3.47 (2.93, 4.11)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1496.1	1.94 (1.65, 2.29)¶
16- to 26-year-old women (0, 2, 6)†	314	238	770.9	1
Anti-HPV 11				
9- to 14-year-old girls (0, 6)†	301	258	1388.9	2.39 (2.03, 2.82)§
9- to 14-year-old boys (0, 6)†	301	264	1423.9	2.45 (2.09, 2.88)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2941.8	5.07 (4.32, 5.94)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1306.3	2.25 (1.90, 2.66)¶
16- to 26-year-old women (0, 2, 6)†	314	238	580.5	1
Anti-HPV 16				
9- to 14-year-old girls (0, 6)†	301	272	8004.9	2.54 (2.14, 3.00)§
9- to 14-year-old boys (0, 6)†	301	273	8474.8	2.69 (2.29, 3.15)§
9- to 14-year-old girls and boys (0, 12)†	300	264	14329.3	4.54 (3.84, 5.37)§
9- to 14-year-old girls (0, 2, 6)†	300	269	6996.0	2.22 (1.89, 2.61)¶
16- to 26-year-old women (0, 2, 6)†	314	249	3154.0	1
Anti-HPV 18				
9- to 14-year-old girls (0, 6)†	301	272	1872.8	2.46 (2.05, 2.96)§
9- to 14-year-old boys (0, 6)†	301	272	1860.9	2.44 (2.04, 2.92)§
9- to 14-year-old girls and boys (0, 12)†	300	266	2810.4	3.69 (3.06, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	270	2049.3	2.69 (2.24, 3.24)¶
16- to 26-year-old women (0, 2, 6)†	314	267	761.5	1
Anti-HPV 31				
9- to 14-year-old girls (0, 6)†	301	272	1436.3	2.51 (2.10, 3.00)§
9- to 14-year-old boys (0, 6)†	301	271	1498.2	2.62 (2.20, 3.12)§
9- to 14-year-old girls and boys (0, 12)†	300	268	2117.5	3.70 (3.08, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	271	1748.3	3.06 (2.54, 3.67)¶
16- to 26-year-old women (0, 2, 6)†	314	264	572.1	1
Anti-HPV 33				
9- to 14-year-old girls (0, 6)†	301	273	1030.0	2.96 (2.50, 3.50)§
9- to 14-year-old boys (0, 6)†	301	271	1040.0	2.99 (2.55, 3.50)§
9- to 14-year-old girls and boys (0, 12)†	300	269	2197.5	6.31 (5.36, 7.43)§
9- to 14-year-old girls (0, 2, 6)†	300	275	796.4	2.29 (1.95, 2.68)¶
16- to 26-year-old women (0, 2, 6)†	314	279	348.1	1
Anti-HPV 45				
9- to 14-year-old girls (0, 6)†	301	274	357.6	1.67 (1.38, 2.03)§
9- to 14-year-old boys (0, 6)†	301	273	352.3	1.65 (1.37, 1.99)§
9- to 14-year-old girls and boys (0, 12)†	300	268	417.7	1.96 (1.61, 2.37)§
9- to 14-year-old girls (0, 2, 6)†	300	275	661.7	3.10 (2.54, 3.77)¶
16- to 26-year-old women (0, 2, 6)†	314	280	213.6	1
Anti-HPV 52				
9- to 14-year-old girls (0, 6)†	301	272	581.1	1.60 (1.36, 1.87)§
9- to 14-year-old boys (0, 6)†	301	273	640.4	1.76 (1.51, 2.05)§
9- to 14-year-old girls and boys (0, 12)†	300	268	1123.4	3.08 (2.64, 3.61)§
9- to 14-year-old girls (0, 2, 6)†	300	275	909.9	2.50 (2.12, 2.95)¶
16- to 26-year-old women (0, 2, 6)†	314	271	364.2	1
Anti-HPV 58				
9- to 14-year-old girls (0, 6)†	301	270	1251.2	2.55 (2.15, 3.01)§
9- to 14-year-old boys (0, 6)†	301	270	1325.7	2.70 (2.30, 3.16)§
9- to 14-year-old girls and boys (0, 12)†	300	265	2444.6	4.98 (4.23, 5.86)§
9- to 14-year-old girls (0, 2, 6)†	300	273	1229.3	2.50 (2.11, 2.97)¶

16- to 26-year-old women (0, 2, 6)[†]	314	261	491.1	1

*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.

[†]2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).

[‡]mMU=milli-Merck Units

[§]Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

[¶]Exploratory analysis; criterion for non-inferiority was not pre-specified

N = Number of individuals randomized to the respective vaccination group who received at least 1 injection

n = Number of individuals contributing to the analysis

CI=Confidence Interval

cLIA=competitive Luminex Immunoassay

GMT=Geometric Mean Titer

14.6 Studies with Menactra and Adacel

In Study 5, the safety and immunogenicity of co-administration of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines one month post vaccination (one dose for Menactra and Adacel and three doses for GARDASIL 9).

Assessments of post-vaccination immune responses included type-specific antibody GMTs for each of the vaccine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertactin, and anti-fimbrial antibodies at four weeks following Adacel; percentage of subjects with anti-tetanus toxin and anti-diphtheria toxin antibody concentrations ≥0.1 IU/mL at four weeks following Adacel; and percentage of subjects with ≥4-fold rise from pre-vaccination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following Menactra. Based on these measures, concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody responses to any of the vaccines when compared with non-concomitant administration of GARDASIL 9 with Menactra and Adacel.

15 REFERENCES

1. Study 1 NCT00543543
2. Study 2 NCT00943722
3. Study 3 NCT01304498
4. Study 4 NCT01047345
5. Study 5 NCT00988884
6. Study 6 NCT01073293
7. Study 7 NCT01651949
8. Study 8 NCT01984697

16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.

Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03

Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care.
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.
- GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
- Since syncope has been reported following HPV vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
- Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
- Provide information regarding benefits and risks associated with vaccination.
- Safety and effectiveness of GARDASIL 9 have not been established in pregnant women. A pregnancy registry is available. Women exposed to GARDASIL 9 around the time of conception or during pregnancy are encouraged to register by calling 1-800-986-8999. *[See Use in Specific Populations (8.1).]*
- It is important to complete the full vaccination series unless contraindicated.
- Report any adverse reactions to their health care provider.

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-v503-i-1802r007

Influenza Virus Vaccine
Fluvirin®
2017-2018 FORMULA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLUVIRIN® (Influenza Virus Vaccine) safely and effectively. See full prescribing information for FLUVIRIN®.

FLUVIRIN® (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2017-2018 Formula
Initial US Approval: 1988

INDICATIONS AND USAGE

- FLUVIRIN® is an inactivated influenza virus vaccine indicated for active immunization of persons 4 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine (1).
- FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group (8.4).

DOSAGE AND ADMINISTRATION

- For intramuscular use only.

Age	Dose	Schedule
4 years through 8 years	One or two doses [a], 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.
"-" indicates information is not applicable

DOSAGE FORMS AND STRENGTHS

FLUVIRIN®, a sterile suspension for intramuscular injection, is supplied in two presentations:

- 0.5 mL single-dose prefilled syringe (3, 11)
- 5.0 mL multi-dose vial containing 10 doses (each dose is 0.5 mL) (3,11)

CONTRAINDICATIONS

- History of severe allergic reactions (e.g., anaphylaxis) to egg proteins, or any component of FLUVIRIN®, or life-threatening reactions to previous influenza vaccinations. (4.1, 11)

WARNINGS AND PRECAUTIONS

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks. (5.1)
- Immunocompromised persons may have a reduced immune response to FLUVIRIN®. (5.2)

- The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

ADVERSE REACTIONS
The most frequently reported adverse reactions are mild hypersensitivity reactions (such as rash), local reactions at the injection site, and influenza-like symptoms. (6)

To report SUSPECTED ADVERSE REACTIONS contact Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

DRUG INTERACTIONS
- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce immune response to FLUVIRIN®. (7.2)

USE IN SPECIFIC POPULATIONS
- Safety and effectiveness of FLUVIRIN® have not been established in pregnant women, nursing mothers or children less than 4 years of age. (8.1, 8.3, 8.4)
- Antibody responses were lower in the geriatric population than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: March 2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine [see DOSAGE FORMS AND STRENGTHS (3)].

FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake the syringe vigorously before administering the vaccine and shake the multidose vial preparation each time before withdrawing a dose of vaccine.

Inspect FLUVIRIN® syringes and multidose vials visually for particulate matter and/or discoloration prior to administration [see DESCRIPTION (11)]. If either of these conditions exists, the vaccine should not be administered.

Between uses, return the multidose vial to the recommended storage conditions between 2º and 8ºC (36º and 46ºF). **Do not freeze.** Discard if the vaccine has been frozen.

A separate sterile syringe and needle must be used for each injection to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and not recapped.

It is recommended that small syringes (0.5 mL or 1 mL) should be used to minimize any product loss.

For intramuscular use only.

2.2 Recommended Dose and Schedule

The dose and schedule for Fluvirin is presented in Table 1.

TABLE 1
Fluvirin Dose and Schedule

Age	Dose	Schedule
4 years through 8 years	One or two doses [a], 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.
"-" indicates information is not applicable

In children, the needle size may range from 7/8 to 1¼ inches, depending on the size of the child's deltoid muscle, and should be of sufficient length to penetrate the muscle tissue. The anterolateral thigh can be used, but the needle should be longer, usually 1 inch.

In adults, a needle of ≥1 inch is preferred because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults. The preferred site for intramuscular injection is the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk.

3 DOSAGE FORMS AND STRENGTHS

FLUVIRIN®, a sterile suspension for intramuscular injection, is supplied in two presentations:

- 0.5 mL single-dose prefilled syringe
- 5.0 mL multi-dose vial containing 10 doses (each dose is 0.5 mL)

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer FLUVIRIN® to anyone with known history of severe allergic reactions (e.g., anaphylaxis) to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.3 Preventing and Managing Allergic Reactions

Prior to administration of any dose of FLUVIRIN®, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

5.5 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including Fluvirin. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving FLUVIRIN® during postmarketing surveillance.

6.2 Clinical Trial Experience

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

Adult and Geriatric Subjects

Safety data were collected in a total of 2768 adult and geriatric subjects (18 years of age and older) who have received FLUVIRIN® in 29 clinical studies since 1982.

In 9 clinical studies since 1997, among 1261 recipients of FLUVIRIN®, 745 (59%) were women; 1211 (96%) were White, 23 (2%) Asian, 15 (1%) Black and 12 (1%) other; 370 (29%) of subjects were elderly (≥65 years of age). All studies have been conducted in the UK, apart from a study run in the US in 2005-2006 where FLUVIRIN® was used as a comparator for an unlicensed vaccine.

After vaccination, the subjects were observed for 30 minutes for hypersensitivity or other immediate reactions. Subjects were instructed to complete a diary card for three days following immunization (i.e. Day 1 to 4) to collect local and systemic reactions (see Tables 2 and 3). All local and systemic adverse events were considered to be at least possibly related to the vaccine. Local and systemic reactions mostly began between day 1 and day 2. The overall adverse events reported in clinical trials since 1998 in at least 5% of the subjects are summarized in Table 4.

TABLE 2
Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥65 years of age) Subjects.

	1998-1999*§		1999-2000*§		2000-2001*§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Local Adverse Events						
Pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Ecchymosis	4 (6%)	1 (2%)	3 (4%)	1 (3%)	4 (5%)	-
Edema	2 (3%)	1 (2%)	1 (1%)	2 (6%)	3 (4%)	1 (3%)
Reaction	2 (3%)	-	2 (3%)	-	4 (5%)	1 (3%)
Hemorrhage	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	7 (11%)	1 (2%)	17 (22%)	3 (9%)	4 (5%)	-
Fatigue	3 (5%)	2 (5%)	4 (5%)	1 (3%)	3 (4%)	-
Malaise	2 (3%)	1 (2%)	2 (3%)	1 (3%)	1 (1%)	-
Myalgia	1 (2%)	-	2 (3%)	-	-	-
Fever	1 (2%)	-	1 (1%)	-	-	-
Arthralgia	-	1 (2%)	-	1 (3%)	-	-
Sweating	-	-	3 (4%)	-	1 (1%)	1 (3%)

	2001-2002*^		2002-2003*^		2004-2005*^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Local Adverse Events						
Pain	12 (16%)	1 (3%)	14 (13%)	7 (8%)	15 (20%)	9 (15%)
Mass	4 (5%)	1 (3%)	-	-	-	-
Ecchymosis	2 (3%)	-	3 (3%)	3 (3%)	2 (3%)	1 (2%)
Edema	2 (3%)	1 (3%)	6 (6%)	2 (2%)	-	-
Erythema	5 (7%)	-	11 (10%)	5 (6%)	16 (22%)	5 (8%)
Swelling	-	-	-	-	11 (15%)	4 (7%)
Reaction	-	-	2 (2%)	-	-	-
Induration	-	-	14 (13%)	3 (3%)	11 (15%)	1 (2%)
Pruritus	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	8 (11%)	1 (3%)	12 (11%)	9 (10%)	14 (19%)	3 (5%)
Fatigue	1 (1%)	1 (3%)	-	-	5 (7%)	2 (3%)
Malaise	3 (4%)	-	3 (3%)	4 (5%)	1 (1%)	1 (2%)
Myalgia	3 (4%)	-	5 (5%)	3 (3%)	8 (11%)	1 (2%)
Fever	-	-	-	1 (1%)	-	-
Arthralgia	-	-	2 (2%)	-	1 (1%)	-
Sweating	3 (4%)	1 (3%)	-	2 (2%)	-	-
Shivering	-	-	-	1 (1%)	-	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reported
* Solicited adverse events in the first 72 hours after administration of FLUVIRIN®
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

TABLE 3
Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Local Adverse Events	
Pain	168 (55%)
Erythema	48 (16%)
Ecchymosis	22 (7%)
Induration	19 (6%)
Swelling	16 (5%)
Systemic Adverse Events	
Headache	91 (30%)
Myalgia	64 (21%)
Malaise	58 (19%)
Fatigue	56 (18%)
Sore throat	23 (8%)
Chills	22 (7%)
Nausea	21 (7%)
Arthralgia	20 (7%)
Sweating	17 (6%)
Cough	18 (6%)
Wheezing	4 (1%)
Chest tightness	4 (1%)
Other difficulties breathing	3 (1%)
Facial edema	-

Results reported to the nearest whole percent
– not reported

TABLE 4
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	1998-1999§		1999-2000§		2000-2001§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Adverse Events						
Fatigue	8 (12%)	2 (5%)	8 (11%)	2 (6%)	5 (7%)	-
Back pain	4 (6%)	3 (7%)	-	-	-	-
Cough increased	2 (3%)	2 (5%)	-	-	-	-
Ecchymosis	4 (6%)	1 (2%)	4 (5%)	1 (3%)	5 (7%)	-
Fever	3 (5%)	-	-	-	-	-
Headache	12 (18%)	5 (11%)	22 (29%)	5 (15%)	14 (19%)	2 (6%)
Infection	3 (5%)	2 (5%)	-	-	-	-
Malaise	4 (6%)	4 (9%)	4 (5%)	1 (3%)	-	-
Migraine	4 (6%)	1 (2%)	-	-	-	-
Myalgia	4 (6%)	1 (2%)	-	-	-	-
Sweating	5 (8%)	1 (2%)	-	-	-	-
Rhinitis	3 (5%)	1 (2%)	-	-	5 (7%)	2 (6%)
Pharingitis	6 (9%)	1 (2%)	10 (13%)	-	6 (8%)	-
Arthralgia	-	-	-	2 (6%)	-	-
Injection site pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Injection site ecchymosis	4 (6%)	1 (2%)	-	-	4 (5%)	-
Injection site mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Injection site edema	-	-	1 (1%)	2 (6%)	-	-
Injection site inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Injection site reaction	-	-	-	-	4 (5%)	1 (3%)

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Fatigue	5 (7%)	4 (11%)	11 (10%)	8 (9%)	4 (5%)	2 (3%)
Hypertension	-	-	1 (1%)	4 (5%)	-	-
Rinorrhea	-	-	2 (2%)	5 (6%)	-	-
Headache	20 (27%)	2 (6%)	35 (33%)	18 (20%)	12 (16%)	1 (2%)
Malaise	6 (8%)	1 (3%)	13 (12%)	8 (9%)	-	-
Myalgia	4 (5%)	1 (3%)	10 (9%)	4 (5%)	-	-
Sweating	3 (4%)	3 (9%)	2 (2%)	5 (6%)	-	-
Rhinitis	4 (5%)	-	-	-	-	-
Pharingitis	-	-	-	-	6 (8%)	-
Arthralgia	-	-	5 (5%)	4 (5%)	-	-
Sore throat	4 (5%)	1 (3%)	5 (5%)	4 (5%)	-	-
Injection site pain	13 (17%)	3 (9%)	14 (13%)	7 (8%)	6 (8%)	2 (3%)
Injection site ecchymosis	4 (5%)	1 (3%)	4 (4%)	4 (5%)	-	-
Injection site erythema	5 (7%)	2 (6%)	11 (10%)	5 (6%)	4 (5%)	-
Injection site mass	4 (5%)	1 (3%)	-	-	-	-
Injection site edema	-	-	6 (6%)	2 (2%)	4 (5%)	1 (2%)
Injection site induration	-	-	14 (13%)	3 (3%)	7 (9%)	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reaching the cut-off of 5%
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

Adults (18 to 64 years of age)

In adult subjects, solicited local adverse events occurred with similar frequency in all trials. The most common solicited adverse events occurring in the first 96 hours after administration (Tables 2 and 3) were associated with the injection site (such as pain, erythema, mass, induration and swelling) but were generally mild/moderate and transient. The most common solicited systemic adverse events were headache and myalgia.

The most common overall events in adult subjects (18-64 years of age) were headache, fatigue, injection site reactions (pain, mass, erythema, and induration) and malaise (Table 4).

Geriatric Subjects (65 years of age and older)

In geriatric subjects, solicited local and systemic adverse events occurred less frequently than in adult subjects. The most common solicited local and systemic adverse events were injection site pain, and headache (Tables 2 and 3). All were considered mild/moderate and were transient.

The most common overall events in elderly subjects (≥65 years of age) were headache and fatigue.

Only 11 serious adverse events in adult and geriatric subjects (18 years and older) have been reported to date from all the trials performed. These serious adverse events were a minor stroke experienced by a 67 year old subject 14 days after vaccination (1990), death of an 82 year old subject 35 days after vaccination (1990) in very early studies; death of a 72 year old subject 19 days after vaccination (1998-1999), a hospitalization for hemorrhoidectomy of a 38 year old male subject (1999-2000), a severe respiratory tract infection experienced by a 74 year old subject 12 days after vaccination (2002-2003), a planned transurethral resection of the prostate in a subject with prior history of prostatism (2004-2005), two cases of influenza (2005-2006), a drug overdose (2005-2006), cholelithiasis (2005-2006) and a nasal septal operation (2005-2006). None of these events were considered causally related to vaccination.

Clinical Trial Experience in Pediatric Subjects

In 1987 a clinical study was carried out in 38 ‘at risk’ children aged between 4 and 12 years (17 females and 21 males). To record the safety of FLUVIRIN®, participants recorded their symptoms on a diary card during the three days after vaccination and noted any further symptoms they thought were attributable to the vaccine. The only reactions recorded were tenderness at the site of vaccination in 21% of the participants on day 1, which was still present in 16% on day 2 and 5% on day 3. In one child, the tenderness was also accompanied by redness at the site of injection for two days. The reactions were not age-dependent and there was no bias towards the younger children.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6 - 47 months). Of these, 285 healthy subjects plus 41 ‘at risk’ subjects received FLUVIRIN®. No serious adverse events were reported.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of FLUVIRIN®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

- *Body as a whole*: Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have lead to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), presyncope, syncope shortly after vaccination.
- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; thrombocytopenia (some very rare cases were severe with platelet counts less than 5,000 per mm^3).
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal*: Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).
- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages*: Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobulbous).
- *General disorders and administration site conditions:* Injection site cellulitis-like reaction (very rare cases of swelling, pain, and redness were large and extended to the entire arm)

6.4 Other Adverse Reactions Associated with Influenza Vaccination

Anaphylaxis has been reported after administration of FLUVIRIN®. Although FLUVIRIN® contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis [see CONTRAINDICATIONS (4)].

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

There are no data to assess the concomitant administration of FLUVIRIN® with other vaccines. If FLUVIRIN® is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites.

FLUVIRIN® should not be mixed with any other vaccine in the same syringe or vial.

7.2 Concurrent Use with Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLUVIRIN®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: A reproductive and developmental toxicity study has been performed in rabbits at a dose level that was approximately 15 times the human dose based on body weight. The study revealed no evidence of impaired fertility or harm to the fetus due to FLUVIRIN®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUVIRIN® on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered FLUVIRIN® by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 15-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, embryo-fetal development, or post-natal development were observed. There were no vaccine related fetal malformations or other evidence of teratogenicity.

8.3 Nursing Mothers

It is not known whether FLUVIRIN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUVIRIN® is administered to a nursing woman.

8.4 Pediatric Use

The safety and immunogenicity of FLUVIRIN® have not been established in children under 4 years of age.

The safety and immunogenicity of FLUVIRIN® have been established in the age group 4 years to 16 years. The use of FLUVIRIN® in these age groups is supported by evidence from adequate and well controlled studies of FLUVIRIN® in adults that demonstrate the immunogenicity of FLUVIRIN® [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14)].

8.5 Geriatric Use

Since 1997, of the total number of geriatric subjects (n = 397) in clinical studies of FLUVIRIN®, 29% were 65 years and over, while 2.1% were 75 years and over.

Antibody responses were lower in the geriatric population than in younger subjects. Adverse events occurred less frequently in geriatric subjects (≥65 years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. [See ADVERSE REACTION (6) and CLINICAL STUDIES (14)].

11 DESCRIPTION

FLUVIRIN® is a trivalent, sub-unit (purified surface antigen) influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs inoculated with a specific type of influenza virus suspension containing neomycin and polymyxin. Each of the influenza virus strains is harvested and clarified separately by centrifugation and filtration prior to inactivation with betapropiolactone. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the presence of nonylphenol ethoxylate, a process which removes most of the internal proteins. The nonylphenol ethoxylate is removed from the surface antigen preparation.

FLUVIRIN® is a homogenized, sterile, slightly opalescent suspension in a phosphate buffered saline. FLUVIRIN® has been standardized according to USPHS requirements for the 2017-2018 influenza season and is formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following 3 viruses:
A/Singapore/GP1908/2015, IVR-180 (an A/Michigan/45/2015 (H1N1)pdm09-like virus; A/Hong Kong/4801/2014, NYMC X-263B (H3N2) (an A/Hong Kong/4801/2014-like virus); and B/Brisbane/60/2008, wild type (a B/Brisbane/60/2008-like virus).

The 0.5 mL prefilled syringe presentation is formulated without preservative. However, thimerosal, a mercury derivative used during manufacturing, is removed by subsequent purification steps to a trace amount (≤ 1 mcg mercury per 0.5 mL dose).

The 5 mL multidose vial formulation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multidose vial contains 25 mcg mercury.

Each dose from the multidose vial or from the prefilled syringe may also contain residual amounts of egg proteins (≤ 1 mcg ovalbumin), polymyxin (≤ 3.75 mcg), neomycin (≤ 2.5 mcg), betapropiolactone (not more than 0.5 mcg) and nonylphenol ethoxylate (not more than 0.015% w/v).

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex. The multidose vial stopper and the syringe stopper/plunger do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some human studies, antibody titer of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects [see REFERENCES (15.1, 15.2)].

Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinin of strains (i.e., typically two type A and one type B), representing the influenza viruses likely to be circulating in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year [see REFERENCES (15.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUVIRIN® has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

Between 1982 and 1991, twelve clinical studies were conducted in healthy adult and geriatric subjects and one in children between 4 and 12 years of age who were considered to be 'at risk'. Since 1991 an annual clinical study has been conducted in the UK in healthy adults aged 18 years or older. FLUVIRIN® was also used as a control in a US clinical trial in adults (18-49 years of age). In all the trials, blood samples were taken prior to vaccination and approximately three weeks after vaccination to assess the immunogenic response to vaccination by measurement of anti-HA antibodies.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6-47 months). Of these, 285 healthy subjects plus 41 'at risk' pediatric subjects received FLUVIRIN®.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

14.1 Immunogenicity in Adults (18 to 64 years of age)

Tables 5 and 6 show the immunogenicity data for the adult age group. The seven clinical studies presented enrolled a total of 774 adult subjects. In the adult group, for all antigens (A/H1N1, A/H3N2 and B) at least one of the following point estimate criteria was met: the proportion of subjects with seroconversion (post-vaccination titer ≥1:40 from a pre-vaccination titer <1:10) or significant increase (at least a four-fold increase from pre-vaccination titer ≥1:10) in antibody titer was greater than 40%; the geometric mean titer (GMT) increase was >2.5; the proportion of subjects with a post-vaccination hemagglutination inhibition (HI) antibody titer ≥1:40 was greater than 70%.

TABLE 5
Summary of the Seroconversion and Proportion of Subjects Achieving an HI titer ≥1:40 for Adult Subjects

Year/Strain	No. of subjects	Seroconversion [∞]			HI titer ≥1:40[¥]		
		N	%	95% CI[φ]	n	%	95% CI[φ]
1998-1999							
A/H1N1		48	73	(62, 83)	50	76	(65, 86)
A/H3N2	66	43	65	(54, 77)	47	71	(60, 82)
B		42	64	(52, 75)	62	94	(88, 100)
1999-2000							
A/H1N1		45	59	(48, 70)	50	66	(55, 76)
A/H3N2	76	51	67	(57, 78)	66	87	(79, 94)
B		53	70	(59, 80)	75	99	(96, 100)
2000-2001							
A/H1N1		41	55	(44, 67)	41	55	(44, 67)
A/H3N2	74	45	61	(50, 72)	52	84	(75, 92)
B		50	68	(57, 78)	73	99	(96, 100)
2001-2002							
A/H1N1		44	59	(48, 70)	48	64	(53, 75)
A/H3N2	75	46	61	(50, 72)	68	91	(84, 97)
B		42	56	(45, 67)	66	88	(81, 95)
2002-2003							
A/H1N1		62	58	(49, 68)	73	69	(60, 78)
A/H3N2	106	72	68	(59, 77)	93	88	(81, 94)
B		78	74	(65, 82)	101	95	(91, 99)
2004-2005							
A/H1N1		52	70	(59, 80)	66	89	(80, 95)
A/H3N2	74	60	81	(70, 89)	73	99	(93, 100)
B		57	77	(66, 86)	69	93	(85, 98)
2005-2006							
A/H1N1		191	63	(57, 68)	296	98	(95, 99)
A/H3N2	303	273	90	(86, 93)	294	97	(94, 99)
B		213	70	(65, 75)	263	87	(82, 90)

[∞] Seroconversion: proportion of subjects with either a post-vaccination HI titer ≥1:40 from a pre-vaccination titer <1:10 or at least a four-fold increase from pre-vaccination HI titer ≥1:10 in antibody titer.

[¥] HI titer ≥1:40: proportion of subjects with a post-vaccination titer ≥ 1:40.

[φ] 95% CI: 95% confidence interval

TABLE 6
Summary of the Geometric Mean Hemagglutination Inhibition Antibody Titers, Pre- and Post-Immunization, for Adult Subjects

Year/Strain	No. of subjects	Geometric Mean Titer (GMT)			
		Pre-vaccination	Post-vaccination	Fold Increase	(95% CI)*
1998-1999					
A/H1N1		7.26	160.87	22.16	(14.25, 34.46)
A/H3N2	66	8.23	87.02	10.57	(6.91, 16.16)
B		20.97	231.07	110.2	(6.90, 17.59)
1999-2000					
A/H1N1		7.43	58.95	7.93	(5.73, 10.97)
A/H3N2	76	15.29	122.83	8.03	(5.80, 11.13)
B		25.70	254.76	9.91	(6.97, 14.10)
2000-2001					
A/H1N1		5.42	33.80	6.24	(4.49, 8.69)
A/H3N2	74	15.98	126.01	7.89	(5.61, 11.09)
B		26.24	308.25	11.75	(7.73, 17.85)
2001-2002					
A/H1N1		7.76	54.78	7.06	(5.24, 9.52)
A/H3N2	75	23.67	153.81	6.50	(4.78, 8.84)
B		19.91	107.53	5.40	(3.95, 7.38)
2002-2003					
A/H1N1		7.78	60.39	7.77	(5.81, 10.39)
A/H3N2	106	23.32	292.03	12.52	(8.77, 17.87)
B		30.20	314.11	10.40	(7.54, 14.34)
2004-2005					
A/H1N1		13	159	12	(8.39, 17)
A/H3N2	74	37	658	18	(12, 26)
B		15	156	11	(7.87, 14)
2005-2006					
A/H1N1		29	232	8	(6.68, 9.59)
A/H3N2	303	14	221	15	(14, 17)
B		13	83	6.5	(5.73, 7.37)

* 95% CI: 95% confidence interval

14.2 Immunogenicity in Geriatric Subjects (65 years of age and older)

Tables 7 and 8 show the immunogenicity of FLUVIRIN® in the geriatric age group. The six clinical studies presented enrolled a total of 296 geriatric subjects. For each of the influenza antigens, the percentage of subjects who achieved seroconversion and the percentage of subjects who achieved HI titers of ≥1:40 are shown, as well as the fold increase in GMT.

For all antigens (A/H1N1, A/H3N2 and B) at least one of the following point estimate criteria was met: the proportion of subjects with seroconversion (post-vaccination titer ≥1:40 from a pre-vaccination titer <1:10) or significant increase (at least a four-fold increase from pre-vaccination titer ≥1:10) in antibody titer was greater than 30%; the geometric mean titer (GMT) increase was >2.0; the proportion of subjects with a post-vaccination hemagglutination inhibition (HI) antibody titer ≥1:40 was greater than 60%. The pre-specified efficacy criteria were met in each study, although a relatively lower immunogenicity of A/H1N1 strain was seen in the last four studies (the same strain was in each of the formulations).

TABLE 7
Summary of the Seroconversion and Proportion of Subjects Achieving an HI titer ≥1:40 for Geriatric Subjects

Year/Strain	No. of subjects	Seroconversion [∞]			HI titer ≥1:40[¥]		
		N	%	95% CI[φ]	N	%	95% CI[φ]
1998-1999							
A/H1N1		33	79	(66, 91)	38	90	(82, 99)
A/H3N2	42	33	79	(66, 91)	36	86	(75, 96)
B		13	31	(17, 45)	42	100	(100, 100)
1999-2000							
A/H1N1		10	29	(14, 45)	23	68	(52, 83)
A/H3N2	34	18	53	(36, 70)	31	91	(82, 100)
B		9	26	(12, 41)	32	94	(86, 100)
2000-2001							
A/H1N1		5	14	(3, 26)	10	29	(14, 44)
A/H3N2	35	22	63	(47, 79)	31	89	(78, 99)
B		13	37	(21, 53)	33	94	(87, 100)
2001-2002							
A/H1N1		5	14	(3, 26)	14	40	(24, 56)
A/H3N2	35	15	43	(26, 59)	33	94	(87, 100)
B		6	17	(5, 30)	32	91	(82, 100)
2002-2003							
A/H1N1		24	27	(18, 36)	52	58	(48, 69)
A/H3N2	89	42	47	(37, 58)	85	96	(91, 100)
B		41	46	(36, 56)	86	97	(93, 100)
2004-2005							
A/H1N1		17	28	(17, 41)	46	75	(63, 86)
A/H3N2	61	29	48	(35, 61)	60	98	(91, 100)
B		38	62	(49, 74)	51	84	(72, 92)

[∞] Seroconversion: proportion of subjects with either a post-vaccination HI titer ≥1:40 from a pre-vaccination titer <1:10 or at least a four-fold increase from pre-vaccination HI titer ≥1:10 in antibody titer

[¥] HI titer ≥1:40: proportion of subjects with a post-vaccination titer ≥1:40

[φ] 95% CI: 95% confidence interval

TABLE 8
Summary of the Geometric Mean Hemagglutination Inhibition Antibody Titers, Pre- and Post-Immunization, for Geriatric Subjects

Year/Strain	No. of subjects	Geometric Mean Titer (GMT)			
		Pre-vaccination	Post-vaccination	Fold Increase	(95% CI)*
1998-1999					
A/H1N1	42	13.92	176.65	12.69	(8.24, 19.56)
A/H3N2		10.69	124.92	11.69	(7.02, 19.46)
B		114.1	273.56	2.40	(1.82, 3.17)
1999-2000					
A/H1N1	34	15.82	50.58	3.20	(2.13, 4.80)
A/H3N2		28.00	133.19	4.76	(2.92, 7.76)
B		57.16	127.86	2.24	(1.56, 3.20)
2000-2001					
A/H1N1	35	6.66	18.85	2.83	(1.91, 4.18)
A/H3N2		25.87	140.68	5.44	(3.72, 7.96)
B		61.24	191.23	3.12	(2.13, 4.59)
2001-2002					
A/H1N1	35	12.69	26.65	2.10	(1.55, 2.84)
A/H3N2		47.33	114.26	2.41	(1.73, 3.38)
B		45.49	91.89	2.02	(1.47, 2.78)
2002-2003					
A/H1N1	89	13.29	31.92	2.40	(1.90, 3.03)
A/H3N2		65.86	272.79	4.14	(3.09, 5.55)
B		74.87	288.57	3.85	(2.89, 5.13)
2004-2005					
A/H1N1	61	21	64	3.13	(2.33, 4.2)
A/H3N2		72	320	4.43	(3.13, 6.27)
B		20	114	5.69	(4.39, 7.38)

* 95% CI: 95% confidence interval

14.3 Immunogenicity in Pediatric Subjects

A small-scale study, was conducted in 1987 to evaluate safety and immunogenicity of FLUVIRIN® in 38 'at risk' children, with diabetes and/or asthma, or lymphoid leukemia. Thirty-eight participants aged between 4 and 12 years of age were assessed. Ten subjects had diabetes, 21 had asthma, two had both diabetes and asthma, and one had lymphoid leukemia. There were four healthy control subjects. All participants received a single 0.5 mL dose of FLUVIRIN®.

Immunogenicity results were obtained for 19 of the 38 subjects enrolled in the study. The point estimate of the percentage of subjects achieving a titer of ≥ 1:40 was 84% for the A/H1N1 strain 79% for the B strain, and 53% for the A/H3N2 strain. The GMT fold increases were 5.8 for the A/H1N1 strain, 40 for the B strain and 17.7 for the A/H3N2 strain.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6-47 months). Of these, 285 healthy subjects plus 41 'at risk' pediatric subjects, received FLUVIRIN®.

In a 1995/1996 clinical study, 41 subjects (aged 6-36 months) at increased risk for influenza-related complications received two 0.25 mL doses of FLUVIRIN®. At least 49% of subjects showed a ≥4-fold increase in HI antibody titer to all three strains. HI

antibody titers of 1:40 or greater were seen in at least 71% of the subjects for all three influenza strains, with increases in geometric mean titer of 6.0-fold or greater to all three strains.

Two clinical studies (1999-2000 and 2004) indicated a lower immunogenicity profile for FLUVIRIN® compared with two commercial split vaccines; in a study in the age group 6-47 months the comparator was a US licensed vaccine, Fluzone®, and in another study in the age group 6-36 months the comparator was a non-US licensed inactivated influenza vaccine. Despite the small sample size (a total of 285 healthy subjects received FLUVIRIN® in these two clinical studies) the lower immunogenicity profile of FLUVIRIN® was greatest versus the comparator vaccines in children <36months but was also evident in those 36-47 months of age, though the differences were less.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

15 REFERENCES

15.1 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004; 103:133-138.

15.2 Hobson D, Curry RL, Beare A, et. al. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972; 767-777.

15.3 Centers for Disease Control and Prevention. Prevention and Control of Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011; 60(33):1128-1132.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FLUVIRIN® product presentations are listed in Table 9 below:

TABLE 9
Fluvirin Product Presentations

Presentation	Carton NDC Number	Components
Pre-filled syringe	70461-120-02	0.5 mL single dose pre-filled syringe, package of 10 syringes per carton (may contain latex) [NDC 70461-120-12]
Multi-dose vial	70461-120-10	5.0 mL multi-dose vial, individually packaged in a carton (contains no latex) [NDC 70461-120-11]

16.2 Storage and Handling

Store FLUVIRIN® refrigerated between 2º and 8ºC (36º and 46ºF).
Do not freeze. Discard if the vaccine has been frozen.
Store in the original package to protect from light.
Do not use after the expiration date.
Between uses, return the multidose vial to the recommended storage conditions.

17 PATIENT COUNSELING INFORMATION

Vaccine recipients and guardians should be informed by their health care provider of the potential benefits and risks of immunization with FLUVIRIN®. When educating

vaccine recipients and guardians regarding the potential side effects, clinicians should emphasize that (1) FLUVIRIN® contains non-infectious particles and cannot cause influenza and (2) FLUVIRIN® is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.

Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their healthcare provider.

Vaccine recipients and guardians should be instructed that annual vaccination is recommended.

Manufactured by: **Seqirus Vaccines Limited** Speke, Liverpool L249GR, UK
Distributed by: **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA
1-855-358-8966

US-20839

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLUMIST® QUADRIVALENT safely and effectively. See full prescribing information for FLUMIST® QUADRIVALENT.

FluMist® Quadrivalent (Influenza Vaccine Live, Intranasal)
Intranasal Spray
2018-2019 Formula
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

FluMist Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1, 11)
FluMist Quadrivalent is approved for use in persons 2 through 49 years of age. (1)

----------DOSAGE AND ADMINISTRATION----------

For intranasal administration by a healthcare provider. (2)

Age	Dose	Schedule
2 years through 8 years	1 or 2 doses[a], 0.2 mL[b] each	If 2 doses, administer at least 1 month apart
9 years through 49 years	1 dose, 0.2 mL[b]	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.
[b] Administer as 0.1 mL per nostril.
"-" indicates information is not applicable.

----------DOSAGE FORMS AND STRENGTHS----------

Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer. (3)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) to any component of FluMist Quadrivalent, including egg protein, or after a previous dose of any influenza vaccine. (4.1, 11)
- Concomitant aspirin therapy in children and adolescents. (4.2)

----------WARNINGS AND PRECAUTIONS----------

- In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal). (5.1)
- Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following the administration of FluMist Quadrivalent. (5.2)
- If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist Quadrivalent should be based on careful consideration of the potential benefits and risks. (5.3)
- FluMist Quadrivalent has not been studied in immunocompromised persons. (5.4)

----------ADVERSE REACTIONS----------

The most common solicited adverse reactions (≥ 10% in vaccine recipients and at least 5% greater than in placebo recipients) reported after FluMist were runny nose or nasal congestion (ages 2 years through 49 years), fever over 100°F (children ages 2 years through 6 years), and sore throat (adults ages 18 years through 49 years). Among children and adolescents 2 through 17 years of age who received FluMist Quadrivalent, 32% reported runny nose or nasal congestion and 7% reported fever over 100°F. Among adults 18 through 49 years of age who received FluMist Quadrivalent, 44% reported runny nose or nasal congestion and 19% reported sore throat. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or VAERS at 1-800-822-7967 or *http://vaers.hhs.gov*.

----------DRUG INTERACTIONS----------

- Antiviral drugs that are active against influenza A and/or B may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after, receipt of the vaccine. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Safety and effectiveness of FluMist Quadrivalent have not been established in pregnant women, nursing mothers, geriatric adults, or children less than 2 years of age. (8.1, 8.2, 8.4, 8.5)
- In clinical trials, in children 6 through 23 months of age, FluMist was associated with an increased risk of hospitalization and wheezing. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FluMist® Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine *[see Description (11)]*.

FluMist Quadrivalent is approved for use in persons 2 through 49 years of age.

2 DOSAGE AND ADMINISTRATION

FOR INTRANASAL ADMINISTRATION BY A HEALTHCARE PROVIDER.

2.1 Dosing Information

Administer FluMist Quadrivalent according to the following schedule:

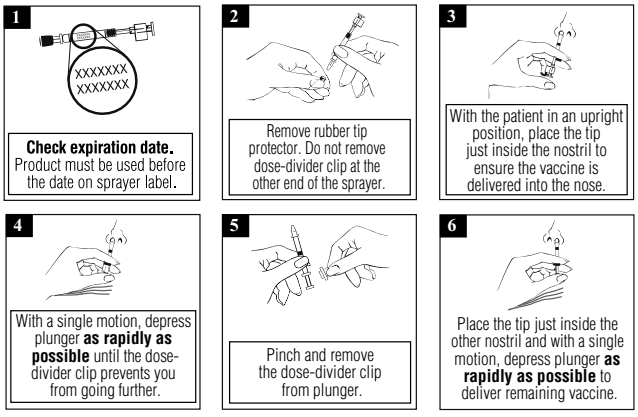
Age	Dose	Schedule
2 years through 8 years	1 or 2 doses[a], 0.2 mL[b] each	If 2 doses, administer at least 1 month apart
9 years through 49 years	1 dose, 0.2 mL[b]	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.
[b] Administer as 0.1 mL per nostril.
"-" indicates information is not applicable.

2.2 Administration Instructions

Each sprayer contains a single dose (0.2 mL) of FluMist Quadrivalent; administer approximately one half of the contents of the single-dose intranasal sprayer into each nostril (each sprayer contains 0.2 mL of vaccine). Refer to Figure 1 for step-by-step administration instructions. Following administration, dispose of the sprayer according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

Figure 1



DO NOT INJECT. DO NOT USE A NEEDLE.

Note: Active inhalation (i.e., sniffing) is not required by the patient during vaccine administration.

3 DOSAGE FORMS AND STRENGTHS

Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer.

4 CONTRAINDICATIONS

4.1 Severe Allergic Reactions

Do not administer FluMist Quadrivalent to persons who have had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine *[see Description (11)]* including egg protein, or after a previous dose of any influenza vaccine.

4.2 Concomitant Aspirin Therapy and Reye's Syndrome in Children and Adolescents

Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza infection *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risks of Hospitalization and Wheezing in Children Younger than 24 Months of Age

In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal) *[see Adverse Reactions (6.1)]*. This observation with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions *[see Description (11)]*.

5.2 Asthma, Recurrent Wheezing, and Active Wheezing

Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist Quadrivalent. FluMist Quadrivalent has not been studied in persons with severe asthma or active wheezing.

5.3 Guillain-Barré Syndrome

The 1976 swine influenza vaccine (inactivated) was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, based on data for inactivated influenza vaccines, it is probably slightly more than 1 additional case per 1 million persons vaccinated[1]. If GBS has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist Quadrivalent should be based on careful consideration of the potential benefits and potential risks.

5.4 Altered Immunocompetence

FluMist Quadrivalent has not been studied in immunocompromised persons. The effectiveness of FluMist has not been studied in immunocompromised persons. Data on safety and shedding of vaccine virus after administration of FluMist in immunocompromised persons are limited to 173 persons with HIV infection and 10 mild to moderately immunocompromised children and adolescents with cancer *[see Clinical Pharmacology (12.2)]*.

5.5 Medical Conditions Predisposing to Influenza Complications

The safety of FluMist Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established.

5.6 Management of Acute Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine *[see Contraindications (4.1)]*.

5.7 Limitations of Vaccine Effectiveness

FluMist Quadrivalent may not protect all individuals receiving the vaccine.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

This safety experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions *[see Description (11)]*. A total of 9537 children and adolescents 1 through 17 years of age and 3041 adults 18 through 64 years of age received FluMist in randomized, placebo-controlled Studies D153-P501, AV006, D153-P526, AV019, and AV009 [3 used Allantoic Fluid containing Sucrose-Phosphate-Glutamate (AF-SPG) placebo, and 2 used saline placebo] described below. In addition, 4179 children 6 through 59 months of age received FluMist in Study MI-CP111, a randomized, active-controlled trial. Among pediatric FluMist recipients 6 months through 17 years of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019, and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), while in D153-P501, 99% of subjects were Asian.

A total of 1382 children and adolescents 2 through 17 years of age and 1198 adults 18 through 49 years of age received FluMist Quadrivalent in randomized, active-controlled Studies MI-CP208 and MI-CP185. Among pediatric FluMist Quadrivalent recipients 2 through 17 years of age, 51% were female; in the study of adults, 55% were female. In Studies MI-CP208 and MI-CP185, subjects were White (73%), Asian (1%), Black or African-American (19%), and Other (7%); overall, 22% were Hispanic or Latino.

FluMist in Children and Adolescents

The safety of FluMist was evaluated in an AF-SPG placebo-controlled study (AV019) conducted in a Health Maintenance Organization (HMO) in children 1 through 17 years of age (FluMist = 6473, placebo = 3216). An increase in asthma events, captured by review of diagnostic codes, was observed in children younger than 5 years of age who received FluMist compared to those who received placebo (Relative Risk 3.53, 90% CI: 1.1, 15.7).

In Study MI-CP111, children 6 through 59 months of age were randomized to receive FluMist or inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia was prospectively monitored from randomization through 42 days post last vaccination. Hospitalization due to all causes was prospectively monitored from randomization through 180 days post last vaccination. Increases in wheezing and hospitalization (for any cause) were observed in children 6 months through 23 months of age who received FluMist compared to those who received inactivated Influenza Virus Vaccine, as shown in Table 1.

Table 1: Percentages of Children with Hospitalizations and Wheezing from Study MI-CP111[a]

Adverse Reaction	Age Group	FluMist (n/N)	Active Control[b] (n/N)
Hospitalizations[c]	6-23 months	4.2% (84/1992)	3.2% (63/1975)
	24-59 months	2.1% (46/2187)	2.5% (56/2198)
Wheezing[d]	6-23 months	5.9% (117/1992)	3.8% (75/1975)
	24-59 months	2.1% (47/2187)	2.5% (56/2198)

[a] NCT00128167; see www.clinicaltrials.gov
[b] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[c] Hospitalization due to any cause from randomization through 180 days post last vaccination.
[d] Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomization through 42 days post last vaccination.

Most hospitalizations observed were due to gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. In post-hoc analysis, rates of hospitalization in children 6 through 11 months of age were 6.1% (42/684) in FluMist recipients and 2.6% (18/683) in inactivated Influenza Virus Vaccine recipients.

Table 2 shows pooled solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo post Dose 1 for Studies D153-P501 and AV006, and solicited adverse reactions post Dose 1 for Study MI-CP111. Solicited adverse reactions were those about which parents/guardians were specifically queried after receipt of FluMist, placebo, or control vaccine. In these studies, solicited reactions were documented for 10 days post vaccination. Solicited reactions following the second dose of FluMist were similar to those following the first dose and were generally observed at a lower frequency.

Table 2: Summary of Solicited Adverse Reactions Observed Within 10 Days after Dose 1 for FluMist and Either Placebo or Active Control Recipients in Children 2 through 6 Years of Age

	Studies D153-P501[a] & AV006		Study MI-CP111[b]	
	FluMist N = 876-1759[e]	Placebo[c] N = 424-1034[e]	FluMist N = 2170[e]	Active Control[d] N = 2165[e]
Event	%	%	%	%
Runny Nose/ Nasal Congestion	58	50	51	42
Decreased Appetite	21	17	13	12
Irritability	21	19	12	11
Decreased Activity (Lethargy)	14	11	7	6
Sore Throat	11	9	5	6
Headache	9	7	3	3
Muscle Aches	6	3	2	2
Chills	4	3	2	2
Fever				
> 100°F Oral	16	11	13	11
> 100 - ≤ 101°F Oral	9	6	6	4
> 101 - ≤ 102°F Oral	4	3	4	3

[a] NCT00192244; see www.clinicaltrials.gov
[b] NCT00128167; see www.clinicaltrials.gov
[c] Study D153-P501 used saline placebo; Study AV006 used AF-SPG placebo.
[d] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[e] Number of evaluable subjects (those who returned diary cards) for each reaction. Range reflects differences in data collection between the 2 pooled studies.

In clinical studies D153-P501 and AV006, unsolicited adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were abdominal pain (2% FluMist vs. 0% placebo) and otitis media (3% FluMist vs. 1% placebo). An additional adverse reaction identified in the active-controlled trial MI-CP111 occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to active control was sneezing (2% FluMist vs. 1% active control).

In a separate saline placebo-controlled trial (D153-P526) in a subset of older children and adolescents 9 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

FluMist Quadrivalent in Children and Adolescents

In the randomized, active-controlled Study MI-CP208 that compared FluMist Quadrivalent and FluMist in children and adolescents 2 through 17 years of age, the rates of solicited adverse reactions reported were similar between subjects who received FluMist Quadrivalent and FluMist. Table 3 includes solicited adverse reactions post Dose 1 from Study MI-CP208 that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist clinical studies *(see Table 2)*. In this study, solicited adverse reactions were documented for 14 days post vaccination. Solicited adverse reactions post Dose 2 were observed at a lower frequency compared to those post Dose 1 for FluMist Quadrivalent and were similar between subjects who received FluMist Quadrivalent and FluMist.

Table 3: Summary of Solicited Adverse Reactions[a] Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208[b] in Children and Adolescents 2 through 17 Years of Age

	FluMist Quadrivalent N = 1341-1377[d]	FluMist[c] N = 901-920[d]
Event	%	%
Runny Nose/Nasal Congestion	32	32
Headache	13	12
Decreased Activity (Lethargy)	10	10
Sore Throat	9	10
Decreased Appetite	6	7
Muscle Aches	4	5
Fever		
> 100°F by any route	7	5
> 100 - ≤ 101°F by any route	3	2
> 101 - ≤ 102°F by any route	2	2

[a] Solicited adverse reactions that occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist trials *(see Table 2)*.
[b] NCT01091246; see www.clinicaltrials.gov
[c] Represents pooled data from the two FluMist study arms *[see Clinical Studies (14.2)]*.
[d] Number of evaluable subjects for each event.

In Study MI-CP208, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

FluMist in Adults

In adults 18 through 49 years of age in Study AV009, solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to AF-SPG placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weakness (26% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14% FluMist vs. 11% placebo), and chills (9% FluMist vs. 6% placebo).

In Study AV009, unsolicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were nasal congestion (9% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

FluMist Quadrivalent in Adults

In the randomized, active-controlled Study MI-CP185 that compared FluMist Quadrivalent and FluMist in adults 18 through 49 years of age, the rates of solicited adverse reactions reported were generally similar between subjects who received FluMist Quadrivalent and FluMist. Table 4 presents solicited adverse reactions that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.

Table 4: Summary of Solicited Adverse Reactions[a] Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP185[b] in Adults 18 through 49 Years of Age

	FluMist Quadrivalent N = 1197[d]	FluMist[c] N = 597[d]
Event	%	%
Runny Nose/Nasal Congestion	44	40
Headache	28	27
Sore Throat	19	20
Decreased Activity (Lethargy)	18	18
Cough	14	13
Muscle Aches	10	10
Decreased Appetite	6	5

[a] Solicited adverse reactions that occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.
[b] NCT00860067; see www.clinicaltrials.gov
[c] Represents pooled data from the two FluMist study arms *[see Clinical Studies (14.4)]*.
[d] Number of evaluable subjects for each event.

In Study MI-CP185, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

6.2 Postmarketing Experience

The following events have been spontaneously reported during post approval use of FluMist. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac disorders: Pericarditis

Congenital, familial, and genetic disorders: Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome)

Gastrointestinal disorders: Nausea, vomiting, diarrhea

Immune system disorders: Hypersensitivity reactions (including anaphylactic reaction, facial edema, and urticaria)

Nervous system disorders: Guillain-Barré syndrome, Bell's Palsy, meningitis, eosinophilic meningitis, vaccine-associated encephalitis

Respiratory, thoracic, and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

7 DRUG INTERACTIONS

7.1 Aspirin Therapy

Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza [see *Contraindications (4.2)*]. Avoid aspirin-containing therapy in these age groups during the first 4 weeks after vaccination with FluMist Quadrivalent unless clearly needed.

7.2 Antiviral Agents Against Influenza A and/or B

Antiviral drugs that are active against influenza A and/or B viruses may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after vaccination. The concurrent use of FluMist Quadrivalent with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. If antiviral agents and FluMist Quadrivalent are administered concomitantly, revaccination should be considered when appropriate.

7.3 Concomitant Administration with Inactivated Vaccines

The safety and immunogenicity of FluMist Quadrivalent when administered concomitantly with inactivated vaccines have not been determined. Studies of FluMist and FluMist Quadrivalent excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment.

7.4 Concomitant Administration with Other Live Vaccines

Concomitant administration of FluMist Quadrivalent with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) or the Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) has not been studied. Concomitant administration of FluMist with MMR and the varicella vaccine was studied in children 12 through 15 months of age *[see Clinical Studies (14.5)]*. Concomitant administration of FluMist with the MMR and the varicella vaccine in children older than 15 months of age has not been studied.

7.5 Intranasal Products

There are no data regarding co-administration of FluMist Quadrivalent with other intranasal preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

FluMist Quadrivalent is not absorbed systemically following intranasal administration and maternal use is not expected to result in fetal exposure to the drug.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal influenza are at increased risk of severe illness associated with influenza infection compared with nonpregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental and reproductive toxicity study, female rats were administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis), 200 microliter/rat/occasion (approximately 150 human dose equivalents), by intranasal instillation revealing no evidence of impaired fertility or harm to the fetus due to FluMist Quadrivalent.

8.2 Lactation

Risk Summary

FluMist is not absorbed systemically by the mother following intranasal administration and breastfeeding is not expected to result in exposure of the child to FluMist.

8.4 Pediatric Use

Safety and effectiveness of FluMist Quadrivalent in children 24 months of age and older is based on data from FluMist clinical studies and a comparison of post-vaccination antibody titers between persons who received FluMist Quadrivalent and those who received FluMist *[see Clinical Studies (14.1, 14.2)]*. FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*.

8.5 Geriatric Use

FluMist Quadrivalent is not approved for use in persons 65 years of age and older because in a clinical study (AV009), effectiveness of FluMist to prevent febrile illness was not demonstrated in adults 50 through 64 years of age *[see Clinical Studies (14.3)]*. In this study, solicited events among individuals 50 through 64 years of age were similar in type and frequency to those reported in younger adults. In a clinical study of FluMist in persons 65 years of age and older, subjects with underlying high-risk medical conditions (N = 200) were studied for safety. Compared to controls, FluMist recipients had a higher rate of sore throat.

11 DESCRIPTION

FluMist Quadrivalent (Influenza Vaccine Live, Intranasal) is a live quadrivalent vaccine for administration by intranasal spray. FluMist Quadrivalent contains four vaccine virus strains: an A/H1N1 strain, an A/H3N2 strain and two B strains. FluMist Quadrivalent contains B strains from both the B/Yamagata/16/88 and the B/Victoria/2/87 lineages. FluMist Quadrivalent is manufactured according to the same process as FluMist.

The influenza virus strains in FluMist Quadrivalent are (a) *cold-adapted* (*ca*) (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive* (*ts*) (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) *attenuated* (*att*) (i.e., they do not produce classic influenza-like illness in the ferret model of human influenza infection).

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) using FluMist *[see Clinical Pharmacology (12.2)]*. For each of the four reassortant strains in FluMist Quadrivalent, the six internal gene segments responsible for *ca*, *ts*, and *att* phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant wild-type influenza viruses. Thus, the four viruses contained in FluMist Quadrivalent maintain the replication characteristics and phenotypic properties of the MDV and express the HA and NA of wild-type viruses. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the *ts* and *att* phenotypes. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the *ts* and *att* properties; five genetic loci in three gene segments control the *ca* property.

Each of the reassortant strains in FluMist Quadrivalent express the HA and NA of wild- type viruses that are related to strains expected to circulate during the 2018-2019 influenza season. Three of the viruses (A/H1N1, A/H3N2 and one B strain) have been recommended by the United States Public Health Service (USPHS) for inclusion in the annual trivalent and quadrivalent influenza vaccine formulations. An additional B strain has been recommended by the USPHS for inclusion in the quadrivalent influenza vaccine formulation.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to allow vaccine virus replication. The allantoic fluid of these eggs is harvested, pooled, and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. The viral harvests are then sterile filtered to produce the monovalent bulks. Each lot is tested for *ca*, *ts*, and *att* phenotypes and is also tested

extensively by *in vitro* and *in vivo* methods to detect adventitious agents. Monovalent bulks from the four strains are subsequently blended and diluted as required to attain the desired potency with stabilizing buffers to produce the quadrivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the four strains: A/Slovenia/2903/2015 (H1N1) (an A/Michigan/45/2015 (H1N1)pdm09-like virus), A/Singapore/INFIMH-16-0019/2016 (H3N2), B/Phuket/3073/2013 (B/Yamagata/16/88 lineage), and B/Colorado/06/2017 (B/Victoria/2/87 lineage). Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, and 0.96 mg/dose monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin (< 0.024 mcg/dose), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 0.37 mcg/dose). FluMist Quadrivalent contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. FluMist Quadrivalent is a colorless to pale yellow suspension and is clear to slightly cloudy.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FluMist Quadrivalent vaccine are not fully understood; serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role.

FluMist and FluMist Quadrivalent contain live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients (shedding) *[see Pharmacodynamics (12.2)]*.

12.2 Pharmacodynamics

Shedding Studies

Shedding of vaccine viruses within 28 days of vaccination with FluMist was evaluated in (1) multi-center study MI-CP129 which enrolled healthy individuals 6 through 59 months of age (N = 200); and (2) multi-center study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 344). In each study, nasal secretions were obtained daily for the first 7 days and every other day through either Day 25 and on Day 28 or through Day 28. In study MI-CP129, individuals with a positive shedding sample at Day 25 or Day 28 were to have additional shedding samples collected every 7 days until culture negative on 2 consecutive samples. Results of these studies are presented in Table 5.

Table 5: Characterization of Shedding with FluMist in Specified Age Groups by Frequency, Amount, and Duration (Study MI-CP129[a] and Study FM026[b])

Age	Number of Subjects	% Shedding[c]	Peak Titer ($TCID_{50}$/mL)[d]	% Shedding After Day 11	Day of Last Positive Culture
6-23 months[e]	99	89	< 5 log_{10}	7.0	Day 23[f]
24-59 months	100	69	< 5 log_{10}	1.0	Day 25[g]
5-8 years	102	50	< 5 log_{10}	2.9	Day 23[h]
9-17 years	126	29	< 4 log_{10}	1.6	Day 28[h]
18-49 years	115	20	< 3 log_{10}	0.9	Day 17[h]

[a] NCT00344305; see www.clinicaltrials.gov
[b] NCT00192140; see www.clinicaltrials.gov
[c] Proportion of subjects with detectable virus at any time point during the 28 days.
[d] Peak titer at any time point during the 28 days among samples positive for a single vaccine virus.
[e] FluMist and FluMist Quadrivalent are not approved for use in children younger than 24 months of age *[see Adverse Reactions (6.1)]*.
[f] A single subject who shed previously on Days 1-3; $TCID_{50}$/mL was less than 1.5 log_{10} on Day 23.
[g] A single subject who did not shed previously; $TCID_{50}$/mL was less than 1.5 log_{10}.
[h] A single subject who did not shed previously; $TCID_{50}$/mL was less than 1.0 log_{10}.

The highest proportion of subjects in each group shed one or more vaccine strains on Days 2-3 post vaccination. After Day 11 among individuals 2 through 49 years of age (n = 443), virus titers did not exceed 1.5 log_{10} $TCID_{50}$/mL.

Studies in Immunocompromised Individuals

Safety and shedding of vaccine virus following FluMist administration were evaluated in 28 HIV-infected adults [median CD4 cell count of 541 cells/mm^3] and 27 HIV-negative adults 18 through 58 years of age. No serious adverse events were reported during the one-month follow-up period. Vaccine strain (type B) virus was detected in 1 of 28 HIV-infected subjects on Day 5 only, and in none of the HIV-negative FluMist recipients.

Safety and shedding of vaccine virus following FluMist administration were also evaluated in children in a randomized (1:1), cross-over, double-blind, AF-SPG placebo-controlled trial in 24 HIV-infected children [median CD4 cell count of 1013 cells/mm^3] and 25 HIV-negative children 1 through 7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial in 243 HIV-infected children and adolescents 5 through 17 years of age receiving stable anti-retroviral therapy. Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following FluMist administration. In the 5 through 17 year old age group, one inactivated influenza vaccine recipient and one FluMist recipient experienced pneumonia within 28 days of vaccination (days 17 and 13, respectively). The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in HIV-infected individuals has not been evaluated.

Twenty mild to moderately immunocompromised children and adolescents 5 through 17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks prior to enrollment) were randomized 1:1 to receive FluMist or AF-SPG placebo. Frequency and duration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in immunocompromised individuals has not been evaluated.

Transmission Study

A prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children younger than 3 years of age to assess the transmission of vaccine viruses from a vaccinated individual to a non-vaccinated individual. A total of 197 children 8 through 36 months of age were randomized to receive one dose of FluMist (N = 98) or AF-SPG placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (A/H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type A (A/H1N1) and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 1-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted (*ca*) and temperature-sensitive (*ts*) phenotypes were preserved in 135 tested of 250 strains isolated at the local laboratory. Ten influenza isolates (9 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One placebo subject had mild symptomatic Type B virus infection confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This Type B isolate retained the *ca*, *ts*, and *att* phenotypes of the vaccine strain and had the same genetic sequence when compared to a Type B virus cultured from a vaccine recipient within the same playgroup. Four of the influenza Type A isolates were confirmed as wild-type A/Panama (H3N2). The remaining isolates could not be further characterized.

Assuming a single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist vaccinee in this daycare setting was 0.58% (95% CI: 0, 1.7) based on the Reed-Frost model. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6) using the Reed-Frost model.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FluMist Quadrivalent has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

14 CLINICAL STUDIES

The effectiveness of FluMist Quadrivalent is based on data demonstrating the clinical efficacy of FluMist in children and the effectiveness of FluMist in adults, and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibodies between individuals receiving FluMist and FluMist Quadrivalent. The clinical experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions *[see Description (11)]*.

14.1 Efficacy Studies of FluMist in Children and Adolescents

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy of FluMist compared to an intramuscularly administered, inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. (active control) in children 6 months to less than 5 years of age during the 2004-2005 influenza season. A total number of 3916 children without severe asthma, without use of bronchodilator or steroids, and without wheezing within the prior 6 weeks were randomized to FluMist and 3936 were randomized to active control. Children who previously received any influenza vaccine received a single dose of study vaccine, while those who never previously received an influenza vaccination (or had an unknown history of influenza vaccination) received two doses. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (CDC-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature ≥ 100°F oral or equivalent) with cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.

Table 6: Comparative Efficacy Against Culture-Confirmed Modified CDC-ILI[a] Caused by Wild-Type Strains (Study MI-CP111)[b,c]

	FluMist			Active Control[d]			%	
	N	# of Cases	Rate (cases/N)	N	# of Cases	Rate (cases/N)	Reduction in Rate for FluMist[e]	95% CI
Matched Strains								
All strains	3916	53	1.4%	3936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	--	--
B	3916	50	1.3%	3936	67	1.7%	27.3%	-4.8, 49.9
Mismatched Strains								
All strains	3916	102	2.6%	3936	245	6.2%	58.2%	47.4, 67.0
A/H1N1	3916	0	0.0%	3936	0	0.0%	--	--
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	66	1.7%	3936	71	1.8%	6.3%	-31.6, 33.3
Regardless of Match								
All strains	3916	153	3.9%	3936	338	8.6%	54.9%	45.4, 62.9
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	16.1%	-7.7, 34.7

ATP Population.

[a] Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.
[b] In children 6 months through 5 years of age
[c] NCT00128167; see www.clinicaltrials.gov
[d] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[e] Reduction in rate was adjusted for country, age, prior influenza vaccination status, and wheezing history status.

A randomized, double-blind, saline placebo-controlled trial (D153-P501) was performed to evaluate the efficacy of FluMist in children 12 through 35 months of age without high-risk medical conditions against culture-confirmed influenza illness. This study was performed in Asia over two successive seasons (2000-2001 and 2001-2002). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza. Respiratory illness that prompted an influenza culture was defined as at least one of the following: fever (≥ 100.4°F rectal or ≥ 99.5°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. A total of 3174 children were randomized 3:2 (vaccine:placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 7 for a description of the results.

During the second year of Study D153-P501, for children who received two doses in Year 1 and one dose in Year 2, FluMist demonstrated 84.3% (95% CI: 70.1, 92.4) efficacy against culture-confirmed influenza illness due to antigenically matched wild-type influenza.

Study AV006 was a second multi-center, randomized, double-blind, AF-SPG placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons (1996-1997 and 1997-1998). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in children who received two doses of vaccine in the first year and a single revaccination dose in the second year. Respiratory illness that prompted an influenza culture was defined as at least one of the following: fever (≥ 101°F rectal or oral; or ≥ 100.4°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. During the first year of the study, 1602 children 15 through 71 months of age were randomized 2:1 (vaccine:placebo). See Table 7 for a description of the results.

Table 7: Efficacy[a] of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness Due to Antigenically Matched Wild-Type Strains (Studies D153-P501[b] & AV006[c], Year 1)

	D153-P501[d]			AV006[e]		
	FluMist n[f] (%)	Placebo n[f] (%)	% Efficacy (95% CI)	FluMist n[f] (%)	Placebo n[f] (%)	% Efficacy (95% CI)
	N[g] = 1653	N[g] = 1111		N[g] = 849	N[g] = 410	
Any strain	56 (3.4%)	139 (12.5%)	72.9%[h] (62.8, 80.5)	10 (1%)	73 (18%)	93.4% (87.5, 96.5)
A/H1N1	23 (1.4%)	81 (7.3%)	80.9% (69.4, 88.5)[i]	0	0	--
A/H3N2	4 (0.2%)	27 (2.4%)	90.0% (71.4, 97.5)	4 (0.5%)	48 (12%)	96.0% (89.4, 98.5)
B	29 (1.8%)	35 (3.2%)	44.3% (6.2, 67.2)	6 (0.7%)	31 (7%)	90.5% (78.0, 95.9)

[a] D153-P501 and AV006 data are for subjects who received two doses of study vaccine.
[b] In children 12 through 35 months of age
[c] In children 15 through 71 months of age
[d] NCT00192244; see www.clinicaltrials.gov
[e] NCT00192179; see www.clinicaltrials.gov
[f] Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.
[g] Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis.
[h] For D153-P501, influenza circulated through 12 months following vaccination.
[i] Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, children remained in the same treatment group as in Year 1 and received a single dose of FluMist or placebo. During the second year, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine, A/Wuhan/359/95; FluMist demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

14.2 Immune Response Study of FluMist Quadrivalent in Children and Adolescents

A multicenter, randomized, double-blind, active-controlled, non-inferiority study (MI-CP208) was performed to assess the immunogenicity of FluMist Quadrivalent compared to FluMist (active control) in children and adolescents 2 through 17 years of age. A total of 2312 subjects were randomized by site at a 3:1:1 ratio to receive either FluMist Quadrivalent or one of two formulations of comparator vaccine FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage or a B strain of the Victoria lineage).

Children 2 through 8 years of age received 2 doses of vaccine approximately 30 days apart; children 9 years of age and older received 1 dose. For children 2 through 8 years of age with a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and at 28 days after the first dose. For children 2 through 8 years of age without a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and 28 days after the second dose. For children 9 years of age and older, immunogenicity assessments were performed prior to vaccination and at 28 days post vaccination.

Immunogenicity was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.3 Effectiveness Study of FluMist in Adults

AV009 was a U.S. multi-center, randomized, double-blind, AF-SPG placebo-controlled trial to evaluate effectiveness of FluMist in adults 18 through 64 years of age without high-risk medical conditions over the 1997-1998 influenza season. Participants were randomized 2:1 (vaccine:placebo). Cultures for influenza virus were not obtained from subjects in the trial, thus efficacy against culture-confirmed influenza was not assessed. The A/Wuhan/359/95 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/05/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was the reduction in the proportion of participants with one or more episodes of any febrile illness, and prospective secondary endpoints were severe febrile illness and febrile upper respiratory illness. Effectiveness for any of the three endpoints was not demonstrated in a subgroup of adults 50 through 64 years of age. Primary and secondary effectiveness endpoints from the age group 18 through 49 years are presented in Table 8. Effectiveness was not demonstrated for the primary endpoint in adults 18 through 49 years of age.

Table 8: Effectiveness of FluMist to Prevent Febrile Illness in Adults 18 through 49 Years of Age During the 7-Week Site-Specific Outbreak Period (Study AV009)

Endpoint	FluMist N = 2411[a] n (%)	Placebo N = 1226[a] n (%)	Percent Reduction	(95% CI)
Participants with one or more events of:[b]				
Primary Endpoint:				
Any febrile illness	331 (13.73)	189 (15.42)	**10.9**	(-5.1, 24.4)
Secondary Endpoints:				
Severe febrile illness	250 (10.37)	158 (12.89)	**19.5**	(3.0, 33.2)
Febrile upper respiratory illness	213 (8.83)	142 (11.58)	**23.7**	(6.7, 37.5)

[a] Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).
[b] The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Effectiveness was shown in a post-hoc analysis using an endpoint of CDC-ILI in the age group 18 through 49 years of age.

14.4 Immune Response Study of FluMist Quadrivalent in Adults

A multicenter, randomized, double-blind, active-controlled, and non-inferiority study (MI-CP185) was performed to assess the safety and immunogenicity of FluMist Quadrivalent compared to those of FluMist (active control) in adults 18 through 49 years of age. A total of 1800 subjects were randomized by site at a 4:1:1 ratio to receive either 1 dose of FluMist Quadrivalent or 1 dose of one of two formulations of comparator vaccine, FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage and a B strain of the Victoria lineage).

Immunogenicity in study MI-CP185 was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.5 Concomitantly Administered Live Virus Vaccines

In Study AV018, concomitant administration of FluMist, MMR (manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) was studied in 1245 subjects 12 through 15 months of age. Subjects were randomized in a 1:1:1 ratio to MMR, Varicella vaccine and AF-SPG placebo (group 1); MMR, Varicella vaccine and FluMist (group 2); or FluMist alone (group 3). Immune responses to MMR and Varicella vaccines were evaluated 6 weeks post-vaccination while the immune responses to FluMist were evaluated 4 weeks after the second dose. No evidence of interference with immune response to measles, mumps, rubella, varicella and FluMist vaccines was observed.

15 REFERENCES

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992 – 1993 and 1993 – 1994 influenza vaccines. N Engl J Med 1998;339(25):1797-802.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FluMist Quadrivalent is supplied in a package of 10 pre-filled, single-dose (0.2 mL) intranasal sprayers. The single-use intranasal sprayer is not made with natural rubber latex.

Carton containing 10 intranasal sprayers: NDC 66019-305-10

Single intranasal sprayer: NDC 66019-305-01

16.2 Storage and Handling

The cold chain [2-8°C (35-46°F)] must be maintained when transporting FluMist Quadrivalent.

FLUMIST QUADRIVALENT SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.

DO NOT FREEZE.

Keep FluMist Quadrivalent sprayer in outer carton in order to protect from light.

A single temperature excursion up to 25°C (77°F) for 12 hours has been shown to have no adverse impact on the vaccine. After a temperature excursion, the vaccine should be returned immediately to the recommended storage condition (2°C – 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

Once FluMist Quadrivalent has been administered or has expired, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

17 PATIENT COUNSELING INFORMATION

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling (Information for Patients and Their Caregivers).

Inform vaccine recipients or their parents/guardians of the need for two doses at least 1 month apart in children 2 through 8 years of age, depending on vaccination history. Provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization.

17.1 Asthma and Recurrent Wheezing

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children younger than 5 years of age, also ask if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group. Inform the vaccinee or their parent/guardian that there may be an increased risk of wheezing associated with FluMist Quadrivalent in persons younger than 5 years of age with recurrent wheezing and persons of any age with asthma *[see Warnings and Precautions (5.2)]*.

17.2 Vaccination with a Live Virus Vaccine

Inform vaccine recipients or their parents/guardians that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

Instruct the vaccine recipient or their parent/guardian to report adverse reactions to their healthcare provider.

MedImmune

Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878
1-877-633-4411

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Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mĭst Kwä-drə-VĀ-lənt)
(Influenza Vaccine Live, Intranasal)

Please read this Patient Information carefully before you or your child is vaccinated with FluMist Quadrivalent.

This is a summary of information about FluMist Quadrivalent. It does not take the place of talking with your healthcare provider about influenza vaccination. If you have questions or would like more information, please talk with your healthcare provider.

What is FluMist Quadrivalent?

FluMist Quadrivalent is a vaccine that is sprayed into the nose to help protect against influenza. It can be used in children, adolescents, and adults ages 2 through 49. FluMist Quadrivalent is similar to MedImmune's trivalent Influenza Vaccine Live, Intranasal (FluMist), except FluMist Quadrivalent provides protection against an additional influenza strain. FluMist Quadrivalent may not prevent influenza in everyone who gets vaccinated.

Who should not get FluMist Quadrivalent?

You should not get FluMist Quadrivalent if you:

- have a severe allergy to eggs or to any inactive ingredient in the vaccine (see "What are the ingredients in FluMist Quadrivalent?")
- have ever had a life-threatening reaction to influenza vaccinations
- are 2 through 17 years old and take aspirin or medicines containing aspirin. Children or adolescents should not be given aspirin for 4 weeks after getting FluMist or FluMist Quadrivalent unless your healthcare provider tells you otherwise.

Please talk to your healthcare provider if you are not sure if the items listed above apply to you or your child.

Children under 2 years old have an increased risk of wheezing (difficulty with breathing) after getting FluMist Quadrivalent.

Who may not be able to get FluMist Quadrivalent?

Tell your healthcare provider if you or your child:

- are currently wheezing
- have a history of wheezing if under 5 years old
- have had Guillain-Barré syndrome
- have a weakened immune system or live with someone who has a severely weakened immune system
- have problems with your heart, kidneys, or lungs
- have diabetes
- are pregnant or nursing
- are taking Tamiflu®, Relenza®, amantadine, or rimantadine

If you or your child cannot take FluMist Quadrivalent, you may still be able to get an influenza shot. Talk to your healthcare provider about this.

How is FluMist Quadrivalent given?

- FluMist Quadrivalent is a liquid that is sprayed into the nose.
- You can breathe normally while getting FluMist Quadrivalent. There is no need to inhale or "sniff" it.
- People 9 years of age and older need one dose of FluMist Quadrivalent each year.
- Children 2 through 8 years old may need 2 doses of FluMist Quadrivalent, depending on their history of previous influenza vaccination. Your healthcare provider will decide if your child needs to come back for a second dose.

What are the possible side effects of FluMist Quadrivalent?

The most common side effects are:

- runny or stuffy nose
- sore throat
- fever over 100°F

Other possible side effects include:

- decreased appetite
- irritability
- tiredness
- cough
- headache
- muscle ache
- chills

Call your healthcare provider or go to the emergency department right away if you or your child experience:

- hives or a bad rash
- trouble breathing
- swelling of the face, tongue, or throat

These are not all the possible side effects of FluMist Quadrivalent. You can ask your healthcare provider for a complete list of side effects that is available to healthcare professionals.

Call your healthcare provider for medical advice about side effects. You may report side effects to VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

What are the ingredients in FluMist Quadrivalent?

Active Ingredient: FluMist Quadrivalent contains 4 influenza virus strains that are weakened (A(H1N1), A(H3N2), B Yamagata lineage, and B Victoria lineage).

Inactive Ingredients: monosodium glutamate, gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, and gentamicin.

FluMist Quadrivalent does not contain preservatives.

How is FluMist Quadrivalent Stored?

FluMist Quadrivalent is stored in a refrigerator (not the freezer) between 35-46°F (2-8°C) upon receipt. FluMist Quadrivalent sprayer must be kept in the carton until use in order to protect from light. FluMist Quadrivalent must be used before the expiration date on the sprayer label.

If you would like more information, talk to your healthcare provider or visit www.flumistquadrivalent.com or call 1-877-633-4411.

MedImmune

Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878

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M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX® (Mumps Virus Vaccine Live), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX® II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.{1,2}

The growth medium for measles and mumps is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and recombinant human albumin) as stabilizer and neomycin.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing recombinant human albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

The cells, virus pools, and fetal bovine serum are all screened for the absence of adventitious agents.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus; 12,500 $TCID_{50}$ of mumps virus; and 1,000 $TCID_{50}$ of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.

CLINICAL PHARMACOLOGY

Measles, mumps, and rubella are three common childhood diseases, caused by measles virus, mumps virus (paramyxoviruses), and rubella virus (togavirus), respectively, that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles. Mumps is associated with aseptic meningitis, deafness and orchitis; and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles, mumps, and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. For measles, 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases; for mumps, 152,209 cases reported in 1968 compared to 840 cases reported in 1995 resulted in a 99.45% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 200 cases reported in 1995 resulted in a 99.65% decrease.{3}

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study{4} of 6-month-old and 15-month-old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6-month-old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15-month-old infants developed NT. This rate of seroconversion is higher than that previously reported for 6-month-old infants born to naturally immune mothers tested by HI assay. When the 6-month-old infants of immunized mothers were revaccinated at 15

months, they developed antibody titers equivalent to the 15-month-old vaccinees. The lower seroconversion rate in 6-month-olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6-month-olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.{5,6}

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components.{7-12} These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.{13-15}

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination.{16-18} See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine{19-25} and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.{26,27} The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.{27-29} The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,{27,29-31} and provide greater confidence for lasting immunity.

INDICATIONS AND USAGE

Recommended Vaccination Schedule

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Individuals first vaccinated at 12 months of age or older should be revaccinated prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12 to 15 months of age and administration of the second dose of M-M-R II at 4 to 6 years of age.{32} In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

Measles Outbreak Schedule

Infants Between 6 to 12 Months of Age

Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination at elementary school entry.{32}

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Other Vaccination Considerations

Non-Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.{33}

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.

The ACIP has stated "If it is practical and if reliable laboratory services are available, women of childbearing age who are potential candidates for vaccination can have serologic tests to determine susceptibility to rubella. However, with the exception of premarital and prenatal screening, routinely performing serologic tests for all women of childbearing age to determine susceptibility (so that vaccine is given only to proven susceptible women) can be effective but is expensive. Also, 2 visits to the health-care provider would be necessary — one for screening and one for vaccination. Accordingly, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing — and may be preferable, particularly when costs of serology are high and follow-up of identified susceptible women for vaccination is not assured."{33}

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

Postpartum Women

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see PRECAUTIONS, *Nursing Mothers*).

Other Populations

Previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in monovalent rubella vaccine or in M-M-R II) to reduce the risk of exposure of the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can either receive the indicated monovalent vaccine (measles, mumps, or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.{34-36}

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel.{33,34,37}

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.{34}

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to wild-type measles virus is increased, as may occur during international travel."{34}

Post-Exposure Vaccination

Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before exposure, substantial protection may be afforded.{34,38,39} There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.{33,37}

Use With Other Vaccines

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin.{40}

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.{41}

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;{41-43} cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis{44} (MIBE), pneumonitis{45} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

WARNINGS

Due caution should be employed in administration of M-M-R II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).{46}

However, the AAP has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of which children will have an immediate hypersensitivity reaction...Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."{47}

Hypersensitivity to Neomycin

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous, pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine."{47}

Thrombocytopenia

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).{42,43}

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).{47}

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.{33} However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine;{48} no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with M-M-R II may not result in protection in 100% of vaccinees.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.{49}

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, CONTRAINDICATIONS, and PRECAUTIONS, *Pregnancy*).

Laboratory Tests

See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

Drug Interactions

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g. nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of [measles, mumps, or rubella vaccine]."{33,34,37}

Immune Globulin

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response.{33,34,47}

See also PRECAUTIONS, *General*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome;{50} (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans;{37} and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type measles during pregnancy.{51,52} There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.{53} In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.{54,55} Caution should be exercised when M-M-R II is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY). Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella:

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia, have also been reported following administration of MERUVAX II.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 12-26%),{17,56,57} and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines.

The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases).{58,59}

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported (see CONTRAINDICATIONS). In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.{60}

Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Respiratory System

Pneumonia; pneumonitis (see CONTRAINDICATIONS); sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash; measles-like rash; pruritis.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site; Henoch-Schönlein purpura; acute hemorrhagic edema of infancy.

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.{61}

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.{49} A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravascularly.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry.{32} See also INDICATIONS AND USAGE, *Measles Outbreak Schedule*.

Immune Globulin (IG) is not to be given concurrently with M-M-R II (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions*).

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. M-M-R II, when reconstituted, is clear yellow.

Use With Other Vaccines

M-M-R II should be given one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB® [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate injection sites and syringes. No impairment of immune response to individually tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine, and varicella vaccine), data from numerous studies have

indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."{62}

HOW SUPPLIED

No. 4681 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

Storage

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the lyophilized vaccine at 36°F to 46°F (2°C to 8°C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. **Do not freeze the diluent.**

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 36°F to 46°F (2°C to 8°C) and discard if not used within 8 hours.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREVNAR 13 safely and effectively. See full prescribing information for PREVNAR 13.

PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])
Suspension for intramuscular injection
Initial US Approval: 2010

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	7/2016
Vaccination Schedule for Adults 18 Years of Age and Older (2.7)	7/2016
Contraindications (4)	7/2016

---------- INDICATIONS AND USAGE ----------

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.1)
- active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)

In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:

- active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.2)

In adults 18 years of age and older, Prevnar 13 is indicated for:

- active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.3)

Limitations of Prevnar 13 Use and Effectiveness

- Prevnar 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

Children 6 weeks through 5 years: The four-dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6, and 12-15 months of age. (2.3)
Children 6 through 17 years of age: a single dose. (2.6)
Adults 18 years and older: a single dose. (2.7)

----------DOSAGE FORMS AND STRENGTHS ----------

0.5 mL suspension for intramuscular injection, supplied in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine. (4)

---------- WARNINGS AND PRECAUTIONS----------

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.3)

---------- --ADVERSE REACTIONS----------

- In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions (>5%) were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%). (6.1)
- In children aged 5 through 17 years, the most commonly reported solicited adverse reactions (>5%) were injection site tenderness (>80%), injection site redness (>30%), injection site swelling (>30%), irritability (>20%), decreased appetite (>20%), increased sleep (>20%), fever (>5%), and decreased sleep (>5%). (6.1)
- In adults aged 18 years and older, the most commonly reported solicited adverse reactions (>5%) were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), vomiting (>5%), fever (>5%), chills (>5%), and rash (>5%). (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

---------- --------DRUG INTERACTIONS----------

In adults, antibody responses to Prevnar 13 were diminished when given with inactivated influenza vaccine, trivalent (IIV3). (14.3)

---------- USE IN SPECIFIC POPULATIONS ----------

Pediatric Use: Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: X/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Children 6 Weeks Through 5 Years of Age

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13® is indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae s*erotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A.

1.2 Children 6 Years Through 17 Years of Age

In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:

- active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

1.3 Adults 18 Years of Age and Older

In adults 18 years of age and older, Prevnar 13 is indicated for:

- active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

1.4 Limitations of Prevnar 13 Use and Effectiveness

- Prevnar 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a homogenous, white suspension in the vaccine container. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration *[see Description (11)]*. This product should not be used if particulate matter or discoloration is found.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

2.2 Administration Information

For intramuscular injection only.

Each 0.5 mL dose is to be injected intramuscularly using a sterile needle attached to the supplied prefilled syringe. The preferred sites for injection are the anterolateral aspect of the thigh in infants and the deltoid muscle of the upper arm in toddlers, children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

2.3 Vaccination Schedule for Infants and Toddlers

Prevnar 13 is to be administered as a four-dose series at 2, 4, 6, and 12-15 months of age.

Table 1: Vaccination Schedule for Infants and Toddlers

Dose	Dose 1[a,b]	Dose 2[b]	Dose 3[b]	Dose 4[c]
Age at Dose	2 months	4 months	6 months	12-15 months

[a] Dose 1 may be given as early as 6 weeks of age.
[b] The recommended dosing interval is 4 to 8 weeks.
[c] The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

2.4 Vaccination Schedule for Unvaccinated Children 7 Months Through 5 Years of Age

For children 7 months through 5 years of age who have not received Prevnar® or Prevnar 13, the catch-up schedule in Table 2 applies:

Table 2: Vaccination Schedule for Unvaccinated Children 7 Months of Age Through 5 Years of Age

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3[a]
12-23 months of age	2[b]
24 months through 5 years of age (prior to the 6th birthday)	1

[a] The first 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.
[b] Two doses at least 2 months apart.

The immune responses induced by this catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12-15 months). In children 24 months through 5 years of age, lower antibody concentrations were observed for some serotypes, compared to antibody concentrations following 3 doses of Prevnar 13 (given at 2, 4, and 6 months).

2.5 Vaccination Schedule for Children Previously Vaccinated With Prevnar Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Children 15 months through 5 years of age who are considered completely immunized with Prevnar may receive one dose of Prevnar 13 to elicit immune responses to the 6 additional serotypes. This catch-up (supplemental) dose of Prevnar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevnar. The immune responses induced by

this Prevnar 13 schedule may result in lower antibody concentrations for the 6 additional serotypes (types 1, 3, 5, 6A, 7F, and 19A), compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12-15 months).

2.6 Vaccination Schedule for Children 6 Years Through 17 Years of Age

In children 6 years through 17 years of age, Prevnar 13 is administered as single dose. If Prevnar was previously administered, then at least 8 weeks should elapse before receiving Prevnar 13.

2.7 Vaccination Schedule for Adults 18 Years of Age and Older

Prevnar 13 is administered as a single dose.

3 DOSAGE FORMS AND STRENGTHS

Prevnar 13 is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 13.

5.2 Altered Immunocompetence

Individuals with altered immunocompetence, including those at higher risk for invasive pneumococcal disease (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome), may have reduced antibody responses to immunization with Prevnar 13 *[see Use in Specific Populations (8.6)]*.

5.3 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience With Prevnar 13 in Children 6 Weeks Through 17 Years of Age

The safety of Prevnar 13 was evaluated in 13 clinical trials in which 4,729 infants (6 weeks through 11 months of age) and toddlers (12 months through 15 months of age) received at least one dose of Prevnar 13 and 2,760 infants and toddlers received at least one dose of Prevnar active control. Safety data for the first three doses are available for all 13 infant studies; dose 4 data are available for 10 studies; and data for the 6-month follow-up are available for 7 studies. The vaccination schedule and concomitant vaccinations used in these infant trials were consistent with country-specific recommendations and local clinical practice. There were no substantive differences in demographic characteristics between the vaccine groups. By race, 84.0% of subjects were White, 6.0% were Black or African-American, 5.8% were Asian and 3.8% were of 'Other' race (most of these being biracial). Overall, 52.3% of subjects were male infants.

Three studies in the US (Studies 1, 2 and 3)[1,2,3] evaluated the safety of Prevnar 13 when administered concomitantly with routine US pediatric vaccinations at 2, 4, 6, and 12-15 months of age. Solicited local and systemic adverse reactions were recorded daily by parents/guardians using an electronic diary for 7 consecutive days following each vaccination. For unsolicited adverse events, study subjects were monitored from administration of the first dose until one month after the infant series, and for one month after the administration of the toddler dose. Information regarding unsolicited and serious adverse events, newly diagnosed chronic medical conditions, and hospitalizations since the last visit were collected during the clinic visit for the fourth-study dose and during a scripted telephone interview 6 months after the fourth-study dose. Serious adverse events were also collected throughout the study period. Overall, the safety data show a similar proportion of Prevnar 13 and Prevnar subjects reporting serious adverse events. Among US study subjects, a similar proportion of Prevnar 13 and Prevnar recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

Serious Adverse Events in All Infant and Toddler Clinical Studies

Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting period may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13 recipients and 7.2% among Prevnar recipients. Serious adverse events observed during different study periods for Prevnar 13 and Prevnar respectively were: 1) 3.7% and 3.5% from dose 1 to the bleed approximately 1 month after the infant series; 2) 3.6% and 2.7% from the bleed after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the bleed approximately 1 month after the toddler dose and 4) 2.5% and 2.8% during the 6 month follow-up period after the last dose.

The most commonly reported serious adverse events were in the 'Infections and infestations' system organ class including bronchiolitis (0.9%, 1.1%), gastroenteritis, (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Prevnar 13 and Prevnar respectively.

There were 3 (0.063%) deaths among Prevnar 13 recipients, and 1 (0.036%) death in Prevnar recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age specific background rates of SIDS from the year 2000.

Among 6,839 subjects who received at least 1 dose of Prevnar 13 in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4,204 subjects who received at least 1 dose of Prevnar in clinical trials conducted globally, there were 3 hypotonic-hyporesponsive episode adverse reactions reported (0.071%). All 4 events occurred in a single clinical trial in Brazil in which subjects received whole cell pertussis vaccine at the same time as Prevnar 13 or Prevnar.

Solicited Adverse Reactions in the Three US Infant and Toddler Studies

A total of 1,907 subjects received at least 1 dose of Prevnar 13 and 701 subjects received at least 1 dose of Prevnar in the three US studies (Studies 1, 2 and 3)[1,2,3]. Most subjects were White (77.3%), 14.2% were Black or African-American, and 1.7% were Asian; 79.1% of subjects were non-Hispanic and non-Latino and 14.6% were Hispanic or Latino. Overall, 53.6% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13 or Prevnar administered to US infants and toddlers are shown in Tables 3 and 4.

Table 3: Percentage of US Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Local Reaction	**Prevnar 13** (N^b=1375-1612) %	**Prevnar** (N^b=516-606) %	**Prevnar 13** (N^b=1069-1331) %	**Prevnar** (N^b=405-510) %	**Prevnar 13** (N^b=998-1206) %	**Prevnar** (N^b=348-446) %	**Prevnar 13** (N^b=874-1060) %	**Prevnar** (N^b=283-379) %
Redness[c]								
Any	24.3	26.0	33.3	29.7	37.1	36.6	42.3	45.5
Mild	23.1	25.2	31.9	28.7	35.3	35.3	39.5	42.7
Moderate	2.2	1.5	2.7	2.2	4.6	5.1	9.6	13.4[d]
Severe	0	0	0	0	0	0	0	0
Swelling[c]								
Any	20.1	20.7	25.2	22.5	26.8	28.4	31.6	36.0[d]
Mild	17.2	18.7	23.8	20.5	25.2	27.5	29.4	33.8
Moderate	4.9	3.9	3.7	4.9	3.8	5.8	8.3	11.2[d]
Severe	0	0	0.1	0	0	0	0	0
Tenderness								
Any	62.5	64.5	64.7	62.9	59.2	60.8	57.8	62.5
Interferes with limb movement	10.4	9.6	9.0	10.5	8.4	9.0	6.9	5.7

[a] Data are from three primary US safety studies (the US Phase 2 infant study [National Clinical Trial (NCT) number NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

[b] Number of subjects reporting Yes for at least 1 day or No for all days.

[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of induration and erythema were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

[d] Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

Table 4: Percentage of US Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a,b]

	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Systemic Events	**Prevnar 13** (N[a]=1360 - 1707) %	**Prevnar** (N[a]=497-640) %	**Prevnar 13** (N[a]=1084-1469) %	**Prevnar** (N[a]=409-555) %	**Prevnar 13** (N[a]=997-1361) %	**Prevnar** (N[a]=354-521) %	**Prevnar 13** (N[a]=850-1227) %	**Prevnar** (N[a]=278-436) %
Fever[c]								
Any	24.3	22.1	36.5	32.8	30.3	31.6	31.9	30.6
Mild	23.6	21.7	34.9	31.6	29.1	30.2	30.3	30.0
Moderate	1.1	0.6	3.4	2.8	4.2	3.3	4.4	4.6
Severe	0.1	0.2	0.1	0.3	0.1	0.7	1.0	0
Decreased appetite	48.3	43.6	47.8	43.6	47.6	47.6	51.0	49.4
Irritability	85.6	83.6	84.8	80.4	79.8	80.8	80.4	77.8
Increased sleep	71.5	71.5	66.6	63.4	57.7	55.2	48.7	55.1
Decreased sleep	42.5	40.6	45.6	43.7	46.5	47.7	45.3	40.3

[a] Number of subjects reporting Yes for at least 1 day or No for all days.
[b] Data are from three primary US safety studies (the US Phase 2 infant study [NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.
[c] Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (>40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 62 to 75% of subjects after any of the 4 doses. There were no statistical differences in frequencies of adverse reactions reported between the Prevnar 13 and Prevnar groups.

The incidence rates of any fever (≥38.0°C) were similar on days 1 and 2 following each dose of Prevnar 13 compared to after each dose of Prevnar administered to US infants and toddlers (day 1 = day of vaccination). After dose 1, fever was reported in 11.0-12.7% on day 1 and 6.4-6.8% on day 2. After dose 2, fever was reported in 12.3-13.1% on day 1 and 12.5-12.8% on day 2. After dose 3, fever was reported in 8.0-9.6% on day 1 and 9.1-10.5% on day 2. And after dose 4, fever was reported in 6.3-6.4% on day 1 and 7.3-9.7% on day 2.

Unsolicited Adverse Reactions in the Three US Infant and Toddler Safety Studies

The following were determined to be adverse drug reactions based on experience with Prevnar 13 in clinical trials.

Reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash.

Reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

Safety Assessments in the Catch-Up Studies in Infants and Children Through 5 Years of Age

In a catch-up study[4] conducted in Poland (Study 4), 354 children (7 months through 5 years of age) receiving at least one dose of Prevnar 13 were also monitored for safety. All subjects in this study were White and non-Hispanic. Overall, 49.6% of subjects were male infants. The incidence and severity of solicited adverse reactions that occurred within 4 days following each dose of Prevnar 13 administered to pneumococcal-vaccine naïve children 7 months through 5 years of age are shown in Tables 5 and 6.

Table 5: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Local Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccination[a]

	7 through 11 months			12 through 23 months		24 months through 5 years
Graded Local Reaction	**Dose 1** N[b]=86 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-82 %	**Dose 1** N[b]=108-110 %	**Dose 2** N[b]=98-106 %	**Dose 1** N[b]=147-149 %
Redness[c]						
Any	48.8	46.0	37.8	70.0	54.7	50.0
Mild	41.9	40.2	31.3	55.5	44.7	37.4
Moderate	16.3	9.3	12.5	38.2	25.5	25.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Swelling[c]						
Any	36.0	32.2	25.0	44.5	41.0	36.9
Mild	32.6	28.7	20.5	36.7	36.2	28.2
Moderate	11.6	14.0	11.3	24.8	12.1	20.3
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness						
Any	15.1	15.1	15.2	33.3	43.7	42.3
Interferes with limb movement	1.2	3.5	6.4	0.0	4.1	4.1

[a] Study conducted in Poland (NCT00452452) Study 4.
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

Table 6: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Systemic Adverse Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccination[a]

	7 through 11 months			12 through 23 months		24 months through 5 years
Systemic Reaction	**Dose 1** N[b]=86-87 %	**Dose 2** N[b]=86-87 %	**Dose 3** N[b]=78-81 %	**Dose 1** N[b]=108 %	**Dose 2** N[b]=98-100 %	**Dose 1** N[b]=147-148 %
Fever[c]						
Mild	3.4	8.1	5.1	3.7	5.1	0.7
Moderate	1.2	2.3	1.3	0.9	0.0	0.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0
Decreased appetite	19.5	17.2	17.5	22.2	25.5	16.3
Irritability	24.1	34.5	24.7	30.6	34.0	14.3
Increased sleep	9.2	9.3	2.6	13.0	10.1	11.6
Decreased sleep	24.1	18.4	15.0	19.4	20.4	6.8

[a] Study conducted in Poland (NCT00452452) Study 4.
[b] Number of subjects reporting Yes for at least 1 day or No for all days.
[c] Fever gradings: Mild (≥38ºC but ≤39ºC), Moderate (>39ºC but ≤40ºC), and Severe (>40ºC). No other systemic event other than fever was graded.

A US study[5] (Study 5) evaluated the use of Prevnar 13 in children previously immunized with Prevnar. In this open label trial, 596 healthy children 15 through 59 months of age previously vaccinated with at least 3 doses of Prevnar, received 1 or 2 doses of Prevnar 13. Children 15 months through 23 months of age (group 1) received 2 doses, and children 24 months through 59 months of age (group 2) received one dose. Most subjects were White (74.3%), 14.9% were Black or African-American, and 1.2% were Asian; 89.3% of subjects were non-Hispanic and non-Latino and 10.7% were Hispanic or Latino. Overall, 52.2% of subjects were male.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 15 months through 59 months of age are shown in Tables 7 and 8.

Table 7: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Doses of Prevnar, Reporting Solicited Local Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination[a]

	15 months through 23 months[b]		24 months through 59 months[c]
Graded Local Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[d]=67-72 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[d]=154-184 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[d]=209-238 %
Redness[e]			
Any	26.4	28.2	35.4
Mild	18.8	24.3	31.1
Moderate	11.4	7.5	12.1
Severe	1.5	0.0	0.0
Swelling[e]			
Any	23.9	19.6	20.7
Mild	18.6	16.4	17.2
Moderate	8.8	8.1	7.5
Severe	0.0	0.0	0.0
Tenderness			
Any	48.6	47.3	62.6
Interferes with limb movement	5.9	6.4	10.7

[a] Study conducted in US NCT00761631 (Study 5).
[b] Dose 2 data not shown.
[c] The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.
[d] Number of subjects reporting Yes for at least 1 day or No for all days.
[e] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

Table 8: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4 Prior Infant Prevnar Doses, Reporting Solicited Systemic Adverse Reactions Within 7 Days After One Supplemental Prevnar 13 Vaccination[a]

	15 through 23 months[b]		24 months through 59 months[c]
Systemic Reaction	**1 dose Prevnar 13 3 prior Prevnar doses** N[d]=66-75 %	**1 dose Prevnar 13 4 prior Prevnar doses** N[d]=154-189 %	**1 dose Prevnar 13 3 or 4 prior Prevnar doses** N[d]=209-236 %
Fever[e]			
Any	19.1	19.9	8.1
Mild	16.2	17.4	7.6
Moderate	6.1	3.9	1.9
Severe	0.0	0.0	0.5
Decreased appetite	44.4	39.3	28.1
Irritability	73.3	65.1	45.8
Increased sleep	35.2	35.3	18.8
Decreased sleep	25.0	29.7	14.8

[a] Study conducted in US NCT00761631 (Study 5).
[b] Dose 2 data not shown.
[c] The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.
[d] Number of subjects reporting Yes for at least 1 day or No for all days.
[e] Fever gradings: Mild (≥38ºC but ≤39ºC), Moderate (>39ºC but ≤40ºC), and Severe (>40ºC). No other systemic event other than fever was graded.

Clinical Trials Experience With Prevnar 13 in Children 5 Through 17 Years of Age

In a US study[5] (Study 5), the safety of Prevnar 13 was evaluated in children 5 through 9 years of age previously immunized with at least one dose of Prevnar, and in children 10 through 17 years of age with no prior pneumococcal vaccination. In this open label trial, 592 children, including those with asthma, received a single dose of Prevnar 13. The percentage of children 5 through 9 years of age who received 3 and 4 prior doses of Prevnar was 29.1% and 54.5% respectively.

Most subjects were White (72.8%), 21.8% were Black or African-American, and 1.5% were Asian; 91.4% of subjects were non-Hispanic and non-Latino and 8.6% were Hispanic or Latino. Overall, 51.2% of subjects were male.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 5 through 17 years of age are shown in Tables 9 and 10.

Table 9: Percentage of Subjects 5 Through 17 Years of Age, Reporting Solicited Local Reactions Within 7 Days After Prevnar 13 Vaccination [a]

	Vaccine Group (as Administered)					
	Prevnar 13 (5 Through 9 Years)			Prevnar 13 (10 Through 17 Years)		
Local Reaction	N[b]	n[c]	%	N[b]	n[c]	%
Redness						
Any	233	100	42.9	232	70	30.2
Mild[d]	226	63	27.9	226	48	21.2
Moderate[d]	218	48	22.0	221	31	14.0
Severe[d]	212	7	3.3	213	4	1.9
Swelling						
Any	226	85	37.6	233	86	36.9
Mild[d]	220	48	21.8	221	50	22.6
Moderate[d]	219	48	21.9	226	48	21.2
Severe[d]	211	7	3.3	214	4	1.9
Tenderness						
Any	265	230	86.8	283	252	89.0
Significant[e]	221	43	19.5	242	106	43.8

[a] Study conducted in US NCT00761631 (Study 5).
[b] N = number of subjects reporting Yes for at least 1 day or No for all days.
[c] n = Number of subjects reporting the specific characteristic.
[d] Mild, 0.5 – 2.0 cm; moderate, 2.5 – 7.0 cm; severe, >7.0 cm.
[e] Significant = present and interfered with limb movement.

Table 10: Percentage of Subjects 5 Through 17 Years of Age, Reporting Solicited Systemic Adverse Reactions Within 7 Days After Prevnar 13 Vaccination[a]

	Vaccine Group (as Administered)					
	Prevnar 13 (5 Through 9 Years)			Prevnar 13 (10 Through 17 Years)		
Systemic Event	N[b]	n[c]	%	N[b]	n[c]	%
Any fever ≥38°C	214	13	6.1	214	12	5.6
Mild[d]	212	9	4.2	214	11	5.1
Moderate[d]	212	5	2.4	212	1	0.5
Severe[d]	210	1	0.5	212	1	0.5
Decreased appetite	227	52	22.9	223	51	22.9
Irritability	234	73	31.2	234	59	25.2
Increased sleep	226	48	21.2	229	61	26.6
Decreased sleep	212	12	5.7	224	42	18.8
Hives (urticaria)	213	4	1.9	214	3	1.4

[a] Study conducted in US NCT00761631 (Study 5).
[b] N = number of subjects reporting Yes for at least 1 day or No for all days.
[c] n = Number of subjects reporting the event.
[d] Fever gradings: Mild (≥38ºC but ≤39ºC), Moderate (>39ºC but ≤40ºC), and Severe (>40ºC). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 45.1% and 33.1% of subjects 5 through 9 years of age and 10 through 17 years of age, respectively.

6.2 Clinical Trials Experience With Prevnar 13 in Adults ≥18 Years of Age

The safety of Prevnar 13 was assessed in 7 clinical studies (Studies 6-12) [6-12] conducted in the US and Europe which included 91,593 adults (48,806 received Prevnar 13) ranging in age from 18 through 101 years.

The 48,806 Prevnar 13 recipients included 899 adults who were aged 18 through 49 years, 2,616 adults who were aged 50 through 64 years, 45,291 adults aged 65 years and older. Of the 48,806 Prevnar 13 recipients, 46,890 adults had not previously received PPSV23 ("PPSV23 unvaccinated") and 1,916 adults were previously vaccinated ("PPSV23 previously vaccinated") with PPSV23 at least 3 years prior to enrollment.

Safety and Immunogenicity Studies

Safety and immunogenicity of Prevnar 13 is supported by 6 clinical studies. Study 6[6] evaluated the safety and immunogenicity of Prevnar 13 in adults 18 through 64 years of age who had not received a previous dose of pneumococcal vaccine. Adults 18 through 59 years of age received a single dose of Prevnar 13, and adults 60 through 64 years of age received a single dose of Prevnar 13 or PPSV23.

Study 7 was randomized and compared the safety and immunogenicity of Prevnar 13 with PPSV23 as a single dose in adults ≥70 years vaccinated with PPSV23 (≥5 years prior to enrollment).[7] Study 8 was randomized and evaluated the safety and immunogenicity of Prevnar 13 and PPSV23 in different sequential order in PPSV23 naive adults aged 60 through 64 years[8].

One clinical safety study[9] (Study 9) of Prevnar 13, conducted in PPSV23 previously vaccinated (≥3 years prior to enrollment) adults aged ≥68 years was a single arm study. Two studies, one in the US[10] (Study 10) in adults aged 50 through 59 years and the other in Europe[11] (Study 11) in adults aged ≥65 years, evaluated the concomitant administration of Prevnar 13 with inactivated influenza vaccine, trivalent (Fluarix®, A/H1N1, A/H3N2, and B, Fall 2007/Spring 2008: IIV3) in these two age groups in PPSV23 unvaccinated adults.

The total safety population in the 6 safety and immunogenicity studies was 7,097. In 5 of the 6 safety and immunogenicity studies, more females than males were enrolled (50.2% - 61.8%). Across the 6 studies the racial distribution included: >85% White; 0.2%-10.7% Black or African American; 0%-1.7% Asian; <1% Native Hawaiian or other Pacific Islander; ≤1%, American Indian or Alaskan Native. Ethnicity data were not collected in Study 11; in the 5 other studies 0.6%-4.8% were Hispanic or Latino.

In five studies,[6-8,10,11] subjects with pre-existing underlying diseases were enrolled if the medical condition was stable (did not require a change in therapy or hospitalization for worsening disease for 12 weeks before receipt of study vaccine) except in Study 9 where subjects were enrolled if the medical condition was stable for 6 or more weeks before receipt of study vaccine.

In the 6 safety and immunogenicity studies,[6-11] subjects were excluded from study participation due to prior receipt of diphtheria toxoid-containing vaccines within 6 months of study vaccine. However, the time of prior receipt of a diphtheria toxoid-containing vaccine was not recorded.

Solicited adverse reactions for Prevnar 13 in the safety and immunogenicity studies were monitored by subjects recording local adverse reactions and systemic reactions daily using an electronic diary for 14 consecutive days following vaccination. Unsolicited serious and non-serious adverse events were collected for one month after each vaccination. In addition, serious adverse events were collected for an additional 5 months after each vaccination (at the 6-month follow-up phone contact) in all studies except Study 11.

Efficacy Study

Study 12[12] was a randomized double-blind placebo-controlled study conducted in the Netherlands in community-dwelling adults aged 65 years and older with no prior pneumococcal vaccination history. A total of 84,496 subjects received either a single dose of Prevnar 13 (42,240) or placebo (42,256) in a 1:1 randomization. Among the 84,496 subjects, 58,072 (68.7%) were ≥65 to <75 years of age, 23,481 (27.8%) were ≥75 and <85 years of age, and 2,943 (3.5%) were ≥85 years of age. In the total safety population, more males (55.9%) were enrolled than females. The racial distribution was 98.5% White, 0.3% Black, 0.7% Asian, 0.5% Other, with <0.1% having missing data.

Adults with immunocompromising conditions or receiving immunosuppressive therapy and adults residing in a long-term care facility or requiring semiskilled nursing care were excluded. Adults with pre-existing medical conditions, as well as subjects with a history of smoking were eligible for enrollment. In the safety population, 42.3% of subjects had pre-existing medical conditions including heart disease (25.4%), lung disease or asthma (15.1%) and type 1 and type 2 diabetes mellitus (12.5%). Smoking was reported at baseline by 12.3% of the subjects.

For a subset of 2,011 subjects (1,006 Prevnar 13 recipients and 1,005 placebo recipients), solicited adverse reactions were monitored by recording local and systemic events using electronic diaries for 7 days after vaccination; unsolicited adverse events were collected for 28 days after vaccination, and serious adverse events were collected for 6 months after

vaccination. For the remaining 41,231 Prevnar 13 and 41,250 placebo vaccinated subjects, serious adverse events were collected for 28 days after vaccination.

Serious Adverse Events in Adult Clinical Studies

Safety and Immunogenicity Studies

Across the 6 safety and immunogenicity studies,[6-11] serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5,057 subjects vaccinated with Prevnar 13, and in 0.4%-1.7% of 1,124 subjects vaccinated after an initial study dose of PPSV23. From 1 month to 6 months after an initial study dose, serious adverse events were reported in 0.2%-5.8% of subjects vaccinated during the studies with Prevnar 13 and in 2.4%-5.5% of subjects vaccinated with PPSV23. One case of erythema multiforme occurred 34 days after receipt of a second dose of Prevnar 13.

Twelve of 5,667 (0.21%) Prevnar 13 recipients and 4 of 1,391 (0.29 %) PPSV23 recipients died. Deaths occurred between Day 3 and Day 309 after study vaccination with Prevnar 13 or PPSV23. Two of 12 deaths occurred within 30 days of vaccination and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving placebo. This subject had received Prevnar 13 and IIV3 one month earlier. The other death was due to peritonitis 20 days after receiving Prevnar 13. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Prevnar 13 were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1) and septic shock (1).

Efficacy Study

In Study 12[12] (subjects 65 years and older), serious adverse events within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Prevnar 13 recipients (352 events) and in 314 of 42,225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1,006 (7%) Prevnar 13 vaccinated subjects (90 events) and 60 of 1,005 (6%) placebo vaccinated subjects (69 events) reported serious adverse events.

During the follow-up period (average of 4 years) for case accumulation there were 3,006 deaths (7.1%) in the Prevnar 13 group and 3,005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevnar 13 group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Prevnar 13 group and 144 deaths (0.3%) in the placebo group within 29 days – 6 months following vaccination. These data do not provide evidence for a causal relationship between deaths and vaccination with Prevnar 13.

Solicited Adverse Reactions in Adult Clinical Studies

The incidence and severity of solicited adverse reactions that occurred within 7 or 14 days following each dose of Prevnar 13, PPSV23, or placebo administered to adults in 5 studies are shown in Tables 11, 12, 13, and 14.

The commonly reported local adverse reactions after Prevnar 13 vaccination in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were redness, swelling and pain at the injection site, or limitation of arm movement (Tables 11 and 12). The commonly reported

systemic adverse reactions in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain (Tables 13 and 14).

Table 11 - Percentage of Subjects With Solicited Local Adverse Reactions Within 7 or 14 Days in PPSV23 Unvaccinated Adults[a]

	Study 6				Study 8		Study 12	
Age in Years	**18-49**	**50-59**	**60-64**		**60-64**		**≥65**	
Local Reaction	**Prevnar 13[b]** N[c]=266-787 %	**Prevnar 13[b]** N[c]=152-322 %	**Prevnar 13** N[c]=193-331 %	**PPSV23** N[c]=190-301 %	**Prevnar 13** N[c]=270-370 %	**PPSV23** N[c]=134-175 %	**Prevnar 13** N[c]=886-914 %	**Placebo** N[c]=859-865 %
Redness[d]								
Any	30.5	15.8	20.2	14.2	12.2	11.2	4.9[g]	1.2
Mild	26.4	15.2	15.9	11.2	8.3	9.7	3.7[g]	0.8
Moderate	11.9	5.0	8.6	4.9	6.4	3.9	1.7[g]	0.3
Severe	2.8	0.7	1.7	0.0	1.2	0.8	0.5	0.1
Swelling[d]								
Any	39.4	21.7	19.3	13.1	10.0	10.4	6.8[g]	1.2
Mild	37.2	20.6	15.6	10.1	8.2	6.1	5.5[g]	0.7
Moderate	15.1	4.3	8.2	4.4	3.8	7.6	2.6[g]	0.6
Severe	1.4	0.0	0.6	1.1	0.0	0.0	0.1	0.1
Pain[e]								
Any	96.7	88.8	80.1	73.4	69.2[g]	58.3	36.1[g]	6.1
Mild	93.2	85.9	78.6[g]	68.6	66.1[g]	52.9	32.9[g]	5.6
Moderate	77.1	39.5	23.3	30.0	20.1	21.7	7.7[g]	0.6
Severe	16.0	3.6	1.7	8.6[g]	2.3	0.8	0.3	0.1
Limitation of arm movement[f]								
Any	75.2	40.7	28.5	30.8	23.5	28.2	14.1[g]	3.2
Mild	71.5	38.6	26.9	29.3	22.7	26.1	12.4[g]	2.5
Moderate	18.5	2.9	2.2	3.8	1.2	3.1	1.7[g]	0.5
Severe	15.6	2.9	1.7	4.3	1.1	2.3	1.2	0.7

[a] Studies conducted in US NCT00427895 (Study 6) and NCT00574548 (Study 8) reported local reactions within 14 days. Study conducted in the Netherlands NCT00744263 (Study 12) reported local reactions within 7 days.
[b] Open label administration of Prevnar 13.
[c] Number of subjects with known values (number of subjects reporting yes for at least one day or no for all days).
[d] Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and Severe is >10.0 cm.
[e] Mild = awareness of symptom but easily tolerated, Moderate = discomfort enough to cause interference with usual activity, Severe = incapacitating with inability to do usual activity.
[f] Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder.
[g] Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

Table 12 - Percentage of Subjects With Solicited Local Adverse Reactions in PPSV23 Previously Vaccinated Adults[a]

	Study 7		Study 9
Age in Years	**≥70**		**≥68**
Local Reaction	**Prevnar 13** N[c]=306-362 %	**PPSV23** N[c]=324-383 %	**Prevnar 13**[b] N[c]=664-777 %
Redness[d]			
Any	10.8	22.2[g]	14.3
Mild	9.5	13.5	12.6
Moderate	4.7	11.5[g]	6.5
Severe	1.7	4.8[g]	1.1
Swelling[d]			
Any	10.4	23.1[g]	12.8
Mild	8.9	14.0[g]	10.9
Moderate	4.0	13.6[g]	5.5
Severe	0.0	4.8[g]	0.6
Pain[e]			
Any	51.7	58.5	51.0
Mild	50.1	54.1	49.4
Moderate	7.5	23.6[g]	9.0
Severe	1.3	2.3	0.2
Limitation of arm movement[f]			
Any	10.5	27.6[g]	16.2
Mild	10.3	25.2[g]	14.8
Moderate	0.3	2.6[g]	1.6
Severe	0.7	3.0[g]	1.6

[a] Study conducted in US and Sweden NCT00546572 (Study 7) reported local reactions within 14 days. Study conducted in US, Sweden and Germany NCT00500266 (Study 9) reported local reactions within 14 days.
[b] Open label administration of Prevnar 13.
[c] Number of subjects with known values.
[d] Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and Severe is >10.0 cm.
[e] Mild = awareness of symptom but easily tolerated, Moderate = discomfort enough to cause interference with usual activity, Severe = incapacitating with inability to do usual activity.
[f] Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder.
[g] Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

Table 13 - Percentage of Subjects With Solicited Systemic Events in PPSV23 Unvaccinated Adults[a]

	Study 6				Study 8		Study 12	
Age in Years	**18-49**	**50-59**	**60-64**		**60-64**		**≥65**	
	Prevnar 13[b] N[c]=221-561 %	**Prevnar 13**[b] N[c]=137-248 %	**Prevnar 13** N[c]=174-277 %	**PPSV23** N[c]=176-273 %	**Prevnar 13** N[c]=261-328 %	**PPSV23** N[c]=127-173 %	**Prevnar 13** N[c]=881-896 %	**Placebo** N[c]=860-878 %
Systemic Event								
Fever								
≥38.0°C	7.2	1.5	4.0	1.1	4.2	1.6	2.9[d]	1.3
38.0°C to 38.4°C	4.2	1.5	4.0	1.1	3.8	0.8	1.1	0.6
38.5°C to 38.9°C	1.9	0.0	0.6	0.0	0.8	0.0	0.6	0.2
39.0°C to 40.0°C	1.4	0.0	0.0	0.0	0.4	0.8	0.7	0.2
>40.0°C[e]	0.5	0.0	0.0	0.0	0.0	0.0	0.8	0.3
Fatigue	80.5	63.3	63.2	61.5	50.5	49.1	18.8[d]	14.8
Headache	81.4	65.9	54.0	54.4	49.7	46.1	15.9	14.8
Chills	38.1	19.6	23.5	24.1	19.9	26.9	9.4	8.4
Rash	21.3	14.2	16.5	13.0	8.6	13.4	3.3[d]	0.8
Vomiting	15.0	6.9	3.9	5.4	3.1	3.1	0.3	0.9
Decreased appetite	55.6	25.3	21.3	21.7	14.7	23.0[d]	5.3	3.7
Generalized new muscle pain	82.0	61.8	56.2	57.8	46.9	51.5	18.4[d]	8.4
Generalized aggravated muscle pain	55.9	39.9	32.6	37.3	22.0	32.5[d]	9.1[d]	4.4
Generalized new joint pain	41.7	31.5	24.4	30.1	15.5	23.8[d]	7.4	5.4
Generalized aggravated joint pain	28.6	25.6	24.9	21.4	14.0	21.1	5.2	4.2

[a] Studies conducted in US NCT00427895 (Study 6) and NCT00574548 (Study 8) reported systemic events within 14 days. Study conducted in the Netherlands NCT00744263 (Study 12) reported systemic events within 7 days.

[b] Open label administration of Prevnar 13.

[c] Number of subjects with known values (number of subjects reporting yes for at least one day or no for all days).

[d] Statistically significant difference $p < 0.05$. No adjustments for multiplicity.

[e] Fevers >40.0°C were confirmed to be data entry errors and remain in the table for the following: 1 case in the 18- to 49- year-old cohort (Study 6), and 7 cases in the Prevnar 13 group and 3 cases in placebo group (Study 12). For the other cohorts in Study 6 and for Study 8, data entry errors were removed.

Table 14 - Percentage of Subjects With Systemic Events in PPSV23 Previously Vaccinated Adults[a]

	Study 7		Study 9
Age in Years	**≥70**		**≥68**
	Prevnar 13 N[c]=299-350 %	**PPSV23** N[c]=303-367 %	**Prevnar 13[b]** N[c]=635-733 %
Systemic Event			
Fever			
≥38.0°C	1.0	2.3	1.1
38.0°C to 38.4°C	1.0	2.0	0.8
38.5°C to 38.9°C	0.0	0.0	0.0
39.0°C to 40.0°C	0.0	0.3	0.3
>40.0°C	0.0	0.0	0.0
Fatigue	34.0	43.3[d]	34.4
Headache	23.7	26.0	26.1
Chills	7.9	11.2	7.5
Rash	7.3	16.4[d]	8.4
Vomiting	1.7	1.3	0.9
Decreased appetite	10.4	11.5	11.2
Generalized new muscle pain	36.8	44.7[d]	25.3
Generalized aggravated muscle pain	20.6	27.5[d]	12.3
Generalized new joint pain	12.6	14.9	12.8
Generalized aggravated joint pain	11.6	16.5	9.7

[a] Study conducted in US and Sweden NCT00546572 (Study 7) reported systemic events within 14 days. Study conducted in US, Sweden and Germany NCT00500266 (Study 9) reported systemic events within 14 days.
[b] Open label administration of Prevnar 13.
[c] Number of subjects with known values.
[d] Statistically significant difference p <0.05. No adjustments for multiplicity.

Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Prevnar 13 and IIV3 (Fluarix)

The safety of concomitant administration of Prevnar 13 with IIV3 was assessed in 2 studies[10,11] in PPSV23 unvaccinated adults aged 50 through 59 years (Study 10) and aged ≥65 years (Study 11).

Frequencies of local reactions within 14 days post-vaccination in adults aged 50 through 59 years and in adults aged ≥65 years were similar after Prevnar 13 was administered with IIV3 compared to Prevnar 13 administered alone, with the exception of mild redness at the injection site, which was increased when Prevnar 13 was administered concomitantly with IIV3 and mild limitation of arm movement, which was increased when Prevnar 13 was administered alone.

An increase in some solicited systemic reactions within 14 days post-vaccination was noted when Prevnar 13 was administered concomitantly with IIV3 compared with IIV3 given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with Prevnar 13 given alone (fatigue, headache, chills, decreased appetite, and joint pain).

6.3 Post-marketing Experience With Prevnar 13 in Infants and Toddlers

The following adverse events have been reported through passive surveillance since market introduction of Prevnar 13. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine. The following adverse events were included based on one or more of

the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Prevnar 13 vaccine.

Administration site conditions: Vaccination-site dermatitis, vaccination-site pruritus, vaccination-site urticaria

Blood and lymphatic system disorders: Lymphadenopathy localized to the region of the injection site

Cardiac disorders: Cyanosis

Immune system disorders: Anaphylactic/anaphylactoid reaction including shock

Nervous system disorders: Hypotonia

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apnea

Vascular disorders: Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

In clinical trials with infants and toddlers, Prevnar 13 was administered concomitantly with the following US licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first three doses and with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A vaccine, Inactivated] (HepA) for dose 4 *[see Clinical Studies (14.2) and Adverse Reactions (6.1)]*.

In children and adolescents, data are insufficient to assess the concomitant administration of Prevnar 13 with Human Papillomavirus Vaccine (HPV), Meningococcal Conjugate Vaccine (MCV4) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap).

In adults, Prevnar 13 was administered concomitantly with US licensed Fluarix (IIV3) for the 2007/2008 influenza season *[see Clinical Studies (14.3) and Adverse Reactions (6.2)]*. There are no data on the concomitant administration of Prevnar 13 with diphtheria toxoid-containing vaccines and other vaccines licensed for use in adults 50 years of age and older.

When Prevnar 13 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

7.2 Immunosuppressive Therapies

Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

7.3 Antipyretics

A post-marketing clinical study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. The data show that 3 doses of acetaminophen (the first dose administered at the time of each vaccination and the subsequent doses at 6 to 8 hour intervals) reduced the antibody response to some serotypes following the third dose of Prevnar 13, compared with responses among infants who received antipyretics only as needed for treatment. Reduced antibody responses were not observed after the fourth dose of Prevnar 13 when acetaminophen was administered prophylactically.

7.4 Prior Vaccination with PPSV23

Prior receipt of Pneumovax®23 (23 valent pneumococcal vaccine polyvalent, PPSV23) within 1 year results in diminished immune responses to Prevnar 13 compared to PPSV23 naïve individuals *[see Clinical Studies (14.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Prevnar 13 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rabbits administered Prevnar 13 prior to mating and during gestation. Each dose was approximately 20 times the human dose. This study revealed no evidence of harm to the fetus due to Prevnar 13 (*see 8.1 Data*).

Data

Animal

In a developmental toxicity study, female rabbits were administered Prevnar 13 by intramuscular injection twice prior to mating (17 days and 3 days prior to mating) and twice during gestation (gestation days 10 and 24), 0.5 mL/rabbit/occasion (each dose approximately 20 times the human dose). No adverse effects on pre-weaning development were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

Data are not available to assess the effects of Prevnar 13 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Prevnar 13 and any potential adverse effects on the breastfed child from Prevnar 13 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks have not been established.

8.5 Geriatric Use

Of the total number of Prevnar 13 recipients aged 50 years and older in clinical studies (N=47,907), 94.5% (45,291 of 47,907) were 65 years and older and 30.3% (14,498 of 47,907) were 75 years and older *[see Clinical Studies (14.1) and (14.3)]*.

8.6 High Risk Populations

Individuals with the diseases or conditions listed below are at increased risk of pneumococcal disease. Immunogenicity and safety data in these populations are limited.

Infants Born Prematurely

Immune responses elicited by Prevnar 13 administered on a US schedule to preterm infants have not been studied. When preterm infants (<37 weeks gestational age, N=100) were administered 4 doses of Prevnar 13 on a non-US schedule, the serotype-specific IgG antibody responses after the third and fourth dose were lower compared to responses among term infants (≥37 weeks gestational age, N=100) for some serotypes; the effectiveness of Prevnar 13 in preterm infants cannot be established from this study.

Children with Sickle Cell Disease

In an open-label, single-arm, descriptive study, 2 doses of Prevnar 13 were administered 6 months apart to children ≥6 to <18 years of age with sickle cell disease who previously received PPSV23 at least 6 months prior to enrollment. Children with a prior history of pneumococcal conjugate vaccination were excluded. For all vaccine serotypes,

anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after the first dose compared to pre-vaccination (N=95-131); OPA GMTs following the first and second dose were comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

Individuals with Hematopoietic Stem Cell Transplant

In an open-label, single-arm, descriptive study, 4 doses of Prevnar 13 were administered to subjects ≥ 2 years of age (range 2 to 71 years) who had received an allogeneic hematopoietic stem cell transplant 3 to 6 months prior to enrollment. All subjects had a history of stable engraftment (absolute neutrophil count>1000/μL, platelet count >50,000/μL), and did not have uncontrolled graft versus host disease. The first three doses of Prevnar 13 were administered one month apart, followed by a fourth dose of Prevnar 13 six months after the third dose. Sera were obtained approximately one month after each vaccination. Immune responses (IgG GMCs) after the first dose of Prevnar 13 were numerically higher for all serotypes compared with baseline. In addition, after each subsequent dose of Prevnar 13, IgG GMCs for all serotypes were numerically higher than responses after the previous dose. A post hoc analysis of the immune responses as measured by OPA antibody assay showed the pattern of functional antibody responses to be consistent with IgG responses for each serotype. The effectiveness of Prevnar 13 in this specific population has not been established.

Individuals with HIV Infection

In an open-label, single-arm, descriptive study, 3 doses of Prevnar 13 were administered 6 months apart to HIV-infected adults ≥18 years of age (median age 48 years), with CD4 counts ≥200 cells/μL and serum HIV RNA titer <50,000 copies/mL. All subjects had been vaccinated previously with PPSV23 at least 6 months prior to enrollment. For all vaccine serotypes anti-pneumococcal OPA GMTs were numerically higher after the first dose compared to pre-vaccination (N=227-253); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

In an open-label, single-arm, descriptive study, 3 doses of Prevnar 13 were administered 1 month apart to HIV-infected subjects ≥6 years of age with CD4 counts ≥200 cells/μL, and serum HIV RNA titer <50,000 copies/mL. Subjects had not previously been vaccinated with a pneumococcal vaccine. For all vaccine serotypes anti-pneumococcal OPA GMTs were numerically higher after the first dose compared to pre-vaccination (N=197-257); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

11 DESCRIPTION

Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM_{197} protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides, which are directly

conjugated by reductive amination to the protein carrier CRM_{197}, to form the glycoconjugate. CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate Prevnar 13. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens and by the saccharide to protein ratios in the individual glycoconjugates. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer and 125 µg aluminum as aluminum phosphate adjuvant.

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prevnar 13, comprised of pneumococcal polysaccharides conjugated to a carrier protein (CRM_{197}), elicits a T-cell dependent immune response. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response.

Nonclinical and clinical data support opsonophagocytic activity, as measured by opsonophagocytic activity (OPA) antibody assay, as a contributor to protection against pneumococcal disease. The OPA antibody assay provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease. OPA antibody titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

In infants that have received Prevnar 13, opsonophagocytic activity correlates well with serotype specific anti-capsular polysaccharide IgG levels as measured by ELISA. A serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL as measured by ELISA one month after the third dose as a single antibody reference concentration was used to estimate the effectiveness of Prevnar 13 against invasive pneumococcal disease (IPD) in infants and children. The assay used for this determination is a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. The single antibody reference value was based on pooled efficacy estimates from three placebo-controlled IPD efficacy trials with either Prevnar or the investigational 9-valent CRM_{197} conjugate pneumococcal polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis. Functional antibodies elicited by the vaccine (as

measured by a dribble opsonophagocytic activity [dOPA] antibody assay) were also evaluated in infants.

In adults, an antipolysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined. Noninferiority trials for Prevnar 13 were designed to show that functional OPA antibody responses (as measured by a microcolony OPA [mcOPA] antibody assay) for the Prevnar 13 serotypes are noninferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23). OPA antibody titers measured in the mcOPA antibody assay cannot be compared directly to titers measured in the dOPA antibody assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Prevnar 13 has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a study in rabbits, no vaccine-related effects were found regarding reproductive performance including female fertility *[see Use in Specific Populations (*8.1*)]*.

14 CLINICAL STUDIES

14.1 Efficacy Data

Prevnar Efficacy Data

Invasive Pneumococcal Disease (IPD)

Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) was licensed in the US for infants and children in 2000, following a randomized, double-blind clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either Prevnar or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of Prevnar against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% CI: 75.4%, 100% and 81.7%, 100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.4% in the per-protocol analysis and 93.9% in the intent-to-treat analysis (95% CI: 82.7%, 99.9% and 79.6%, 98.5%, respectively).

Acute Otitis Media (AOM)

The efficacy of Prevnar against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the efficacy trial in US infants at Northern California Kaiser Permanente (NCKP).

The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either Prevnar or a control vaccine

Recombivax HB (Hepatitis B vaccine (Recombinant) [Hep B]) at 2, 4, 6, and 12-15 months of age. In this study, conducted between December 1995 and March 1999, parents of study participants were asked to bring their children to the study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of Prevnar against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either Prevnar (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population.

The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial, was 57% (95% CI: 44%, 67%) in the per-protocol population and 54% (95% CI: 41%, 64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 19A, 23A), also assessed in the Finnish trial, was 51% (95% CI: 27, 67) in the per-protocol population and 44% (95% CI: 20, 62) in the intent-to-treat population. There was a nonsignificant increase in AOM episodes caused by serotypes unrelated to the vaccine in the per-protocol population, compared to children who received the control vaccine, suggesting that children who received Prevnar appeared to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine. However, vaccination with Prevnar reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI: 4%, 10%) and 6% (95% CI: 4%, 9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the two trials.

Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI: 3%, 15% in per-protocol and 95% CI: 4%, 14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of tympanostomy tubes in the per-protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in Prevnar group and 18,941 in MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

Prevnar 13 Adult Efficacy Data

The efficacy of Prevnar 13 against vaccine-type (VT) pneumococcal community-acquired pneumonia (CAP) and IPD was assessed in a randomized, double-blind, placebo-controlled study conducted over ~ 4 years in the Netherlands[12] (Study 12). A total of 84,496 subjects 65 years and older received a single dose of either Prevnar 13 or placebo in a 1:1 randomization; 42,240 subjects were vaccinated with Prevnar 13 and 42,256 subjects were vaccinated with placebo.

The primary objective was to demonstrate the efficacy of Prevnar 13 in the prevention of a first episode of confirmed VT-CAP (defined as presence of ≥2 specified clinical criteria; chest X-ray consistent with CAP as determined by a central committee of radiologists; and positive VT-specific Urinary Antigen Detection assay (UAD) or isolation of VT S. pneumoniae from blood or other sterile site). The secondary objectives were to demonstrate the efficacy of Prevnar 13 in the prevention of a first episode of 1) confirmed nonbacteremic/noninvasive (NB/NI) VT-CAP (an episode of VT-CAP for which the blood culture result and any other sterile site culture results were negative for S. pneumoniae) and 2) VT-IPD (the presence of *S. pneumoniae* in a sterile site).

Surveillance for suspected pneumonia and IPD began immediately after vaccination and continued through identification of a prespecified number of cases. Subjects who had a CAP or IPD episode with symptom onset less than 14 days after vaccination were excluded from all analyses.

The median duration of follow up per subject was 3.93 years. Prevnar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing first episodes of VT pneumococcal CAP, nonbacteremic/noninvasive (NB/NI) VT pneumococcal CAP, and VT-IPD (Table 15).

Table 15 - Vaccine Efficacy for the Primary and Secondary Efficacy Endpoints – Per-Protocol Population

		Vaccine Group			
		Prevnar 13	Placebo		
		N=42240	N=42256		
Efficacy Endpoint	**Total Number of Episodes**	**n**	**n**	**VE (%)**	**(95.2% CI)**
Primary endpoint: First case of confirmed VT pneumococcal CAP	139	49	90	45.6	(21.8, 62.5)
Secondary endpoint: First episode of confirmed NB/NI VT pneumococcal CAP	93	33	60	45	(14.2, 65.3)
Secondary endpoint: First episode of VT-IPD	35	7	28	75	(41.1, 90.9)

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; NB/NI = nonbacteremic/noninvasive; IPD = invasive pneumococcal disease; VE = vaccine efficacy; VT = vaccine-type.

14.2 Prevnar 13 Clinical Trials in Children 6 Weeks Through 17 Years of Age Infants and Children 6 Weeks Through 17 Months of Age

Prevnar 13 effectiveness against invasive pneumococcal disease was inferred from comparative studies to a US licensed 7-valent pneumococcal conjugate vaccine, Prevnar, in which Prevnar 13 elicited antipolysaccharide binding and functional OPA antibodies, as measured by ELISA and dOPA assays, respectively. These studies were designed to evaluate immunologic noninferiority of Prevnar 13 to Prevnar.

Clinical trials have been conducted in the US using a 2, 4, 6, and 12-15 month schedule.

The US noninferiority study[2] (Study 2) was a randomized, double-blind, active-controlled trial in which 2 month-old infants were randomly assigned to receive either Prevnar 13 or Prevnar in a 1:1 ratio. The two vaccine groups were well balanced with respect to race, ethnicity, and age and weight at enrollment. Most subjects were White (69.1%), 19.6% were Black or African-American, and 2.4% were Asian; 82.1% of subjects were non-Hispanic and non-Latino and 17.3% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

In Study 2, immune responses were compared in subjects receiving either Prevnar 13 or Prevnar using a set of noninferiority criteria. Co-primary endpoints included the percentage of subjects with serum pneumococcal anti-capsular polysaccharide IgG ≥0.35 μg/mL measured one month after the third dose and serum pneumococcal anti-capsular polysaccharide IgG geometric mean concentrations (GMCs) one month after the fourth dose. The assay used for this determination was a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. Responses to the 7 common serotypes in Prevnar 13 and Prevnar recipients were compared directly. Responses to the 6 additional serotypes in Prevnar 13 recipients were each compared to the lowest response observed among the Prevnar serotypes in Prevnar recipients.

Pneumococcal Immune Responses Following Three Doses

In Study 2, the noninferiority criterion for the proportion of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose was met for 10 of the 13 serotypes. The exceptions were serotypes 6B, 9V, and 3. Although the response to serotypes 6B and 9V did not meet the pre-specified noninferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥0.35 μg/mL one month after the third dose is shown below (Table 16).

Table 16: Percentage of Subjects With Anti-capsular Antibody Concentration ≥0.35 µg/mL One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2[a,b,c,d]

Serotype	Prevnar 13 N=249-252 (95% CI)	Prevnar N=250-252 (95% CI)	Difference in % responders (95% CI)
Prevnar Serotypes			
4	94.4 (90.9, 96.9)	98.0 (95.4, 99.4)	-3.6 (-7.3, -0.1)
6B	87.3 (82.5, 91.1)	92.8 (88.9, 95.7)	-5.5 (-10.9, -0.1)
9V	90.5 (86.2, 93.8)	98.4 (96.0, 99.6)	-7.9 (-12.4, -4.0)
14	97.6 (94.9, 99.1)	97.2 (94.4, 98.9)	0.4 (-2.7, 3.5)
18C	96.8 (93.8, 98.6)	98.4 (96.0, 99.6)	-1.6 (-4.7, 1.2)
19F	98.0 (95.4, 99.4)	97.6 (99.4, 99.1)	0.4 (-2.4, 3.4)
23F	90.5 (86.2, 93.8)	94.0 (90.4, 96.6)	-3.6 (-8.5, 1.2)
Additional Serotypes[e]			
1	95.6 (92.3, 97.8)	e	2.8 (-1.3, 7.2)
3	63.5 (57.1, 69.4)	e	-29.3 (-36.2, -22.4)
5	89.7 (85.2, 93.1)	e	-3.1 (-8.3, 1.9)
6A	96.0 (92.8, 98.1)	e	3.2 (-0.8, 7.6)
7F	98.4 (96.0, 99.6)	e	5.6 (1.9, 9.7)
19A	98.4 (96.0, 99.6)	e	5.6 (1.9, 9.7)

[a] Studies conducted in US NCT00373958 (Study 2).
[b] Evaluable Immunogenicity Population.
[c] Noninferiority was met when the lower limit of the 95% CI for the difference between groups (Prevnar 13 minus Prevnar) was greater than -10%.
[d] Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.
[e] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 6B (92.8%; 95% CI: 88.9, 95.7).

Functional dOPA antibody responses were elicited for all 13 serotypes, as shown in Table 17.

Table 17: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2[a,b,c]

Serotype	Prevnar 13 N=91-94 (95% CI)	Prevnar N=89-94 (95% CI)
Prevnar Serotypes		
4	359 (276, 468)	536 (421, 681)
6B	1055 (817, 1361)	1514 (1207, 1899)
9V	4035 (2933, 5553)	3259 (2288, 4641)
14	1240 (935, 1646)	1481 (1133, 1934)
18C	276 (210, 361)	376 (292, 484)
19F	54 (40, 74)	45 (34, 60)
23F	791 (605, 1034)	924 (709, 1204)
Additional Serotypes		
1	52 (39, 69)	4 (4, 5)
3	121 (92, 158)	7 (5, 9)
5	91 (67, 123)	4 (4, 4)
6A	980 (783, 1226)	100 (66, 152)
7F	9494 (7339, 12281)	128 (80, 206)
19A	152 (105, 220)	7 (5, 9)

[a] Studies conducted in US NCT00373958 (Study 2).
[b] The dOPA (opsonophagocytic activity) antibody assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.
[c] Evaluable Immunogenicity Population.

Pneumococcal Immune Responses Following Four Doses

In Study 2, post-dose 4 antibody concentrations were higher for all 13 serotypes than those achieved after the third dose. The noninferiority criterion for pneumococcal anti-capsular polysaccharide GMCs after 4 doses was met for 12 of the 13 pneumococcal serotypes. The noninferiority criterion was not met for the response to serotype 3 (Table 18).

Table 18: Pneumococcal IgG GMCs (µg/mL) One Month After a Four Dose Series Administered at 2, 4, 6 and 12-15 Months, Study 2[a,b,c,d]

Serotype	Prevnar 13 N=232-236 (95% CI)	Prevnar N=222-223 (95% CI)	GMC Ratio (95% CI)
Prevnar Serotypes			
4	3.73 (3.28, 4.24)	5.49 (4.91, 6.13)	0.68 (0.57, 0.80)
6B	11.53 (9.99, 13.30)	15.63 (13.80, 17.69)	0.74 (0.61, 0.89)
9V	2.62 (2.34, 2.94)	3.63 (3.25, 4.05)	0.72 (0.62, 0.85)
14	9.11 (7.95, 10.45)	12.72 (11.22, 14.41)	0.72 (0.60, 0.86)
18C	3.20 (2.82, 3.64)	4.70 (4.18, 5.28)	0.68 (0.57, 0.81)
19F	6.60 (5.85, 7.44)	5.60 (4.87, 6.43)	1.18 (0.98, 1.41)
23F	5.07 (4.41, 5.83)	7.84 (6.91, 8.90)	0.65 (0.54, 0.78)
Additional Serotypes[e]			
1	5.06 (4.43, 5.80)	e	1.40 (1.17, 1.66)
3	0.94 (0.83, 1.05)	e	0.26 (0.22, 0.30)
5	3.72 (3.31, 4.18)	e	1.03 (0.87, 1.20)
6A	8.20 (7.30, 9.20)	e	2.26 (1.93, 2.65)
7F	5.67 (5.01, 6.42)	e	1.56 (1.32, 1.85)
19A	8.55 (7.64, 9.56)	e	2.36 (2.01, 2.76)

[a] Studies conducted in US NCT00373958 (Study 2).
[b] Evaluable Immunogenicity Population.
[c] Noninferiority was declared if the lower limit of the 2-sided 95% CI for Geometric Mean Ratio (Prevnar 13:Prevnar) was greater than 0.5.
[d] Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.
[e] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 9V (3.63; 95% CI 3.25, 4.05).

Following the fourth dose, the functional dOPA antibody response for each serotype was quantitatively greater than the response following the third dose (see Table 19).

Table 19: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After the Fourth Dose-Evaluable Toddler Immunogenicity Population, Study 2[a,b]

Serotype	Prevnar 13 N=88-92 (95% CI)	Prevnar N=92-96 (95% CI)
Prevnar Serotypes		
4	1180 (847, 1643)	1492 (1114, 1999)
6B	3100 (2337, 4111)	4066 (3243, 5098)
9V	11856 (8810, 15955)	18032 (14125, 23021)
14	2002 (1453, 2760)	2366 (1871, 2992)
18C	993 (754, 1308)	1722 (1327, 2236)
19F	200 (144, 276)	167 (121, 230)
23F	2723 (1961, 3782)	4982 (3886, 6387)
Additional Serotypes		
1	164 (114, 237)	5 (4, 6)
3	380 (300, 482)	12 (9, 16)
5	300 (229, 393)	5 (4, 6)
6A	2242 (1707, 2945)	539 (375, 774)
7F	11629 (9054, 14938)	268 (164, 436)
19A	1024 (774, 1355)	29 (19, 44)

[a] Studies conducted in US NCT00373958 (Study 2).
[b] The dOPA (opsonophagocytic activity) antibody assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.

Previously Unvaccinated Older Infants and Children 7 Months Through 5 Years of Age

In an open-label descriptive study of Prevnar 13 in Poland[4] (Study 4), children 7 months through 11 months of age, 12 months through 23 months of age and 24 months through 5 years of age (prior to the 6th birthday) who were naïve to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevnar 13 respectively, according to the age-appropriate schedules in Table 2.

Serum IgG concentrations were measured one month after the final dose in each age group and the data are shown in Table 20.

Table 20: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After the Final Prevnar 13 Catch-Up Dose in Pneumococcal Vaccine Naïve Children 7 Months Through 5 Years of Age by Age Group, Study 4[a,b]

Serotype	3 doses Prevnar 13 7 through 11 months N=83-84 (95% CI)	2 doses Prevnar 13 12 through 23 months N=104-110 (95% CI)	1 dose Prevnar 13 24 months through 5 years N=135-152 (95% CI)
1	2.88 (2.44, 3.39)	2.74 (2.37, 3.16)	1.78 (1.52, 2.08)
3	1.94 (1.68, 2.24)	1.86 (1.60, 2.15)	1.42 (1.23, 1.64)
4	3.63 (3.11, 4.23)	4.28 (3.78, 4.86)	3.37 (2.95, 3.85)
5	2.85 (2.34, 3.46)	2.16 (1.89, 2.47)	2.33 (2.05, 2.64)
6A	3.72 (3.12, 4.45)	2.62 (2.25, 3.06)	2.96 (2.52, 3.47)
6B	4.77 (3.90, 5.84)	3.38 (2.81, 4.06)	3.41 (2.80, 4.16)
7F	5.30 (4.54, 6.18)	5.99 (5.40, 6.65)	4.92 (4.26, 5.68)
9V	2.56 (2.21, 2.96)	3.08 (2.69, 3.53)	2.67 (2.32, 3.07)
14	8.04 (6.95, 9.30)	6.45 (5.48, 7.59)	2.24 (1.71, 2.93)
18C	2.77 (2.39, 3.23)	3.71 (3.29, 4.19)	2.56 (2.17, 3.03)
19A	4.77 (4.28, 5.33)	4.94 (4.31, 5.65)	6.03 (5.22, 6.97)
19F	2.88 (2.35, 3.54)	3.07 (2.68, 3.51)	2.53 (2.14, 2.99)
23F	2.16 (1.82, 2.55)	1.98 (1.64, 2.39)	1.55 (1.31, 1.85)

[a] Studies conducted in Poland NCT00452452 (Study 4).
[b] Open label administration of Prevnar 13.
Note – ClinicalTrials.gov NCT number is as follows: NCT00452452 (Poland).

Children 15 Months Through 59 Months of Age Previously Vaccinated with Prevnar

In an open-label descriptive study in the US[5] (Study 5), children 15 months through 59 months previously vaccinated with 3 or 4 doses of Prevnar, received 2 doses of Prevnar 13 (children >15 through 23 months of age) or 1 dose of Prevnar 13 (children 24 months through 59 months of age). The data following one dose of Prevnar 13 in children 24 months through 59 months of age are shown in Table 21.

Table 21: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) One Month After One Prevnar 13 Catch-Up Dose in Children 24 Through 59 Months of Age With 3 or 4 Prior Doses of Prevnar, US Catch-Up Study 5[a,b]

Serotype	1 dose Prevnar 13 24 months through 59 months N=173-175 (95% CI)
1	2.43 (2.15, 2.75)
3	1.38 (1.17, 1.61)
5	2.13 (1.89, 2.41)
6A	12.96 (11.04, 15.21)
7F	4.22 (3.74, 4.77)
19A	14.18 (12.37, 16.25)

[a] Studies conducted in US NCT00761631 (Study 5).
[b] Open label administration of Prevnar 13.

Children 5 Through 17 Years of Age

In a US study[5] (Study 5), a single dose of Prevnar 13 was administered to children 5 through 9 years of age, who were previously vaccinated with at least one dose of Prevnar, and to pneumococcal vaccine-naïve children 10 through 17 years of age.

In children 5 through 9 years of age, serotype-specific IgG concentrations measured 1 month after vaccination were noninferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of

>0.5) to the corresponding IgG concentrations in toddlers (Study 3) 1 month after a fourth pneumococcal vaccination (after the 4th dose of Prevnar for the 7 common serotypes and after the 4th dose of Prevnar 13 for the 6 additional serotypes) as shown in Tables 22 and 23 respectively.

Table 22: Pneumococcal IgG GMCs (µg/mL) One Month After Vaccination for 7 Common Serotypes, Prevnar 13 in Children 5 through 9 Years of Age in Study 5 Relative to Prevnar in Study 3 (Post-toddler)[a,g,h]

	Vaccine Group (as Enrolled/Randomized)							
	Prevnar 13 5 Through 9 Years (Study 5)			Prevnar Post-Toddler Dose (Study 3)				
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	GMC Ratio[e]	(95% CI[f])
Common								
4	169	8.45	(7.24, 9.87)	173	2.79	(2.45, 3.18)	3.03	(2.48, 3.71)
6B	171	53.56	(45.48, 63.07)	173	9.47	(8.26, 10.86)	5.66	(4.57, 6.99)
9V	171	9.51	(8.38, 10.78)	172	1.97	(1.77, 2.19)	4.83	(4.10, 5.70)
14	169	29.36	(24.78, 34.78)	173	8.19	(7.31, 9.18)	3.58	(2.93, 4.39)
18C	171	8.23	(7.13, 9.51)	173	2.33	(2.05, 2.65)	3.53	(2.91, 4.29)
19F	171	17.58	(14.95, 20.67)	173	3.31	(2.87, 3.81)	5.31	(4.29, 6.58)
23F	169	11.26	(9.79, 12.95)	173	4.49	(3.86, 5.23)	2.51	(2.04, 3.08)

[a] Studies conducted in US NCT00761631 (Study 5) and NCT00444457 (Study 3).
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after a 4-dose vaccination series with Prevnar (Study 3, post-toddler).
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs: Prevnar 13 (Study 5) to Prevnar (Study 3) reference.
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13 (Study 5) – Prevnar (Study 3)].
[g] Evaluable Immunogenicity Population.
[h] Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.

Table 23: Pneumococcal IgG GMCs (µg/mL) One Month After Vaccination for Additional 6 Serotypes, Prevnar 13 in Children 5 through 9 Years of Age in Study 5 Relative to Prevnar 13 in Study 3 (Post-toddler)[a,g,h]

	Vaccine Group (as Enrolled/Randomized)							
	Prevnar 13 5 Through 9 Years (Study 5)			Prevnar 13 Post-Toddler Dose (Study 3)				
Serotype	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	GMC Ratio[e]	(95% CI[f])
Additional								
1	171	3.57	(3.05, 4.18)	1068	2.90	(2.75, 3.05)	1.23	(1.07, 1.42)
3	171	2.38	(2.07, 2.74)	1065	0.75	(0.72, 0.79)	3.17	(2.78, 3.62)
5	171	5.52	(4.82, 6.32)	1068	2.85	(2.72, 2.98)	1.94	(1.71, 2.20)
6A	169	21.51	(18.15, 25.51)	1063	7.11	(6.78, 7.46)	3.03	(2.64, 3.47)
7F	170	6.24	(5.49, 7.08)	1067	4.39	(4.18, 4.61)	1.42	(1.24, 1.62)
19A	170	17.18	(15.01, 19.67)	1056	8.44	(8.05, 8.86)	2.03	(1.78, 2.32)

[a] Studies conducted in US NCT00761631 (Study 5) and NCT00444457 (Study 3).
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after a 4-dose vaccination series with Prevnar 13 (Study 3, post-toddler).
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs: Prevnar 13 (Study 5) to Prevnar 13 (Study 3).
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13 (Study 5) – Prevnar 13 (Study 3)].
[g] Evaluable Immunogenicity Population.
[h] Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.

In children 10 through 17 years of age OPA GMTs, as measured by the mcOPA assay, 1 month after vaccination were noninferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of >0.5) to mcOPA GMTs in the 5 through 9 year old group for 12 of 13 serotypes (except for serotype 3), as shown in Table 24.

Table 24: Comparison of Pneumococcal mcOPA GMTs One Month After Vaccination, Prevnar 13, in Children 10 through 17 Years of Age Relative to Prevnar 13 in Children 5 through 9 Years of Age[a,g,h,i]

	Vaccine Group (as Enrolled)							
	Prevnar 13 (10 through 17 Years)			Prevnar 13 (5 through 9 Years)				
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	GMT Ratio[e]	(95% CI[f])
Common								
4	188	6912	(6101, 7831)	181	4629	(4017, 5334)	1.5	(1.24, 1.80)
6B	183	14224	(12316, 16427)	178	14996	(13164, 17083)	0.9	(0.78, 1.15)
9V	186	4485	(4001, 5028)	180	4733	(4203, 5328)	0.9	(0.80, 1.12)
14	187	6894	(6028, 7884)	176	4759	(4120, 5497)	1.4	(1.19, 1.76)
18C	182	6263	(5436, 7215)	175	8815	(7738, 10041)	0.7	(0.59, 0.86)
19F	184	2280	(1949, 2668)	178	1591	(1336, 1893)	1.4	(1.14, 1.81)
23F	187	3808	(3355, 4323)	176	3245	(2819, 3736)	1.2	(0.97, 1.42)
Additional								
1	189	322	(275, 378)	179	191	(165, 221)	1.7	(1.36, 2.10)
3	181	114	(101, 130)	178	203	(182, 226)	0.6	(0.48, 0.67)
5	183	360	(298, 436)	178	498	(437, 568)	0.7	(0.57, 0.91)
6A	182	9928	(8457, 11655)	178	7514	(6351, 8891)	1.3	(1.05, 1.67)
7F	185	6584	(5829, 7436)	178	10334	(9099, 11737)	0.6	(0.53, 0.76)
19A	187	1276	(1132, 1439)	180	1180	(1048, 1329)	1.1	(0.91, 1.28)

[a] Studies conducted in US NCT00761631 (Study 5).
[b] n= Number of subjects with a determinate antibody titer for the specified serotype.
[c] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs: Prevnar 13(10 through 17 years of age) to Prevnar 13 (5 through 9 years of age).
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13(10 through 17 years of age) – Prevnar 13(5 through 9 years of age)] Study 5.
[g] Evaluable Immunogenicity Population.
[h] Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.
[i] Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

14.3 Prevnar 13 Immunogenicity Clinical Trials in Adults

Five Phase 3 clinical trials[6-8,10,11] were conducted in the US and Europe evaluating the immunogenicity of Prevnar 13 in different adult age groups, in individuals who were either not previously vaccinated with PPSV23 (PPSV23 unvaccinated) or who had received one dose of PPSV23 (PPSV23 previously vaccinated).

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease, and medical risk conditions and behaviors (e.g., alcoholism and smoking) that are known to increase the risk of serious pneumococcal pneumonia and invasive pneumococcal disease. A stable medical condition was defined as a medical condition not requiring significant change in therapy (i.e., change to new therapy category due to worsening disease) or hospitalization for worsening disease 12 weeks prior to receipt of the study vaccine.

Immune responses elicited by Prevnar 13 and PPSV23 were measured by a mcOPA antibody assay for the 13 pneumococcal serotypes contained in Prevnar 13. Serotype-specific mcOPA antibody GMTs measured 1 month after each vaccination were calculated. For the 12 serotypes in common to both vaccines, noninferiority between vaccines was met if the lower limit of the

2-sided 95% confidence interval (CI) of the GMT ratio (Prevnar 13/PPSV23) was greater than 0.5.

The response to the additional serotype 6A, which is contained in Prevnar 13 but not in PPSV23, was assessed by demonstration of a ≥4-fold increase in the anti-6A mcOPA antibody titer above preimmunization levels. A statistically significantly greater response for Prevnar 13 was defined, for the difference in percentages (Prevnar 13 minus PPSV23) of adults achieving a ≥4-fold increase in anti-6A mcOPA antibody titer, as the lower limit of the 2-sided 95% CI greater than zero. For comparison of mcOPA antibody GMTs, a statistically greater response for serotype 6A was defined as the lower limit of the 2-sided 95% CI of the GMT ratio (Prevnar 13/PPSV23) greater than 2.

Of the 5 Phase 3 clinical trials, 2 noninferiority trials[6,7] were conducted in which the immune responses to Prevnar 13 were compared with the immune responses to PPSV23; one in PPSV23 unvaccinated adults aged 18 through 64 years[6] (Study 6), and one in PPSV23 prevaccinated adults aged ≥70 years[7] (Study 7). A third study compared immune responses to a single dose of Prevnar 13 to the response to Prevnar 13 administered one year after a dose of PPSV23 in adults aged 60 through 64 years who were PPSV23 unvaccinated at enrollment[8] (Study 8). The study also compared immune responses of PPSV23 as a single dose to the responses to PPSV23 administered one year after a dose of Prevnar 13. Two studies assessed the concomitant administration of Prevnar 13 with seasonal inactivated Fluarix (IIV3) in the US[10] (Study 10) and Europe[11] (Study 11).

Overall across the clinical studies evaluating the immunogenicity of Prevnar 13 in adults, persons 18 through 64 years of age responded at least as well as persons 65 years and older, the age group evaluated in a clinical endpoint efficacy trial.

Clinical Trials Conducted in PPSV23 Unvaccinated Adults

In an active-controlled modified[a] double-blind clinical trial[6] (Study 6) of Prevnar 13 in the US, PPSV23 unvaccinated adults aged 60 through 64 years were randomly assigned (1:1) to receive Prevnar 13 or PPSV23. In addition, adults aged 18 through 49 years and 50 through 59 years were enrolled and received one dose of Prevnar 13 (open-label).

In adults aged 60 through 64 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines (see Table 24). In addition, the lower limit of the 95% confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 8 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a ≥4-fold increase after Prevnar 13 (88.5%) was statistically significantly greater than after PPSV23 (49.3%) in PPSV23-unvaccinated adults aged 60 through 64 years. OPA antibody GMTs for

[a] Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23 (see Table 25).

The mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 50 through 59 years were noninferior to the corresponding mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

In adults aged 18 through 49 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

Table 25: mcOPA Antibody GMTs in PPSV23-Unvaccinated Adults Aged 18 Through 49 Years or Aged 50 Through 59 Years Given Prevnar 13 and in Adults Aged 60 Through 64 Years Given Prevnar 13 or PPSV23 (Study 6)[a,b,c,d,e]

	Prevnar 13	Prevnar 13	Prevnar 13	PPSV23	Prevnar 13 18-49 Relative to 60-64 Years	Prevnar 13 50-59 Relative to 60-64 Years	Prevnar 13 Relative to PPSV23, 60-64 Years[g]
	18-49 Years[f] N=836-866	50-59 Years[f] N=350-384	60-64 Years N=359-404	60-64 Years N=367-402			
Serotype	GMT	GMT	GMT	GMT	GMT Ratio (95% CI)	GMT Ratio (95% CI)	GMT Ratio (95% CI)
1	353	211	158	119	2.4 (2.03, 2.87)	1.3 (1.07, 1.65)	1.3 (1.07, 1.65)
3	91	94	96	90	1.0 (0.84, 1.13)	1.0 (0.82, 1.18)	1.1 (0.89, 1.29)
4	4747	2904	2164	1405	2.3 (1.92, 2.76)	1.3 (1.06, 1.70)	1.5 (1.18, 2.00)
5	386	322	236	198	1.9 (1.55, 2.42)	1.4 (1.08, 1.74)	1.2 (0.95, 1.50)
6A[h]	5746	4469	2766	343	2.2 (1.84, 2.67)	1.6 (1.28, 2.03)	8.1 (6.11, 10.67)
6B	9813	3350	2212	998	4.9 (4.13, 5.93)	1.5 (1.20, 1.91)	2.2 (1.70, 2.89)
7F	3249	1807	1535	829	2.9 (2.41, 3.49)	1.2 (0.98, 1.41)	1.9 (1.52, 2.26)
9V	3339	2190	1701	1012	2.9 (2.34, 3.52)	1.3 (1.08, 1.53)	1.7 (1.40, 2.02)
14	2983	1078	733	819	4.9 (4.01, 5.93)	1.5 (1.14, 1.89)	0.9 (0.69, 1.16)
18C	3989	2077	1834	1074	2.3 (1.91, 2.79)	1.1 (0.89, 1.44)	1.7 (1.32, 2.21)
19A	1580	968	691	368	2.3 (2.02, 2.66)	1.4 (1.17, 1.68)	1.9 (1.53, 2.30)
19F	1533	697	622	636	3.0 (2.44, 3.60)	1.1 (0.89, 1.41)	1.0 (0.78, 1.23)
23F	1570	531	404	87	4.2 (3.31, 5.31)	1.3 (0.96, 1.80)	4.6 (3.37, 6.38)

GMT, Geometric Mean Titer.
[a] Study conducted in US NCT00427895 (Study 6).
[b] Noninferiority was defined for the 13 serotypes in adults aged 18 to 49 years, for the 12 common serotypes in adults aged 60 to 64 years and for the 13 serotypes in adults aged 50 to 59 years as the lower limit of the 2-sided 95% CI for GMT ratio greater than 0.5.
[c] mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[d] Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.
[e] Evaluable Immunogenicity Population.
[f] Open label administration of Prevnar 13.
[g] For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined for analysis in cohort 1 as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.
[h] 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

Clinical Trials Conducted in PPSV23 Previously Vaccinated Adults

In a Phase 3 active-controlled, modified double-blind clinical trial[7] (Study 7) of Prevnar 13 in the US and Sweden, PPSV23 prevaccinated adults aged ≥70 years who had received one dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either Prevnar 13 or PPSV23.

The mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common, when Prevnar 13 or PPSV23 were administered at a minimum of 5 years after a prior dose of PPSV23. In addition, the lower limit of the 95%

confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 9 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a ≥4-fold increase in mcOPA antibody titers after Prevnar 13 (71.1%) was statistically significantly greater than after PPSV23 (27.3%) in PPSV23-prevaccinated adults aged ≥70 years. mcOPA antibody GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥70 years and prevaccinated with PPSV23 ≥5 years prior, vaccination with Prevnar 13 elicited noninferior immune responses as compared with re-vaccination with PPSV23 (see Table 26).

Table 26: mcOPA Antibody GMTs in PPSV23-Previously Vaccinated Adults Aged ≥70 Years Given Prevnar 13 or PPSV23 (Study 7)[a,b,c,d,e,f]

Serotype	Prevnar 13 N=400-426 GMT	PPSV23 N=395-445 GMT	Prevnar 13 Relative to PPSV23	
			GMT Ratio	(95% CI)
1	93	66	1.4	(1.14, 1.72)
3	59	53	1.1	(0.92, 1.31)
4	613	263	2.3	(1.76, 3.10)
5	100	61	1.6	(1.35, 2.00)
6A[g]	1056	160	6.6	(5.14, 8.49)
6B	1450	565	2.6	(2.00, 3.29)
7F	559	481	1.2	(0.97, 1.39)
9V	622	491	1.3	(1.08, 1.49)
14	355	366	1.0	(0.76, 1.23)
18C	972	573	1.7	(1.33, 2.16)
19A	366	216	1.7	(1.40, 2.07)
19F	422	295	1.4	(1.16, 1.77)
23F	177	53	3.3	(2.49, 4.47)

GMT, Geometric Mean Titer.
[a] Study conducted in US and Sweden NCT00546572 (Study 7).
[b] For the 12 common serotypes, noninferiority was defined as the lower limit of the 2-sided 95% CI for GMT ratio (Prevnar 13/PPSV23) greater than 0.5.
[c] For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.
[d] mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[e] Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.
[f] Evaluable Immunogenicity Population.
[g] 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

Clinical Trial of Sequential Vaccination of Prevnar 13 and PPSV23 in PPSV23 Unvaccinated Adults

In a randomized clinical trial conducted in PPSV23-unvaccinated adults 60 through 64 years of age[8] (Study 8), 223 subjects received PPSV23 followed by Prevnar 13 one year later (PPSV23/Prevnar 13), and 478 received only Prevnar 13. mcOPA antibody titers were measured 1 month after vaccination with Prevnar 13 and are shown in Table 26. mcOPA antibody GMTs in those that received Prevnar 13 one year after PPSV23 were diminished when compared to those who received Prevnar 13 alone. Similarly, in exploratory analyses in PPSV23-pre-vaccinated adults ≥70 years of age in Study 7, diminished mcOPA antibody GMTs were observed in those that received Prevnar 13 one year after PPSV23 when compared to those who received Prevnar 13 alone.

Table 27: mcOPA Antibody GMTs for the Prevnar 13 Serotypes in PPSV23 Unvaccinated Adults Aged 60 Through 64 Years Given Prevnar 13 Alone or Prevnar 13 One Year After PPSV23 (Study 8) (PPSV23/Prevnar 13)[a,b,c,d]

	Prevnar 13 N=410-457		PPSV23/Prevnar 13 N=180-196	
Serotype	**GMT**	**(95% CI)**	**GMT**	**(95% CI)**
1	219	(191, 252)	88	(72, 109)
3	78	(69, 88)	54	(45, 65)
4	2590	(2257, 2973)	988	(802, 1218)
5	258	(218, 305)	112	(90, 139)
6A[e]	2947	(2536, 3426)	1210	(962, 1522)
6B	2165	(1845, 2540)	832	(654, 1059)
7F	1518	(1339, 1721)	407	(342, 485)
9V	1279	(1142, 1432)	495	(426, 575)
14	790	(663, 941)	515	(402, 659)
18C	1683	(1437, 1971)	650	(504, 839)
19A	717	(629, 818)	299	(248, 361)
19F	812	(702, 939)	360	(293, 442)
23F	384	(312, 472)	142	(104, 193)

GMT =Geometric Mean Titer.
[a] Study conducted in US NCT00574548 (Study 8).
[b] Evaluable Immunogenicity Population.
[c] mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[d] Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.
[e] 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

Also in Study 8, 266 subjects received Prevnar 13 followed by PPSV23 one year later (Prevnar 13/PPSV23). mcOPA antibody GMTs following PPSV23 administered one year after Prevnar 13 (Prevnar 13/PPSV23) were noninferior to those following a single dose of PPSV23 (N=237) for the 12 common serotypes [the lower limit of the 95% CI for the GMT ratio [Prevnar 13/PPSV23 relative to PPSV23] was >0.5] (see Table 27). In Study 6, which was conducted in PPSV23-unvaccinated adults 60 through 64 years of age, 108 subjects received PPSV23 3.5 to 4 years after Prevnar 13 (Prevnar 13/PPSV23) and 414 received a single dose of PPSV23. Higher serotype-specific mcOPA antibody GMT ratios [(Prevnar 13/PPSV23) / PPSV23] were generally observed compared to the one year dosing interval in Study 8.

Table 28: mcOPA Antibody GMTs for the Prevnar 13 Serotypes in PPSV23-Unvaccinated Adults Aged 60 Through 64 Years Given PPSV23 One Year After Prevnar 13 Relative to PPSV23 Alone (Study 8)[a,b,c,d]

	Prevnar 13/PPSV23 N=216-233		PPSV23 N=214-229		GMT Ratio (Prevnar 13/PPSV23) / PPSV23	
Serotype	**GMT**	**95% CI**	**GMT**	**95% CI**	**Ratio**	**95% CI**
1	155	(131, 182)	161	(131, 198)	1.0	(0.74, 1.25)
3	127	(111, 145)	83	(71, 98)	1.5	(1.23, 1.87)
4	1409	(1202, 1651)	1468	(1139, 1893)	1.0	(0.71, 1.29)
5	220	(184, 264)	178	(144, 222)	1.2	(0.93, 1.64)
6A[e]	1366	(1122, 1663)	400	(306, 524)	3.4	(2.45, 4.77)
6B	1345	(1113, 1625)	875	(689, 1111)	1.5	(1.14, 2.08)
7F	748	(653, 857)	719	(598, 865)	1.0	(0.83, 1.31)
9V	848	(731, 984)	824	(694, 977)	1.0	(0.82, 1.29)
14	711	(580, 872)	869	(677, 1115)	0.8	(0.59, 1.13)
18C	1115	(925, 1344)	912	(707, 1177)	1.2	(0.89, 1.67)
19A	471	(408, 543)	390	(318, 477)	1.2	(0.94, 1.55)
19F	819	(697, 963)	626	(504, 779)	1.3	(1.00, 1.71)
23F	216	(169, 277)	84	(62, 114)	2.6	(1.74, 3.79)

GMT =Geometric Mean Titer.
[a] Study conducted in US NCT00574548 (Study 8).
[b]Evaluable Immunogenicity Population.
[c] mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.
[d] Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.
[e] 6A is a serotype unique to Prevnar 13 but not contained in PPSV23. Anti-6A mcOPA antibody GMTs were descriptive in nature.

14.4 Concomitant Vaccine Administration

Infants and Toddlers

The concomitant administration of routine US infant vaccines *[see Drug Interactions (7.1)]* with Prevnar 13 was evaluated in two studies: Study 2 *[see Clinical Studies (14.2)]*, Pneumococcal Immune Responses Following Three Doses[2] and the US lot consistency study[3] (Study 3). In Study 3, subjects were randomly assigned to receive one of 3 lots of Prevnar 13 or Prevnar in a 2:2:2:1 ratio. The total number of infants vaccinated was 663[2] (Study 2) and 1699[3] (Study 3). Immune responses to concomitant vaccine antigens were compared in infants receiving Prevnar and Prevnar 13. Responses to diphtheria toxoid, tetanus toxoid, pertussis, polio types 1, 2, and 3, hepatitis B, PRP-T, PRP-OMP, measles, and varicella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

Adults

Two randomized, double-blind clinical trials evaluated the immunogenicity of Prevnar 13 given with IIV3 (Fall 2007/ Spring 2008 Fluarix, A/H1N1, A/H3N2, and B strains) in PPSV23 unvaccinated adults aged 50 through 59 years[10] (Study 10, conducted in the U.S.) and in adults ≥65 years[11] (Study 11, conducted in Europe).

In each clinical trial one group received Prevnar 13 and IIV3 concurrently, followed approximately one month later by placebo. The other group received IIV3 and placebo concurrently, followed approximately one month later by Prevnar 13.

Antibody responses elicited by IIV3 were measured by hemagglutination inhibition assay (HAI) one month after IIV3 vaccination. The proportion of subjects achieving a ≥4-fold increase in HAI titer (responder) for each IIV3 strain was evaluated 1 month after vaccination.

Noninferiority was demonstrated for each IIV3 vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders between the two groups [concomitant minus (IIV3+Placebo)] was greater than -10%.

In subjects 50 through 59 years of age, noninferiority was demonstrated for each of the 3 IIV3 strains after Prevnar 13 given concomitantly with IIV3 compared with IIV3 given alone.

In subjects ≥65 years of age, noninferiority was demonstrated for A/H1N1 and B-strains, but not for A/H3N2, which had a lower limit of the 95% CI of -10.4%.

The studies also assessed the antibody responses of Prevnar 13 when Prevnar 13 was given concomitantly with IIV3 compared with Prevnar 13 given alone. The antipolysaccharide binding antibody responses (IgG) were measured by ELISA IgG one month after Prevnar 13 vaccination in a subset of subjects. Noninferiority was demonstrated if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevnar 13+ IIV3 relative to Prevnar 13 alone) was >0.5. In a post hoc analysis, mcOPA antibody response was evaluated using the same criterion.

In subjects 50 through 59 years of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for all 13 serotypes after Prevnar 13 was given concomitantly with IIV3 compared to Prevnar 13 given alone, and noninferiority of the mcOPA antibody GMT ratios was observed for 10 of 13 serotypes.

In subjects ≥65 years of age, Prevnar 13 IgG antibody responses, as measured by ELISA, met noninferiority for 12 of 13 serotypes after Prevnar 13 was given concomitantly with IIV3 compared with Prevnar 13 given alone, and noninferiority of the mcOPA antibody GMT ratios was observed for all of the 13 serotypes.

15 REFERENCES

ClinicalTrials.gov identifiers for studies included below:

1. Study 1 NCT00205803
2. Study 2 NCT00373958
3. Study 3 NCT00444457
4. Study 4 NCT00452452
5. Study 5 NCT00761631
6. Study 6 NCT00427895
7. Study 7 NCT00546572
8. Study 8 NCT00574548
9. Study 9 NCT00500266
10. Study 10 NCT00521586

11. Study 11 NCT00492557

12. Study 12 NCT00744263

16 HOW SUPPLIED/STORAGE AND HANDLING

Prefilled Syringe, 1 Dose (10 per package) – NDC 0005-1971-02.

Prefilled Syringe, 1 Dose (1 per package) – NDC 0005-1971-05.

After shipping, Prevnar 13 may arrive at temperatures between 2ºC to 25ºC (36ºF to 77ºF).

Upon receipt, store refrigerated at 2ºC to 8ºC (36ºF to 46ºF).

Do not freeze. Discard if the vaccine has been frozen.

Prevnar 13 is stable at temperatures up to 25°C (77°F) for 4 days. These data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Prior to administration of this vaccine, inform the individual, parent, guardian, or other responsible adult of the following:

- The potential benefits and risks of immunization with Prevnar 13 *[see Warnings and Precautions (5) and Adverse Reactions (6)]*.
- The importance of completing the immunization series unless contraindicated.
- Any suspected adverse reactions should be reported to their healthcare professional.

Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

US Govt. License No. 3
LAB-0469-14.1
CPT Code 90670

INJECTION

AquaMEPHYTON®

(PHYTONADIONE)

Aqueous Colloidal Solution of Vitamin K_1

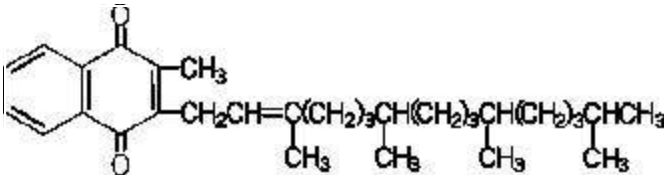
WARNING - INTRAVENOUS AND INTRAMUSCULAR USE

Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of AquaMEPHYTON* (Phytonadione), even when precautions have been taken to dilute the AquaMEPHYTON and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following INTRAMUSCULAR administration. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving AquaMEPHYTON for the first time. Therefore the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70.

Phytonadione is 2-methyl-3-phytyl-1, 4-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is:



AquaMEPHYTON injection is a yellow, sterile, aqueous colloidal solution of vitamin K_1, with a pH of 5.0 to 7.0, available for injection by the intravenous, intramuscular, and subcutaneous routes.

Each milliliter contains:

Phytonadione	2 mg or 10 mg
Inactive ingredients:	
Polyoxyethylated fatty acid derivative	70 mg
Dextrose	37.5 mg
Water for Injection, q.s.	1 mL
Added as preservative:	
Benzyl alcohol	0.9%

CLINICAL PHARMACOLOGY

AquaMEPHYTON aqueous colloidal solution of vitamin K_1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive

* Registered trademark of MERCK & CO., Inc.

to the levels of three of these four factors — II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Phytonadione is readily absorbed following intramuscular administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors.

The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or two and hemorrhage is usually controlled within 3 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogues.

INDICATIONS AND USAGE

AquaMEPHYTON is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

AquaMEPHYTON injection is indicated in:

— anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives;
— prophylaxis and therapy of hemorrhagic disease of the newborn;
— hypoprothrombinemia due to antibacterial therapy;
— hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis;
— other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, e.g., salicylates.

CONTRAINDICATION

Hypersensitivity to any component of this medication.

WARNINGS

Benzyl alcohol as a preservative in Bacteriostatic Sodium Chloride Injection has been associated with toxicity in newborns. Data are unavailable on the toxicity of other preservatives in this age group. There is no evidence to suggest that the small amount of benzyl alcohol contained in AquaMEPHYTON, when used as recommended, is associated with toxicity.

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1 to 2 hours for measurable improvement in the prothrombin time. Whole blood or component therapy may also be necessary if bleeding is severe.

Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditions which originally permitted

thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

PRECAUTIONS

General

Vitamin K_1 is fairly rapidly degraded by light; therefore, always protect AquaMEPHYTON from light. Store AquaMEPHYTON in closed original carton until contents have been used. (See also HOW SUPPLIED**,** *Storage.)*

Drug Interactions

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

Laboratory Tests

Prothrombin time should be checked regularly as clinical conditions indicate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of carcinogenicity, mutagenesis or impairment of fertility have not been conducted with AquaMEPHYTON.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with AquaMEPHYTON. It is also not known whether AquaMEPHYTON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AquaMEPHYTON should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AquaMEPHYTON is administered to a nursing woman.

Pediatric Use

Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, may be related to the dose of AquaMEPHYTON. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Deaths have occurred after intravenous and intramuscular administration. (See Box Warning.)

Transient "flushing sensations" and "peculiar" sensations of taste have been observed, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Pain, swelling, and tenderness at the injection site may occur.

The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind.

Infrequently, usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; rarely, these have progressed to scleroderma-like lesions that have persisted for long periods. In other cases, these lesions have resembled erythema perstans.

Hyperbilirubinemia has been observed in the newborn following administration of phytonadione. This has occurred rarely and primarily with doses above those recommended. (See PRECAUTIONS, *Pediatric Use*.)

OVERDOSAGE

The intravenous LD_{50} of AquaMEPHYTON in the mouse is 41.5 and 52 mL/kg for the 0.2% and 1% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, AquaMEPHYTON should be given by the subcutaneous route (see Box Warning). When intravenous administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg per minute.

Protect from light at all times.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Dilution

AquaMEPHYTON may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or 5% Dextrose and Sodium Chloride Injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. *Therefore, all of the above diluents should be preservative-free* (see WARNINGS). *Other diluents should not be used*. When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the ampul.

Prophylaxis of Hemorrhagic Disease of the Newborn

The American Academy of Pediatrics recommends that vitamin K_1 be given to the newborn. A single intramuscular dose of AquaMEPHYTON 0.5 to 1 mg within one hour of birth is recommended.

Treatment of Hemorrhagic Disease of the Newborn

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time in 2 to 4 hours) following administration of vitamin K_1 is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

AquaMEPHYTON 1 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and AquaMEPHYTON should be given concurrently.

Anticoagulant-Induced Prothrombin Deficiency in Adults

To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy — 2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition (see WARNINGS). If in 6 to 8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

AquaMEPHYTON

Summary of Dosage Guidelines
(See circular text for details)

Newborns	Dosage
Hemorrhagic Disease of the Newborn	
Prophylaxis	0.5 - 1 mg IM within 1 hour of birth

Treatment	1 mg SC or IM (Higher doses may be necessary if the mother has been receiving oral anticoagulants)

Adults	Initial Dosage
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg - 10 mg or up to 25 mg (rarely 50 mg)
Hypoprothrombinemia due to other causes (Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)	2.5 mg - 25 mg or more (rarely up to 50 mg)

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Hypoprothrombinemia Due to Other Causes in Adults

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to administering concurrent AquaMEPHYTON. The severity of the coagulation disorder should determine whether the immediate administration of AquaMEPHYTON is required in addition to discontinuation or reduction of interfering drugs.

HOW SUPPLIED

Injection AquaMEPHYTON is a yellow, sterile, aqueous colloidal solution and is supplied in the following concentrations:

No. 7780 — 10 mg of vitamin K_1 per mL

NDC 0006-7780-38 boxes of 5 × 1 mL ampuls

NDC 0006-7780-66 five boxes of 5 × 1 mL ampuls.

No. 7784 — 1 mg of vitamin K_1 per 0.5 mL

NDC 0006-7784-33 five boxes of 5 × 0.5 mL ampuls.

Storage

Store container in original carton. Always protect AquaMEPHYTON from light. Store container in closed original carton until contents have been used. (See PRECAUTIONS, *General*.)

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued February 2002
Printed in USA

VITAMIN K_1 INJECTION
Phytonadione
Injectable Emulsion, USP

®N+

Aqueous Dispersion of Vitamin K_1

Ampul
Rx only

Protect from light. Keep ampuls in tray until time of use.

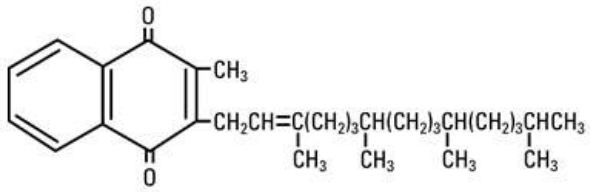
WARNING – INTRAVENOUS AND INTRAMUSCULAR USE

Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following INTRAMUSCULAR administration. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. Therefore the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70.

Phytonadione is 2-methyl-3-phytyl-1, 4-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$ and its structural formula is:



Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) is a yellow, sterile, nonpyrogenic aqueous dispersion available for injection by the intravenous, intramuscular and subcutaneous routes. Each milliliter contains phytonadione 2 or 10 mg, polyoxyethylated fatty acid derivative 70 mg, dextrose, hydrous 37.5 mg in water for injection; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment. pH is 6.3 (5.0 to 7.0). Phytonadione is oxygen sensitive.

CLINICAL PHARMACOLOGY

Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) aqueous dispersion of vitamin K_1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of three of these four factors—II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxy-glutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Phytonadione is readily absorbed following intramuscular administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors.

The action of the aqueous dispersion, when administered intravenously, is generally detectable within an hour or two and hemorrhage is usually controlled within 3 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogues.

INDICATIONS AND USAGE

Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

Vitamin K_1 Injection is indicated in:

- anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives;
- prophylaxis and therapy of hemorrhagic disease of the newborn;
- hypoprothrombinemia due to antibacterial therapy;
- hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis;
- other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, e.g., salicylates.

CONTRAINDICATION

Hypersensitivity to any component of this medication.

WARNINGS

Benzyl alcohol as a preservative in Bacteriostatic Sodium Chloride Injection has been associated with toxicity in newborns. Data are unavailable on the toxicity of other preservatives in this age group. There is no evidence to suggest that the small amount of benzyl alcohol contained in Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP), when used as recommended, is associated with toxicity.

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1 to 2 hours for measurable improvement in the prothrombin time. Whole blood or component therapy may also be necessary if bleeding is severe.

Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditions which originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they required large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

Drug Interactions

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

Laboratory Tests

Prothrombin time should be checked regularly as clinical conditions indicate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of carcinogenicity, mutagenesis or impairment of fertility have not been conducted with Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP).

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Vitamin K_1 Injection. It is also not known whether Vitamin K_1 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vitamin K_1 Injection should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Vitamin K_1 Injection is administered to a nursing woman.

Pediatric Use

Hemolysis, jaundice, and hyperbilirubinemia in neonates, particularly those that are premature, may be related to the dose of Vitamin K_1 Injection. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Deaths have occurred after intravenous and intramuscular administration. (See Box Warning.)

Transient "flushing sensations" and "peculiar" sensations of taste have been observed, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Pain, swelling, and tenderness at the injection site may occur.

The possibility of allergic sensitivity including an anaphylactoid reaction, should be kept in mind.

Infrequently, usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; rarely, these have progressed to scleroderma-like lesions that have persisted for long periods. In other cases, these lesions have resembled erythema perstans.

Hyperbilirubinemia has been observed in the newborn following administration of phytonadione. This has occurred rarely and primarily with doses above those recommended. (See PRECAUTIONS, Pediatric Use.)

OVERDOSAGE

The intravenous LD_{50} of Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) in the mouse is 41.5 and 52 mL/kg for the 0.2% and 1% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) should be given by the subcutaneous route. (See Box Warning.) When intravenous administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg per minute.

Protect from light at all times.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Dilution

Vitamin K_1 Injection may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or 5% Dextrose and Sodium Chloride Injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. **Therefore, all of the above diluents should be preservative-free** (see WARNINGS). **Other diluents should not be used.** When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the ampul.

Prophylaxis of Hemorrhagic Disease of the Newborn

The American Academy of Pediatrics recommends that vitamin K_1 be given to the newborn. A single intramuscular dose of Vitamin K_1 Injection 0.5 to 1 mg within one hour of birth is recommended.

Treatment of Hemorrhagic Disease of the Newborn

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time in 2 to 4 hours) following administration of vitamin K_1 is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

Vitamin K_1 Injection 1 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and Vitamin K_1 Injection should be given concurrently.

Anticoagulant-Induced Prothrombin Deficiency in Adults

To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy—2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition (see WARNINGS). If in 6 to 8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) Summary of Dosage Guidelines (See circular text for details)

Newborns	Dosage
Hemorrhagic Disease of the Newborn Prophylaxis	0.5 to 1 mg IM within 1 hour of birth
Treatment	1 mg SC or IM (Higher doses may be necessary if the mother has been

receiving oral anticoagulants)

Adults	Initial Dosage
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg to 10 mg or up to 25 mg (rarely 50 mg)
Hypoprothrombinemia due to other causes (Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)	2.5 mg to 25 mg or more (rarely up to 50 mg)

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Hypoprothrombinemia Due to Other Causes in Adults

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates; antibiotics) is suggested as an alternative to administering concurrent Vitamin K_1 Injection. The severity of the coagulation disorder should determine whether the immediate administration of Vitamin K_1 Injection is required in addition to discontinuation or reduction of interfering drugs.

HOW SUPPLIED

Vitamin K_1 Injection (Phytonadione Injectable Emulsion, USP) is supplied in a package of 25 as follows:

NDC No.	Container	Amount of Vitamin K_1 Inj. in Container	Volume	Concentration
0409-9157-25	1 mL Ampul	1 mg	0.5 mL	2 mg/mL
0409-9158-25	1 mL Ampul	10 mg	1 mL	10 mg/mL

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Protect from light. Keep ampuls in tray until time of use.

EN-3196

02/2013

Manufactured by Hospira, Inc., Lake Forest, IL 60045 USA

N+ and NOVAPLUS are registered trademarks of Novation, LLC.

NOVAPLUS®

PRINCIPAL DISPLAY PANEL - 0.5 mL Ampul Label

NDC 0409-9157-25
Rx only

0.5 mL

VITAMIN K_1 Inj.
Phytonadione Injectable
Emulsion, USP

1 mg/0.5 mL

Neonatal Concentration

Contains no more than 100 mcg/L
of aluminum.

Protect from light.
RL-4148

Mfd. by
Hospira, Inc., Lake Forest, IL 60045 USA

100 mcg/L Aluminum

Neonatal/infant dose = 0.5 - 1 mg

1 mg dose per 0.5mL solution

Amount of aluminum in 0.5mL =

1 L = 1000mL

(0.5mL)(100mcg/1000mL) = 0.05mcg/mL

0.025 mcg Aluminum per 0.5mL dose

PRINCIPAL DISPLAY PANEL - 0.5 mL Ampul Tray Label

5/**NDC** 0409-9157-25
Rx only
0.5 mL
Single-dose Ampul

VITAMIN K_1 Injection
Phytonadione Injectable Emulsion, USP

1 mg/0.5 mL

Neonatal Concentration

Protect from light. Keep ampuls in tray until time of use.
For I.M., S.C., or I.V. (with caution).

Each mL contains phytonadione 2 mg; polyoxyethylated fatty acid derivative 70 mg; dextrose, hydrous 37.5 mg; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment. pH 6.3 (5.0 to 7.0). Usual dosage: See insert. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Manufactured by Hospira, Inc., Lake Forest, IL 60045 USA
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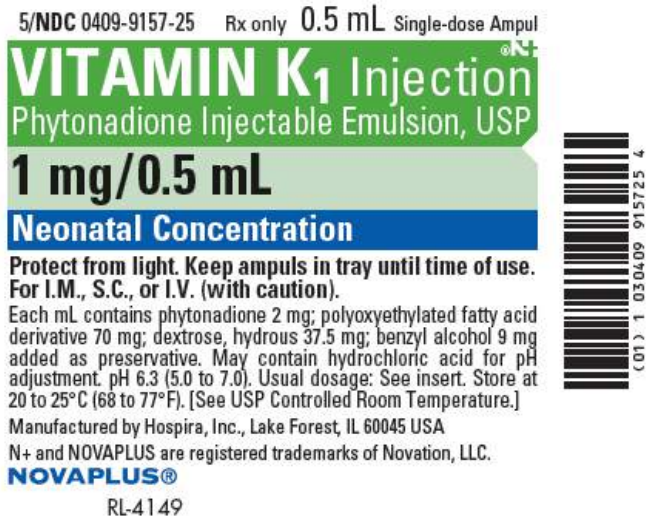
NOVAPLUS®

RL-4149



PHYTONADIONE INJECTABLE EMULSION, USP

Aqueous Colloidal Solution of Vitamin K_1

Rx Only

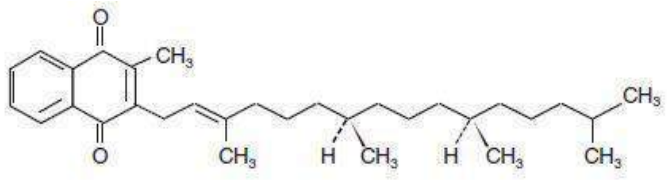
WARNING - INTRAVENOUS USE

Severe reactions, including fatalities, have occurred during and immediately after the parenteral administration of Phytonadione. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving Phytonadione for the first time. The majority of these reported events occurred following intravenous administration, even when precautions have been taken to dilute the Phytonadione and to avoid rapid infusion. Therefore, the INTRAVENOUS route should be restricted to those situations where another route is not feasible and the increased risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70.

Phytonadione is 2-methyl-3-phytyl-1, 4-naphthoquinone. Its empirical formula is $C_{31}H_{46}0_2$ and its structural formula is:



E component

Phytonadione Injectable Emulsion, USP, is a yellow, sterile, aqueous colloidal solution of vitamin K1, with a pH of 3.5 to 7.0. It is available for injection by the intravenous, intramuscular, and subcutaneous routes.

Each 0.5 mL contains 1 mg phytonadione (Vitamin K_1), 10 mg polysorbate 80, 10.4 mg propylene glycol, 0.17 mg sodium acetate anhydrous, and 0.00002 mL glacial acetic acid. Additional glacial acetic acid or sodium acetate anhydrous may have been added to adjust pH to meet USP limits of 3.5 to 7.0. The air above the liquid in the individual containers has been displaced by flushing with nitrogen during the filling operation.

CLINICAL PHARMACOLOGY

Phytonadione aqueous colloidal solution of vitamin K_1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of three of these four factors—II, Vll, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Phytonadione is readily absorbed following intramuscular administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors.

The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or two and hemorrhage is usually controlled within 3 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogues.

INDICATIONS AND USAGE

Phytonadione is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

Phytonadione Injectable Emulsion, USP is indicated in:
— anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives;

— prophylaxis and therapy of hemorrhagic disease of the newborn;
— hypoprothrombinemia due to antibacterial therapy;
— hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis;
— other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, e.g., salicylates.

CONTRAINDICATION

Hypersensitivity to any component of this medication.

WARNINGS

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1 to 2 hours for measurable improvement in the prothrombin time. Whole blood or component therapy may also be necessary if bleeding is severe. Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditionswhich originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

PRECAUTIONS

Drug Interactions

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

Laboratory Tests

Prothrombin time should be checked regularly as clinical conditions indicate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of carcinogenicity, mutagenesis or impairment of fertility have not been conducted with phytonadione.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with phytonadione. It is also not known whether phytonadione can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when phytonadione is administered to a nursing woman.

Pediatric Use

Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, may be related to the dose of phytonadione. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Severe hypersensitivity reactions, including anaphylactoid reactions and deaths have been reported following parenteral administration. The majority of these reported events occurred following intravenous administration (see Box Warning.)

The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind following parenteral administration.

Transient “flushing sensations” and “peculiar” sensations of taste have been observed, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Pain, swelling, and tenderness at the injection site may occur.

Infrequently, usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; rarely, these have progressed to scleroderma-like lesions that have persisted for long periods. In other cases, these lesions have resembled erythema perstans.

Hyperbilirubinemia has been observed in the newborn following administration of phytonadione. This has occurred rarely and primarily with doses above those recommended. (See PRECAUTIONS, Pediatric Use.)

OVERDOSAGE

The intravenous LD_{50} of Phytonadione Injectable Emulsion, USP in the mouse is 41.5 and 52 mL/kg for the 0.2% and 1.0% concentrations, respectively.

DOSAGE AND ADMINISTRATION

Whenever possible, phytonadione should be given by the subcutaneous route (see Box WARNING). When intravenous or intramuscular administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg per minute.

Protect from light at all times.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration,whenever solution and container permit.

Directions for Dilution

Phytonadione may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or 5% Dextrose and Sodium Chloride Injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. Therefore, all of the above diluents should be preservative-free. (See WARNINGS) Other diluents should not be used. When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the vial.

Prophylaxis of Hemorrhagic Disease of the Newborn

The American Academy of Pediatrics recommends that vitamin K1 be given to the newborn. A single intramuscular dose of phytonadione 0.5 to 1 mg within one hour of birth is recommended.

Treatment of Hemorrhagic Disease of the Newborn

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time in 2 to 4 hours) following administration of vitamin K_1 is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

Phytonadione 1 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and phytonadione should be given concurrently.

Anticoagulant-Induced Prothrombin Deficiency in Adults

To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy 2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition (see WARNINGS). If in 6 to 8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should berepeated.

Phytonadione
Summary of Dosage Guidelines
(See insert text for details)

Newborns	**Dosage**
Hemorrhagic Disease of the Newborn Prophylaxis	0.5 - 1 mg IM within 1 hour of birth
Treatment	1 mg SC or IM (Higher doses may be necessary if the mother has been receiving oral anti-coagulants)
Adults	**Initial Dosage**
Anticoagulant - Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5 mg - 10 mg or up to 25 mg (rarely 50 mg)

Newborns	Dosage
Hypoprothrombinemia due to other causes (Antibiotics; Salicylates or other drugs; Factors limiting absorption or synthesis)	2.5 mg - 25 mg or more (rarely up to 50 mg)

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Hypoprothrombinemia Due to Other Causes in Adults

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to administering concurrent phytonadione. The severity of the coagulation disorder should determine whether the immediate administration of phytonadione is required in addition to discontinuation or reduction of interfering drugs.

HOW SUPPLIED

In unit use packages containing one single dose vial and a SAF-T-Jet® vial injector, 27 G. x 1/2" needle.

Phytonadione Injection USP, 1 mg in 0.5 mL

Stock No. 1240 NDC 76329-1240-1

10 individual cartons shrink wrapped as a group of 10 cartons.

Syringe Assembly Directions:

See User Guide

USE ASEPTIC TECHNIQUE

Do not remove from carton or assemble until ready to use.

*CAUTION: IMPROPER ENGAGING MAY CAUSE GLASS BREAKAGE AND SUBSEQUENT INJURY.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [see USP].

Protect from light.

INTERNATIONAL MEDICATION SYSTEMS, LIMITED
SO. EL MONTE, CA 91733, U.S.A.
An Amphastar Pharmaceuticals Company Rev. 7-13

PRINCIPLE DISPLAY PANEL: Syringe Label

IMS, LIMITED

So. El Monte, CA 91733, U.S.A.

7612400C 7-13

0.5 mL 1 mg 1 mg / 0.5 mL

PHYTONADIONE INJECTABLE EMULSION, USP

NEONATAL CONCENTRATION

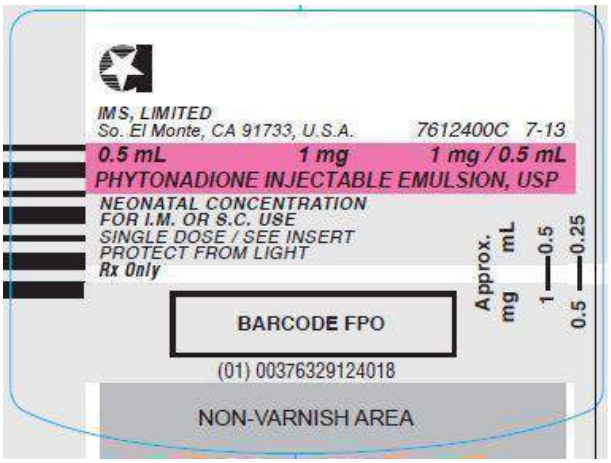
FOR I.M. OR S.C. USE

SINGLE DOSE / SEE INSERT

PROTECT FROM LIGHT

Rx Only

Approx. mg mL 1 0.5 0.5 0.25



PRINCIPLE DISPLAY PANEL: Carton

SAF-T-JET®

NDC 76329-1240-1

STOCK NO. 1240

Rx Only

SAF-T-JET®

27 G. X 1/2" NEEDLE

PHYTONADIONE INJECTABLE EMULSION USP

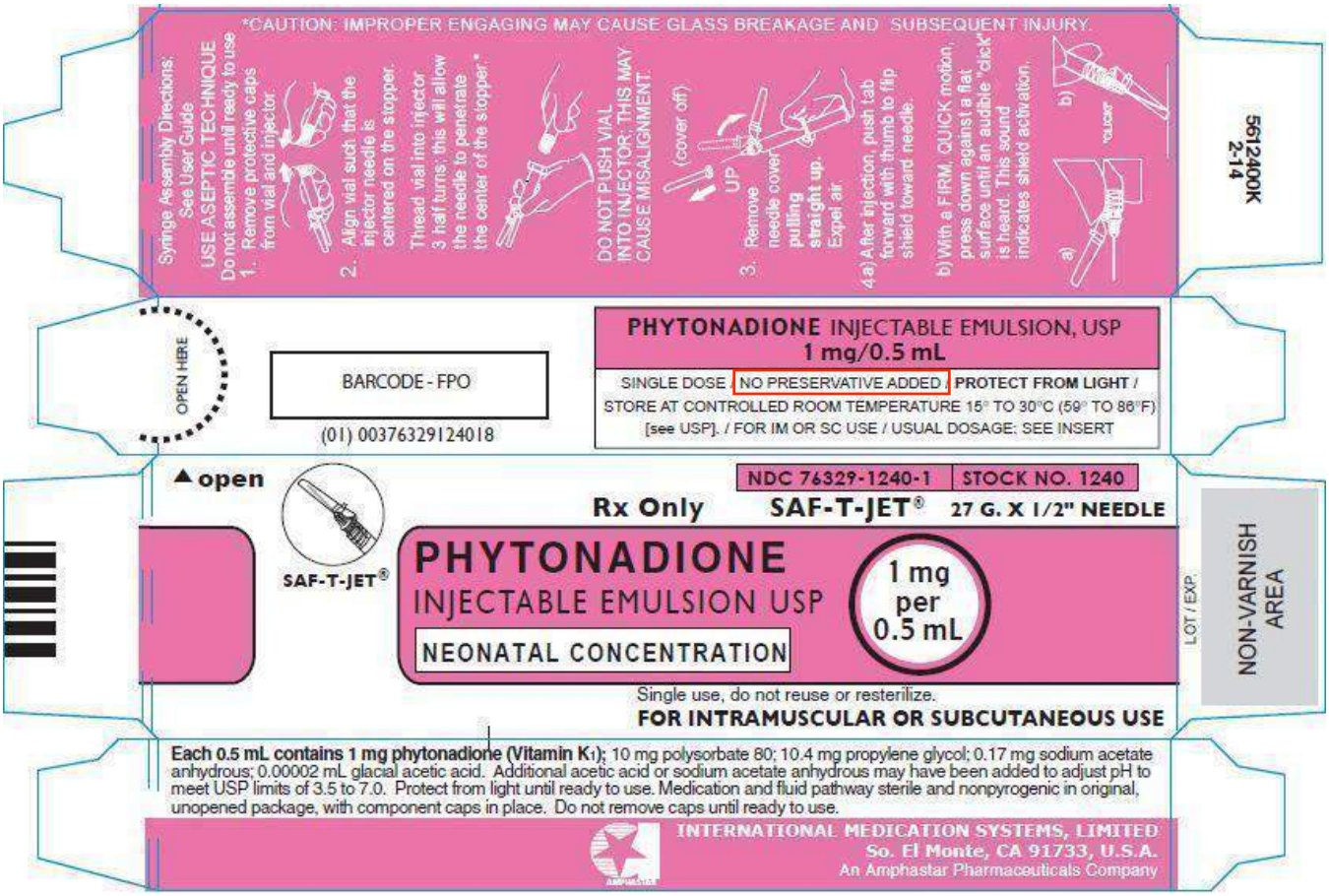
NEONATAL CONCENTRATION

1 mg per 0.5 mL

Single use, do not reuse or resterilize.

FOR INTRAMUSCULAR OR SUBCUTANEOUS USE

"No preservative added"



Vaccine Excipient & Media Summary

Excipients Included in U.S. Vaccines, by Vaccine

In addition to weakened or killed disease antigens (viruses or bacteria), vaccines contain very small amounts of other ingredients – excipients or media.

Some excipients are added to a vaccine for a specific purpose. These include:
Preservatives, to prevent contamination. For example, thimerosal.
Adjuvants, to help stimulate a stronger immune response. For example, aluminum salts.
Stabilizers, to keep the vaccine potent during transportation and storage. For example, sugars or gelatin.

Others are residual trace amounts of materials that were used during the manufacturing process and removed. These include:
Cell culture materials, used to grow the vaccine antigens. For example, egg protein, various culture media.
Inactivating ingredients, used to kill viruses or inactivate toxins. For example, formaldehyde.
Antibiotics, used to prevent contamination by bacteria. For example, neomycin.

The following table lists all components, other than antigens, shown in the manufacturers' package insert (PI) for each vaccine. Each of these PIs, which can be found on the FDA's website (see below) contains a description of that vaccine's manufacturing process, including the amount and purpose of each substance. In most PIs, this information is found in Section 11: "Description."

All information was extracted from manufacturers' package inserts.
If in doubt about whether a PI has been updated since this table was prepared, check the FDA's website at:
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

Vaccine	Contains
Adenovirus	human-diploid fibroblast cell cultures (strain WI-38), Dulbecco's Modified Eagle's Medium, fetal bovine serum, sodium bicarbonate, monosodium glutamate, sucrose, D-mannose, D-fructose, dextrose, human serum albumin, potassium phosphate, plasdone C, anhydrous lactose, microcrystalline cellulose, polacrilin potassium, magnesium stearate, cellulose acetate phthalate, alcohol, acetone, castor oil, FD&C Yellow #6 aluminum lake dye
Anthrax (Biothrax)	amino acids, vitamins, inorganic salts, sugars, aluminum hydroxide, sodium chloride, benzethonium chloride, formaldehyde
BCG (Tice)	glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, iron ammonium citrate, lactose
Cholera (Vaxchora)	casamino acids, yeast extract, mineral salts, anti-foaming agent, ascorbic acid, hydrolyzed casein, sodium chloride, sucrose, dried lactose, sodium bicarbonate, sodium carbonate
DT (Sanofi)	aluminum phosphate, isotonic sodium chloride, formaldehyde, casein, cystine, maltose, uracil, inorganic salts, vitamins, dextrose
DTaP (Daptacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion
DTaP (Infanrix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, sodium chloride, polysorbate 80 (Tween 80)
DTaP-IPV (Kinrix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, VERO cells, a continuous line of monkey kidney cells, Calf serum, lactalbumin hydrolysate, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B
DTaP-IPV (Quadracel)	modified Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion, formaldehyde, aluminum phosphate, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, MRC-5 cells, normal human diploid cells, CMRL 1969 medium supplemented with calf serum, Medium 199 without calf serum, 2-phenoxyethanol, polysorbate 80, glutaraldehyde, neomycin, polymyxin B sulfate

Vaccine	Contains
DTaP-HepB-IPV (Pediarix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, glutaraldehyde, modified Stainer-Scholte liquid medium, VERO cells, a continuous line of monkey kidney cells, calf serum and lactalbumin hydrolysate, aluminum hydroxide, aluminum phosphate, aluminum salts, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B, yeast protein.
DTaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, sucrose, formaldehyde, glutaraldehyde, bovine serum albumin, 2-phenoxyethanol, neomycin, polymyxin B sulfate, modified Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin. MRC-5 cells (a line of normal human diploid cells), CMRL 1969 medium supplemented with calf serum, Medium 199 without calf serum, modified Mueller and Miller medium
Hib (ActHIB)	sodium chloride, modified Mueller and Miller medium (the culture medium contains milk-derived raw materials [casein derivatives]), formaldehyde, sucrose
Hib (Hiberix)	saline, synthetic medium, formaldehyde, sodium chloride, lactose
Hib (PedvaxHIB)	complex fermentation media, amorphous aluminum hydroxyphosphate sulfate, sodium chloride
Hep A (Havrix)	MRC-5 human diploid cells, formalin, aluminum hydroxide, amino acid supplement, phosphate-buffered saline solution, polysorbate 20, neomycin sulfate, aminoglycoside antibiotic
Hep A (Vaqta)	MRC-5 diploid fibroblasts, amorphous aluminum hydroxyphosphate sulfate, non-viral protein, DNA, bovine albumin, formaldehyde, neomycin, sodium borate, sodium chloride
Hep B (Engerix-B)	aluminum hydroxide, yeast protein, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate
Hep B (Recombivax)	soy peptone, dextrose, amino acids, mineral salts, phosphate buffer, formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, yeast protein
Hep B (Heplisav-B)	vitamins and mineral salts, yeast protein, yeast DNA, deoxycholate, phosphorothioate linked oligodeoxynucleotide, phosphate buffered saline, sodium phosphate, dibasic dodecahydrate, monobasic dehydrate, polysorbate 80
Hep A/Hep B (Twinrix)	MRC-5 human diploid cells, formalin, aluminum phosphate, aluminum hydroxide, amino acids, sodium chloride, phosphate buffer, polysorbate 20, neomycin sulfate, yeast protein
Human Papillomavirus (HPV) (Gardasil 9)	vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein
Influenza (Afluria) Trivalent & Quadrivalent	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, ovalbumin, sucrose, neomycin sulfate, polymyxin B, beta-propiolactone, thimerosal (multi-dose vials)
Influenza (Fluad)	squalene, polysorbate 80, sorbitan trioleate, sodium citrate dehydrate, citric acid monohydrate, neomycin, kanamycin, barium, egg proteins, cetyltrimethylammonium bromide (CTAB), formaldehyde
Influenza (Fluarix) Trivalent & Quadrivalent	octoxynol-10 (TRITON X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, sodium deoxycholate, sodium phosphate-buffered isotonic sodium chloride
Influenza (Flublok) Trivalent & Quadrivalent	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20 (Tween 20), baculovirus and *Spodoptera frugiperda* cell proteins, baculovirus and cellular DNA, Triton X-100, lipids, vitamins, amino acids, mineral salts
Influenza (Flucelvax) Trivalent & Quadrivalent	Madin Darby Canine Kidney (MDCK) cell protein, protein other than HA, MDCK cell DNA, polysorbate 80, cetyltrimethlyammonium bromide, and β-propiolactone
Influenza (Flulaval) Trivalent & Quadrivalent	ovalbumin, formaldehyde, sodium deoxycholate, α-tocopheryl hydrogen succinate, polysorbate 80, thimerosal (multi-dose vials)
Influenza (Fluvirin)	ovalbumin, polymyxin, neomycin, betapropiolactone, nonylphenol ethoxylate, thimerosal
Influenza (Fluzone) Quadrivalent	formaldehyde, egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, thimerosal (multi-dose vials), sucrose
Influenza (Fluzone) High Dose	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, formaldehyde, sucrose

Vaccine	Contains
Influenza (Fluzone) Intradermal	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, sucrose
Influenza (FluMist) Quadrivalent	monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, ovalbumin, gentamicin sulfate, ethylenediaminetetraacetic acid (EDTA)
Japanese Encephalitis (Ixiaro)	aluminum hydroxide, protamine sulfate, formaldehyde, bovine serum albumin, host cell DNA, sodium metabisulphite, host cell protein
Meningococcal (MenACWY-Menactra)	Watson Scherp media containing casamino acid, modified culture medium containing hydrolyzed casein, ammonium sulfate, sodium phosphate, formaldehyde, sodium chloride
Meningococcal (MenACWY-Menveo)	formaldehyde, amino acids, yeast extract, Franz complete medium, CY medium
Meningococcal (MenB – Bexsero)	aluminum hydroxide, *E. coli*, histidine, sucrose, deoxycholate, kanamycin
Meningococcal (MenB – Trumenba)	defined fermentation growth media, polysorbate 80, histidine buffered saline
MMR (MMR-II)	chick embryo cell culture, WI-38 human diploid lung fibroblasts, vitamins, amino acids, fetal bovine serum, sucrose, glutamate, recombinant human albumin, neomycin, sorbitol, hydrolyzed gelatin, sodium phosphate, sodium chloride
MMRV (ProQuad) (Frozen)	chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells, sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride; potassium phosphate dibasic, neomycin, bovine calf serum
MMRV (ProQuad) (Refrigerator Stable)	chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells, sucrose, hydrolyzed gelatin, urea, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate, recombinant human albumin, sodium bicarbonate, potassium phosphate, potassium chloride, neomycin, bovine serum albumin
Pneumococcal (PCV13 – Prevnar 13)	soy peptone broth, casamino acids and yeast extract-based medium, CRM197 carrier protein, polysorbate 80, succinate buffer, aluminum phosphate
Pneumococcal (PPSV-23 – Pneumovax)	phenol
Polio (IPV – Ipol)	Eagle MEM modified medium, calf bovine serum, M-199 without calf bovine serum, vero cells (a continuous line of monkey kidney cells), phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B
Rabies (Imovax)	human albumin, neomycin sulfate, phenol red indicator, MRC-5 human diploid cells, beta-propriolactone
Rabies (RabAvert)	chicken fibroblasts, β-propiolactone, polygeline (processed bovine gelatin), human serum albumin, bovine serum, potassium glutamate, sodium EDTA, ovalbumin, neomycin, chlortetracycline, amphotericin B
Rotavirus (RotaTeq)	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum, vero cells *[DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.]*
Rotavirus (Rotarix)	amino acids, dextran, Dulbecco's Modified Eagle Medium (sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-250 glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red), sorbitol, sucrose, calcium carbonate, sterile water, xanthan *[Porcine circovirus type 1 (PCV-1) is present in Rotarix. PCV-1 is not known to cause disease in humans.]*
Smallpox (Vaccinia) (ACAM2000)	African Green Monkey kidney (Vero) cells, HEPES, human serum albumin, sodium chloride, neomycin, polymyxin B, Glycerin, phenol
Td (Tenivac)	aluminum phosphate, formaldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate
Td (Mass Biologics)	aluminum phosphate, formaldehyde, thimerosal, modified Mueller's media which contains bovine extracts, ammonium sulfate

Vaccine	Contains
Tdap (Adacel)	aluminum phosphate, formaldehyde, 2-phenoxyethanol, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, glutaraldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate, modified Mueller's growth medium
Tdap (Boostrix)	modified Latham medium derived from bovine casein, Fenton medium containing a bovine extract, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, sodium chloride, polysorbate 80
Typhoid (Typhim Vi)	hexadecyltrimethylammonium bromide, formaldehyde, phenol, polydimethylsiloxane, disodium phosphate, monosodium phosphate, semi-synthetic medium
Typhoid (Vivotif Ty21a)	yeast extract, casein, dextrose, galactose, sucrose, ascorbic acid, amino acids, lactose, magnesium stearate. gelatin
Varicella (Varivax) *Frozen*	human embryonic lung cell cultures, guinea pig cell cultures, human diploid cell cultures (WI-38), human diploid cell cultures (MRC-5), sucrose, hydrolyzed gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, EDTA (Ethylenediaminetetraacetic acid), neomycin, fetal bovine serum
Varicella (Varivax) *Refrigerator Stable*	human embryonic lung cell cultures, guinea pig cell cultures, human diploid cell cultures (WI-38), human diploid cell cultures (MRC-5), sucrose, hydrolyzed gelatin, urea, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, neomycin, bovine calf serum
Yellow Fever (YF-Vax)	sorbitol, gelatin, sodium chloride, egg protein
Zoster (Shingles) (Zostavax) *Frozen*	sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride; MRC-5 cells, neomycin, bovine calf serum
Zoster (Shingles) (Zostavax) *Refrigerator Stable*	sucrose, hydrolyzed porcine gelatin, urea, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, MRC-5 cells, neomycin, bovine calf serum
Zoster (Shingles) (Shingrix)	sucrose, sodium chloride, dioleoyl phosphatidylcholine (DOPC), potassium dihydrogen phosphate, cholesterol, sodium dihydrogen phosphate dihydrate, disodium phosphate anhydrous, dipotassium phosphate, polysorbate 80, Chinese Hamster Ovary (CHO) cell proteins, DNA

A table listing vaccine excipients and media *by excipient* can be found in:

Grabenstein JD. *ImmunoFacts: Vaccines and Immunologic Drugs* – 2013 (38th revision). St Louis, MO: Wolters Kluwer Health, 2012.

March 2018

Vaccine Ingredients and Manufacturer Information

(alphabetical order by vaccine)

We have listed **vaccine ingredients** (substances that appear in the final vaccine product), **process ingredients** (substances used to create the vaccine that may or may not appear in the final vaccine product), and **growth mediums** (the substances vaccines are grown in) for vaccines approved by the Food & Drug Administration (FDA) and commonly recommended by the Centers for Disease Control (CDC.) Controversial products used to make vaccines: African Green Monkey (Vero) cells, aluminum, cow products, Cocker Spaniel cells, formaldehyde, human fetal lung tissue cells, insect products, and mouse brains.

Though not listed, each vaccine contains strains of the virus being vaccinated against. Each vaccine entry links to the manufacturer's package insert that contains information about dosage, ingredient quantity, and how the vaccine is made. Some vaccines, like influenza vaccines, are modified frequently and you may wish to consult the package inserts online and your doctor for the most current information.

I. VACCINES AND INGREDIENTS

1. Adenovirus
2. Anthrax
3. BCG (tuberculosis)
4. Cholera
5. DT (diphtheria & tetanus)
6. DTap (diphtheria, tetanus, & pertussis)
7. DTap-IPV (diphtheria, tetanus, pertussis, & polio)
8. DTap-HepB-IPV (diphtheria, tetanus, pertussis, hepatitis B, & polio)
9. DTap-IPV/Hib (diphtheria, tetanus, pertussis, polio, & haemophilus influenzae type B)
10. Hib (haemophilus influenzae type B)
11. Hib/Hep B (haemophilus influenzae type B & hepatitis B)
12. Hep A (hepatitis A)
13. Hep B (hepatitis B)
14. Hep A/Hep B (hepatitis A & hepatitis B)
15. HPV (human papillomavirus)
16. Influenza A (H1N1) (swine flu)
17. Influenza A (H5N1) (bird flu)
18. Influenza A & B
19. Japanese Encephalitis
20. Meningococcal
21. Measles
22. MMR (measles, mumps, & rubella)
23. Pneumococcal
24. Polio
25. Rabies
26. Rotavirus
27. Rubella
28. Smallpox
29. TD (tetanus & diphtheria)
30. Tdap (tetanus, diphtheria, & pertussis)
31. Typhoid
32. Varicella (chickenpox)
33. Yellow Fever
34. Zoster (shingles)

Product	Possible Ingredients (Ingredients depend on which modification is used.)
2-Phenoxyethanol	2-Phenoxyethanol is a glycol ether used as a preservative in vaccines.
Aluminum	Aluminum is used in vaccines as an adjuvant, which helps the vaccine work more quickly and more powerfully.
Bovine casein	A casein is a family of phosphoproteins commonly found in mammalian milk. 80% of the proteins in cow's milk are casein.
Bovine serum	Bovine "[s]erum is the centrifuged fluid component of either clotted or defibrinated whole blood. Bovine serum comes from blood taken from domestic cattle. Serum from other animals is also collected and processed but bovine serum is processed in the greatest volume." "Bovine serum is a by-product of the meat industry. Bovine blood may be taken at the time of slaughter, from adult cattle, calves, very young calves or (when cows that are slaughtered are subsequently found to be pregnant) from bovine fetuses. It is also obtained from what are called 'donor' animals, which give blood more than once. Blood is available from bovine fetuses only because a proportion of female animals that are slaughtered for meat for human consumption are found (often unexpectedly) to be pregnant. Blood is available from very young calves because calves, especially males from dairy breeds, are often slaughtered soon, but not necessarily immediately, after birth because raising them will not be economically beneficial. Older animals are, of course, slaughtered for meat. Only donor cattle are raised for the purpose of blood donation. Donor cattle are invariably kept in specialized, controlled herds. Blood is taken from these animals in a very similar way to that used for human blood donation. Irrespective of whether blood is taken at slaughter or from donors, the age of the animal is an important consideration because it impacts the characteristics of the serum. Bovine serum is categorised according to the age of the animal from which the blood was collected as follows: •'Fetal bovine serum' comes from fetuses •'Newborn calf serum' comes from calves less than three weeks old •'Calf serum' comes from calves aged between three weeks and 12 months •'Adult bovine serum' comes from cattle older than 12 months Serum processed from donor blood is termed 'donor bovine serum'. Donor animals can be up to three years old."

Chicken Eggs	Viruses can be grown in chicken eggs before being used in vaccinations.
CMRL-1969	L-alanine, L-arginine (free base)[b], L-aspartic acid, L-cysteine-HCL, L-cystine, L-glutamic acid-H20, L-glutamine, glycine, L-histidine (free base)[b], L-hydroxyproline, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, *p*-aminobenzoic acid, ascorbic acid, *d*-biotin, calcium pantothenate, cholesterol, choline chloride, ethanol, folic acid, glutathione, *i*-inositol, menadione, nicotinamide, nicotinic acid, pyridoxal-HCL, pyridoxine-HCL, riboflavine, riboflavine-5-phosphate, sodium acetate-3H2O, thiamine-HCL, Tween 80, vitamin A acetate, vitamin D (calciferol), vitamin E (a-tocopherol phosphate), D-glucose, phenol red, sodium chloride, potassium chloride, calcium chloride, magnesium culphate heptahydrate, sodium phosphate dibasic, sodium dihydrogen phosphate, monopotassium phosphate, sodium bicarbonate, iron nitrate nonahydrate
Dulbecco's Modified Eagle's Serum	glucose, sodium bicarbonate, L-glutamine, pyridoxine HCl, pyridocal HCl, folic acid, phenol red, HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid), L-methionine, L-cystine, sodium phosphate mono-basic, sodium pyruvate, vitamins
Earle's Balanced Salt Medium	inorganic salts, D-glucose, phenol red, calcium, magnesium salts
Fenton Medium	bovine extract
Formaldehyde	Formaldehyde is used in vaccines to inactivate the virus so the person being inoculated does not contract the disease.
Human albumin	Human albumin is a blood plasma protein produced in the liver that, among other functions, transports hormones, fatty acids, and other compounds, and buffers pH.
Insect Cells	Cabbage moth and fall armyworm cells are used to grow viruses for vaccines.
Latham Medium	bovine casein
MDCK (Madin-Carby canine kidney cells)	cells from normal female adult Cocker Spaniel (harvested in 1958 by SH Madin and NB Darby), EMEM(EBSS) (Eagle's Minimum Essential Medium with Earle's Balanced Salt Solution), glutamine, non essential amino acids, foetal bovine serum
Mouse Brains	Live mice brains are inoculated with the Japanese encephalitis virus to grow the virus used in the vaccine.
MRC-5	Medical Research Council 5, human diploid cells (cells containing two sets of chromosomes) derived from the normal lung tissues of a 14-week-old male fetus aborted for "psychiatric reasons" in 1966 in the United Kingdom, Eagle's Basal Medium in Earle's balanced salt solution with bovine serum.

Mueller-Miller Medium	glucose, sodium chloride, sodium phosphate dibasic, monopotassium, phosphate, magnesium sulfate hydrate, ferrous sulfate heptaphydrate, cystine hydrochloride, tyrosine hydrochloride, urasil hydrochloride, Ca-pantothenate in ethanol, thiamine in ethanol, pyridoxin-hydrochloride in ethanol, riboflavin in ethanol, biotin in ethanol, sodium hydroxide, beef heart infusion (de-fatted beef heart and distilled water), casein solution
Polysorbate 80	Also called Tween 80, Alkest 80, or Canarcel 80 (brand names). Polysorbate 80 is used as an excipient (something to basically thicken a vaccine for proper dosing) and an emulsifier (something to bond the ingredients).
Porcine gelatin	Gelatin is used to protect viruses in vaccines from freeze-drying or heat and to stabilize vaccines so they stay stable.
Stainer-Scholte Liquid Medium	tris hydrochloride, tris base, glutamate (monosodium salt), proline, salt, monopotassium phosphate, potassium chloride, magnesium chloride, calcium chloride, ferrous sulfate, ascorbic acid, niacin, glutathione
Thimerosal	Thimerosal is an organomercury compound used as a preservative.
Vero Cells (African Green Monkey Cells)	cells derived from the kidney of a normal, adult African Green monkey in 1962 by Y. Yasumura and Y. Kawakita
WI-38 human diploid cells	Winstar Institute 38, human diploid lung fibroblasts derived from the lung tissues of a female fetus aborted because the family felt they had too many children in 1964 in the United States

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Commentary

An aluminium adjuvant in a vaccine is an acute exposure to aluminium

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1. Introduction

Aluminium salts are common adjuvants in vaccines given to children. Their physical, chemical and biological properties have recently been reviewed [1]. However, a debate continues as to whether neonate and infant exposure to aluminium through vaccination is biologically significant with respect to their exposure to aluminium through other routes and especially diet. For example, paediatricians, responsible for administering the vaccine schedule for children, seem in particular, to be uninformed about the properties of aluminium adjuvants and their mode of action in vaccines. This apparent ignorance of the published scientific literature is unexpected in those charged with the wellbeing of neonates and infants and especially in the light of Janeway's description of alum adjuvant as 'the immunologist's dirty little secret' [2]. Paediatricians such as recently (07/04/2019) Andrew Pollard in The Sunday Times, have a habit of reverting to pure 'baby talk' when for example; describing how much aluminium is present in an infant vaccine. They use terms such as 'minuscule' and 'teeny-weeny' to tell anyone, who asks, how little aluminium there is in a vaccine. They usually then proceed to compare the amount of aluminium in a vaccine with the amount of aluminium in (an adult's) diet. There are, of course, more accurate, understandable ways to inform parents and other interested parties how much aluminium is present in a vaccine, and I shall endeavour to achieve this herein. An appreciation of how much aluminium is present in a single injection of a vaccine is critical to understanding how aluminium adjuvants are effective in stimulating the immune response.

2. How much aluminium is found in vaccines?

Currently about 20 childhood vaccines include an aluminium adjuvant. Vaccine industry literature (for example; https://www.medicines.org.uk/emc/product/2586/smpc) expresses the aluminium content of an individual vaccine as an amount (weight) of aluminium (not aluminium salt) per unit volume of a vaccine (usually 0.5 mL). Industry does this to account for the fact that there are no strict molecular weights for the polymeric aluminium salts that are used as adjuvants in vaccinations. They prepare acid digests of the adjuvants and measure their total aluminium using ICP MS. This is not explained in the literature they provide with vaccines and can cause confusion for some as the actual weight of hydrated aluminium salt (e.g. aluminium oxyhydroxide, aluminium hydroxyphosphate and aluminium hydroxyphosphatesulphate) in any vaccine preparation is actually approximately ten fold higher. The aluminium salt is the major component of a vaccine (after water) and its high content is why vaccine preparations are invariably cloudy in appearance [1]. As an example, GlaxoSmithKline's Infanrix Hexa vaccine is reported by the manufacturer to contain 0.82 mg of aluminium per vaccine (0.5 mL). Thus, the weight of aluminium salt in this vaccine is approximately 8 mg, which is approximately ten times the weight of all of the other components of the vaccine when combined. An aluminium-adjuvanted vaccine is essentially a very high concentration of an aluminium salt (8 mg/0.5 mL or 16 mg/mL or 16 g/L) in which just μg of other vaccine components including antigens and other excipients are occluded.

3. Is the amount of aluminium in a vaccine 'minuscule'?

Generally, in the United Kingdom the first dose of Infanrix Hexa vaccine is injected into muscle when an infant is 8 weeks old. All 8 mg of the aluminium salt (or 0.82 mg of aluminium) will immediately be systemic; it is inside the infant's body. The repercussions of this being that the injected aluminium may only leave the body through its excretion in either the infant's urine or sweat. What is the immediate biological response to this exposure to aluminium adjuvant? Aluminium is described as a silent visitor to the human body. What this means is that in the evolution of life on Earth and latterly human evolution, no historic signature is found as evidence for previous exposure to aluminium [3]. By way of comparison with another toxic and non-essential metal, if the adjuvant used in a vaccine was composed of a cadmium salt its injection would immediately initiate a counter-response by the body in an attempt to remove the toxicant. Proteins known to bind and help in the detoxification of cadmium are produced and this is a sure sign that biochemistry had previously encountered non-essential cadmium and selected it out of essential biochemical pathways. Such restorative attempts at detoxification are not triggered for biologically available aluminium and so the 'processing' of aluminium adjuvant at the injection site of a vaccine is completely adventitious and one might suggest, random and chaotic. The latter because the fate of aluminium in the body, unlike essential and other non-essential metals, is not subject to any form of homeostasis. Myriad

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chemical and biological processes will initiate the slow redistribution of the injected aluminium throughout the infant's body. These steps will involve the processes of disaggregation, dissolution, complexation, precipitation, distribution, cellular uptake and translocation. The description of each one of these processes is an essay in itself and we have addressed them all in many complementary publications [1]. An important and vaccination-specific distinction to make at this point and to carry forward to the following discussion is that aluminium injected into muscle as an adjuvant in a vaccine potentially has uninterrupted access to the infant brain. This is because there is no prerequisite for its passage via the liver, the most prominent organ of detoxification in humans.

We asked if 0.82 mg of systemically available aluminium administered as a single dose in a vaccine is, as some paediatricians would suggest, a minuscule amount of aluminium, for example, as compared to aluminium in the diet. Infants receiving Infanrix Hexa vaccine at 8 weeks of age are concurrently either being breast or formula fed. Data show that the former is likely to result in an 8 week old infant ingesting up to 0.1 mg of aluminium each day [4,5]. On the day an infant receives 8 mg of an aluminium salt, or 0.82 mg of aluminium, in a vaccine it will also ingest 0.1 mg of aluminium in breast milk. However, what proportion of this 0.1 mg of dietary aluminium will be absorbed across the infant gut? Previous research has asked a similar question [6]. The reality is that data for the absorption of aluminium across the infant gut do not presently exist and one has to apply gastrointestinal absorption data obtained for adults. The oft-cited value for adults is that less than 0.1% of ingested aluminium in diet is actually absorbed [7]. The infant gut at 8 weeks is incomplete [8] and is likely to be much more permeable to dietary aluminium, perhaps as much as 100 times more permeable. Applying such clearly conditional criteria it can be estimated that 10% of ingested aluminium or 0.01 mg/day of aluminium in breast milk is absorbed across the infant gastrointestinal tract. However, the blood carrying nutrients and toxins that have been absorbed from the gut, to the rest of the body must first pass through the liver, the major detoxification system of the body. Data on the efficiency of the liver in removing aluminium from the blood is, at best, incomplete in adults [9] and completely unknown in infants. If it is estimated that the liver is 75% efficient in this respect for adults then it is probably only 50% efficient in an infant. When these various conditional factors are accounted for it can be estimated that an infant's exposure to systemically available aluminium from breast-feeding is approximately 0.005 mg of aluminium each day. In essence during the first 8 weeks or 56 days of life, breast-feeding ostensibly drip feeds an infant with a combined total of 0.28 mg of systemically available aluminium. On day 56 the infant receives a single dose of 0.82 mg of aluminium in the Infanrix Hexa vaccine, a dose equivalent to 3 times the amount of aluminium the infant received during the entire 55 days of life prior to its vaccination. It is well known, if highly unfortunate, that infant formulas are heavily contaminated with aluminium [10,11] and in a worst-case scenario an infant only being formula-fed from birth might be exposed to 0.030 mg of aluminium each day up to vaccination on day 56. Even in this worst-case scenario, the exposure to systemically available aluminium on vaccination day is 25 times higher through the vaccine than through the diet.

4. Acute versus chronic exposure to aluminium

Breast or formula feeding in an infant is a chronic exposure to aluminium. The infant is exposed to a small but continuous supply of systemically available aluminium, aluminium that has the potential to be stored in the infant's body and excreted from the infant's body in the urine. Perhaps, at no point during continuous chronic (drip feed) exposure in infancy (0–12 months of age) does the concentration of aluminium in any one physiological compartment increase to bring about overt toxicity. How does dietary exposure to aluminium in infants compare to exposure through vaccination, for example, a single Infanrix Hexa vaccine at 8 weeks of age? The concentration of aluminium (not aluminium salt) in an Infanrix Hexa vaccine upon its injection into muscle is, according to the manufacturer, 0.82 mg/0.5 mL or 1.64 mg/mL or 1.64 g/L or approximately 60 mmol/L. This is the concentration of total systemically available aluminium immediately present at the injection site of the vaccine and available to bring about biological effect. Aluminium adjuvants are not inert depots at the vaccine injection site; they are sources of biologically reactive aluminium [1]. This concentration of total aluminium at the injection site of a vaccine can be put into context by examining the cellular toxicity of aluminium [12] and specifically as identified in recent scientific publications. We can ask the question if we would expect this concentration of aluminium to produce biological effects including cell death at the vaccine injection site. A relevant cell to investigate are lymphocytes and research has demonstrated significant genotoxicity in lymphocytes exposed to only 0.020 mmol/L total aluminium [13]. Similarly, in another study using lymphocytes 0.6 mmol/L total aluminium resulted in significant immunosuppression in both T and B-lymphocytes [14]. Clearly, we would expect profound effects on lymphocytes at the injection site of a vaccine where the total aluminium concentration is 60 mmol/L. Macrophages, a characteristically robust cell, are susceptible to aluminium toxicity demonstrating 50% cell death at a total aluminium concentration of 10 mmol/L [15]. Other more sensitive cell lines would include neuroblastoma where cell viability is reduced by 50% by less than 1 mmol/L total aluminium [16] and similarly for primary hippocampal neurons exposed to only 0.05 mmol/L total aluminium [17]. The concentration of systemically available aluminium immediately present at the injection site of a vaccine is very high in comparison to studies on cell cytotoxicity in the scientific literature. It is an acute exposure to aluminium and it results in significant cytotoxicity including necrotic cell death [1]. The resulting tissue inflammation is the characteristic red mark on the skin at the injection point. This acute toxicity in the immediate vicinity of the injection site underlies the success of aluminium salts as adjuvants in vaccinations [1]. However, while some cells, both present at and infiltrating the injection site, are compromised and especially immediately, other cells act to remedy the situation by taking up aluminium adjuvant into their cytoplasm [18]. This action reduces the concentration of biologically reactive (toxic) aluminium at the injection site and locks away potentially cytotoxic aluminium in intracellular vesicles. Herein may be the real issue linking aluminium adjuvants and severe adverse events following a vaccine. These aluminium-loaded cells remain viable for days, potentially weeks, which means that they can transport their cargo of aluminium anywhere in the body including the infant brain. The recruitment of systemic cells including macrophages to the central nervous system is a widely documented phenomenon [19]. There is now a viable mechanism for the accelerated loading of an infant's brain with aluminium and evidence to support such a mechanism was demonstrated in our recent paper on aluminium in brain tissue in autism [20].

5. Conclusion: is the amount of aluminium in a vaccine 'minuscule'?

Simply by looking at just one dose of a vaccine given at 8 weeks of age it is abundantly clear that science does not support this contention, as espoused regularly by many infant paediatricians. In fact, just a single dose of Infanrix Hexa vaccine represents a severe acute exposure to systemically available aluminium. A single dose of this vaccine is equivalent to the exposure to aluminium that an infant would receive from 150 days breast-feeding. It is equivalent to 25 times the daily dose of aluminium received from the most contaminated of infant formulas. It is pertinent to emphasise that an infant would receive a further two doses of this vaccine during the aforementioned 150 day period. It is also highly relevant that other aluminium adjuvanted vaccines, for example Prevenar 13 (https://www.medicines.org.uk/emc/product/453/smpc) and Men B (https://www.medicines.org.uk/emc/product/

5168/smpc) are also part of the infant vaccine schedule for this same period. In the United Kingdom it is not uncommon for an infant to receive all three of these aluminium adjuvanted vaccines on the same day. A combined daily exposure of 1.445 mg of aluminium (according to the manufacturer's data), equivalent to 260 days exposure to aluminium through breast feeding. Exposure to aluminium through a vaccine is, in comparison to diet, an acute exposure and an infant's physiology will respond differently to exposure to a high concentration of aluminium over a very short time period. The latter, acute versus chronic exposure, while not yet being taken into account in infant vaccination programmes, must now be considered to help to ensure that future vaccination schedules are safe. Currently the EMA and the FDA limit the aluminium content of a vaccine to 1.25 mg (See for example, https://www.ecfr.gov/cgi-bin/text-idx?SID=832c22988b6c802fe810e16ea34ace1a&mc=true&node=se21.7.610_115&rgn=div8). This limit is based upon the aluminium adjuvant's efficacy in inducing antibody titres. Perhaps now is the time to revise this limit based upon additional factors of vaccine safety.

Author contributions

CE conceived and wrote the manuscript.

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Declaration of Competing Interest

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Research Article

Aluminium Involvement in Neurotoxicity

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The aetiology of neurodegenerative diseases (ND) seems to involve susceptibility genes and environmental factors. Toxic metals are considered major environmental pollutants. Following our study of a case of multiple sclerosis (MS) improvement due to removal of aluminium (Al) and other toxic metals, we have examined the possible relationship between Al intoxication and ND. We used the slow intravenous treatment with the chelating agent EDTA (calcium disodium ethylene diamine tetraacetic acid) (chelation test) to remove Al and detected it in the urine collected from the patients for 12 hours. Patients affected by MS represented 85.6% of total ND. Al was present in 44.8% of cases comprehensive of ND and healthy patients. Al levels were significantly higher in ND patients than in healthy subjects. We here show that treatment of patients affected by Al burden with ten EDTA chelation therapies (EDTA intravenous administration once a week) was able to significantly reduce Al intoxication.

1. Introduction

Exposure of human populations to toxic metals can result in damage to a variety of organ systems.

One of the most commonly toxic metals studied, aluminum (Al), is implicated in many diseases. Al is a highly abundant and ubiquitously distributed as environmental and industrial toxicant and is also contained in many food products, being involved in skeletal, haematological, and neurological diseases [1]. Al toxicity is caused by disruption of homeostasis of metals such as magnesium, calcium, and iron (Fe): in fact, Al mimics these metals in their biological functions and triggers many biochemical alterations [2]. In particular, Al both exerts direct genotoxicity in primary human neural cells [3] and induces neurodegeneration, through an increase in Fe accumulation and oxygen reactive species (ROS) production [4]. Al-induced oxidative damage to DNA has been previously associated with neurodegeneration in different regions of rat brain [5]. In addition, more recently Al^{3+} has been shown to provoke transporter-mediated dopamine neuron degeneration in the nematode *Caenorhabditis elegans* [6].

The removal of toxic metal from human body can represent a useful tool to avoid the beginning or progression of many diseases related to metal intoxication.

The methods useful to determine some metal content in biological samples for monitoring purposes were developed some years ago. Indeed, both toxic and essential metals have been assayed in blood, urine, and hair by atomic absorption spectroscopy [7]. Successively, methods for trace-element analysis in human biological materials have been developed and inductively coupled plasma mass spectrometry (ICP-MS) was considered preferable for screening of multiple elements [8]. However, it seems difficult to show metal excess in blood and urine in conditions different from acute metal intoxication. In fact, blood toxic metal increase reflects only recent exposure to metals [9]. After acute exposure, toxic metals rapidly move from blood to many tissues, where they are sequestered, as in central nervous system (CNS). The only way able to remove accumulated toxic metals from human organs is to bind these metals by means of chelating agents, with the aim of forming complexes able to be excreted in the urine. Toxic metal levels can be examined in the urine samples collected from patients, following "challenge" with a chelating agent ("chelation test"). We have selected, among known chelating agents, calcium disodium ethylenediamine tetraacetic acid ($CaNa_2EDTA$ or EDTA), which was intravenously administered. The stability constants of aluminium and other metals of biochemical

interest with various chelating agents including EDTA have been previously studied [10]. The development of a set of metal complex constants served to correlate chemical and functional properties of the metals and suggested that EDTA was able to mobilize aluminium.

In the past, toxic levels of Al have been associated with neurodegenerative diseases (ND). A possible link between Al and Alzheimer's disease has been highlighted [11]. In 1991, treatment with low dose intramuscular desferrioxamine (DFO), a trivalent chelator that can remove excessive iron and/or aluminium from the body, was reported to slow the progression of Alzheimer's disease [12].

In the present work we have decided to study whether Al was involved in neurotoxicity. Indeed we evaluated the Al body burden in patients affected or not by ND. We studied also the possible reduction of this burden following treatments with the chelating agent EDTA.

2. Materials and Methods

2.1. Study Design and Patient Recruitment. Out of 471 consecutive subjects who had undergone a medical checkup in an outpatient medical center, only 211 were selected and enrolled for this study due to evidence of their Al burden and compliance in following the protocol, for example, receiving chelation therapy once a week by personal choice. The ND examined in this study were multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD). Many MS patients had been previously treated with conventional drugs used in such pathology (e.g., immunosuppressant agents, as mitoxantrone and azathioprine, broad-spectrum immunomodulatory agents, as glatiramer acetate and interferon β, and monoclonal antibodies, as rituximab and natalizumab). Some MS patients had never been previously treated with drugs. Patients not affected by known diseases (healthy subject or controls) as well as patients affected by nonneurodegenerative pathologies (not ND, which refers to diseases not classified as ND as fibromyalgia) have also been recruited. Some healthy patients who had been previously exposed to environmental or working toxic metals preferred to examine their possible intoxication by evaluating the presence of such metals in hair samples. Indeed, they were excluded from the present study. All patients provided informed consent to participate in this study. They were between 18 and 75 years old.

2.2. Chelation Test and Evaluation of Urine Al. Patients have been subjected to the chelation test to show possible Al intoxication. Indeed, they were invited to collect the urine samples before and after the intravenous treatment with the chelating agent EDTA (ethylenediamine tetraacetic acid, e.g., calcium disodium edetate, 2 g/10 mL diluted in 500 mL physiological saline, Farmax srl, Brescia, Italy). EDTA was intravenously slowly administered (the infusion lasted about 2 hours) to the patients. The time of urine collection following chelation lasted 12 h. Samples recovered from such collection were accurately enveloped in sterile vials and transported to the Laboratory of Toxicology (Doctor's Data Inc., St. Charles, IL, USA), where they have been processed. Samples were acid-digested with certified metal-free acids; digestion took place in a closed-vessel microwave digestion system. For sample dilution ultrapure water was used.

To avoid contamination, only plastic materials were used. All laboratory ware (pipette tips, volumetric flasks, etc.) was immersed for at least 48 h in a 10% (v/v) HNO_3/ethanol solution and, shortly before use, washed with Milli-Q purified water. To avoid contamination from the air, all steps in the preparation of samples and reagents were carried out on a class 100 clean bench [13, 14].

Testing was performed via inductively coupled plasma mass spectrometry (ICP-MS) utilizing collision/reaction cell methods coupled with ion-molecule chemistry, a new reliable method for interference reduction. The method has been recently used for biomonitoring of 20 trace elements in blood and urine of occupationally exposed workers [15]. Certified urine standards and in-house standards were used for quality control and to validate results. To avoid the potentially great margin of error that can result from fluid intake and sample volume, results were reported in micrograms (μg) per g creatinine. Creatinine was measured by reverse-phase high-performance liquid chromatography and was used to correct the total volume of urinary Al for differences in the glomerular filtration rates of individuals at the time of the spot sample [16]. The research program entitled "Effects of Chelation Therapy with EDTA in Patients Affected by Pathologies Related to Exposition (Acute or Chronic) to Toxic Metals" has been approved by Ethical Commitment of The University of Milan (Italy) (number 64/2014).

2.3. Clinical Evaluation of Patient's Symptom Improvement in MS. In the absence of a diagnostic test specific for MS, the neurological community has adopted diagnostic criteria which were replaced in the time [17]. Magnetic resonance imaging (MRI), analysis of cerebrospinal fluid, and visual evoked potential, added to clinical diagnosis, have been considered to present limitations of sensitivity and specificity. Successively MRI has gained an importance. However, the diagnosis of improvement in patient's symptoms is currently based on clinical criteria, as reduction of neurological disability (paresthesia, gait ataxia, spasticity, optic neuritis, and bladder dysfunction) and fatigue. Sometimes, symptoms of ALS, as paresis, muscle atrophy, and dysarthria, are associated with MRI and cerebrospinal fluid abnormalities typical of MS. Indeed, we have considered the improvement of patient's symptoms the recover from clinical disability, for example, ability to work, reduction of spasticity, relapse delay, and/or fatigue disappearance.

2.4. Effect of EDTA Chelation Therapy on Al Intoxication. Patients who revealed Al intoxication (by examination of its levels in urine samples) were subjected to EDTA chelation therapy. EDTA (2 g in 500 mL physiological saline) was intravenously infused in each patient in about 2 hours. Treatment was given once a week and lasted ten weeks. At the end of treatments urine Al levels were analysed, as previously described.

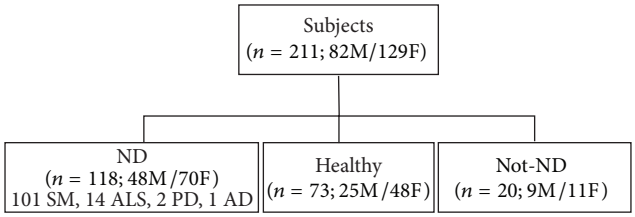

Figure 1: Scheme of enrolled subject's characteristics.

2.5. Data Analysis. Statistical analysis was performed using Microsoft Excel 2010 and IBM SPSS Statistics 20 (IBM Armonk, New York, USA). A logistic regression analysis was used to examine the relative contributions of several variables to the operation outcomes. $P < 0.05$ was considered significant.

3. Results

3.1. Patient's Characteristics. Figure 1 reports the distribution of patients who displayed Al intoxication.

The most represented patients affected by ND were those with MS (85.6% of total ND). Indeed, we compared both the group of MS patients and the group of ND patients with the group of healthy patients.

3.2. Al Intoxication. All patients did not show Al intoxication before EDTA challenge (data not shown). All patients affected by ND displayed intoxication by different toxic metals (data not shown). After challenge with EDTA, Al was present in 44.8% of cases comprehensive of ND and healthy patients. The levels of Al intoxication, as obtained from evaluation of μg/g creatinine content of Al in the urine samples collected following the first intravenous treatment with EDTA (chelation test), are reported in Figure 2. The data indicate that Al values were significantly higher in the urine samples of SM and ND patients than in those healthy patients.

3.3. Usefulness of EDTA Chelation Therapy. The effect of EDTA chelation therapy is reported also in Figure 2. Indeed, the patients who have shown Al intoxication following chelation test underwent chelation therapy (EDTA intravenous administration once a week). After ten therapies, the levels of Al in the urine samples were further evaluated and compared with that obtained following chelation test. EDTA administration was demonstrated to be significantly efficient in removing Al burden, as shown in Figure 2. Our results showed that reduction in the time of Al intoxication well related with improved clinical conditions of the patients. In fact they presented, at different extent, reduction of neurological disability and fatigue.

Noteworthily, the efficacy of EDTA chelation therapy was more evident in ND than in healthy patients.

4. Discussion

Toxic metals, pesticides, and phenols are considered major environmental pollutants [18]. Toxic metals are classified as

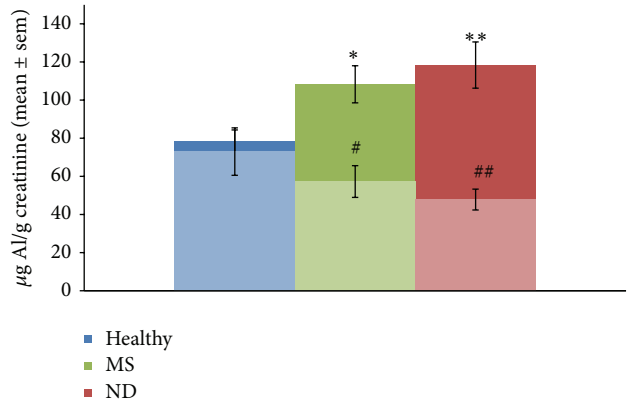

Figure 2: Aluminium (Al) levels evaluated in the urine samples of examinated subjects, following chelation test (dark) and after ten chelation therapies with EDTA (light), expressed as mean ± SEM of μg/g creatinine. The studied subjects were healthy patients, patients affected by multiple sclerosis (MS), and patients affected by all neurodegenerative diseases (ND). The levels of Al in both MS and ND patients were significantly higher with respect to those obtained in healthy subjects following chelation test ($^{*}P/^{**}P < 0.05$ versus healthy). After chelation therapies with EDTA, the levels of Al were significantly lower than that obtained following chelation test ($^{\#}P < 0.05$ versus $^{*}P$ and $^{\#\#}P < 0.05$ versus $^{**}P$).

nonbiodegradable substances, as well as plastics and detergents, because they are not degraded by microorganisms. They represent a global health risk because of their ability to contribute to a variety of diseases. In this context, Al (which is a highly reactive element and ubiquitous environmental contaminant) has been associated with some diseases [1]. In fact, osteomalacia is a skeletal disease related to Al toxic effects, such as phosphate deficiency, Ca-uptake impairment, and dysfunctional osteoblast proliferation [19]. Moreover, Al exposure can impair Fe intestinal absorption, promoting an anemic state [20]. In addition, Al may play an active role in the pathogenetic mechanisms of neurological diseases. In particular, Al has been shown to be responsible for critical neuropathologic lesions in AD and other related disorders for its ability to cross-link hyperphosphorylated proteins [21]. Al has been detected in amyloid fibers in the cores of senile plaques in brains of AD patients [22]. The presence of Al in biological systems could lead to an important prooxidant activity, by promoting superoxide generation through Fenton reaction [23]. More recently, Al removal in AD patients by treatment with DFO has been further proposed [24]. Successful treatment with DFO (both at low and at standard dose) has been performed for Al overload among haemodialysis patients [25]. Moreover, DFO has been shown to be able to exert protective effects in the brain tissue of mice against Al-induced structural and metabolic alterations [26]. However, since some patients can have intolerance to DFO or develop DFO side effects such as allergic reactions, neurological symptoms, or obvious gastrointestinal upset, we decided to use EDTA as a chelating agent. The chelator N-(2-hydroxyethyl) ethylenediamine triacetic acid (HEDTA), similar to EDTA, has been shown to be efficient, also

in association with selenium, against Al-induced oxidative stress in rat brain [27].

Elevated urinary excretion of Al and Fe has been previously shown in MS patients [28].

We have previously studied the case of a young man affected by MS, who has been unsuccessfully treated for some years with current therapies [29]. Symptoms revealed by the patient were subacute vision loss, diplopia, and pain with eye movements as the first symptoms of optic neuritis; disturbance of fine motor skills; paresthesia and gait ataxia; bladder dysfunction; and significant tiredness. We examined his levels of toxic metals in the urine, following intravenous "challenge" with EDTA. The patient displayed elevated levels of Al, Pb, and Hg in the urine. Indeed, he was subjected to treatment with EDTA twice a month. Under treatment, the patient revealed in time improved symptoms suggestive of MS remission. In fact, he recovered eye vision and bladder function and paresthesia disappeared as well as tiredness. Because the most represented toxic metal in this patient was Al, we decided to examine the possible relationship of Al intoxication with ND.

Our results show that Al levels measured in urine samples of patients affected by both MS separately studied and total ND studied were significantly higher than that of healthy patients, as reported in Figure 2. Healthy patients displayed about 80 μg/g creatinine, as mean Al levels, even if normal values are 35 μg/g creatinine. These data suggest that Al intoxication is not necessarily related to onset of ND clinical symptoms. Moreover, control patients are possibly able to limit further Al burden through neuroprotective or antioxidant mechanisms which are absent in ND patients. Clinical evaluations of each patient suggested the presence of an important relation between Al intoxication and impairment of movements, paresthesia, ataxia, and other symptoms displayed by subjects affected by ND. Indeed, the patients who displayed maximal values of Al in the urine sample displayed also the most serious features of disease at clinical level. The objection that mobilizing (by chelating agents) Al from relatively safe sites such as bone and depositing this highly neurotoxic metal in the CNS can be dangerous is opposed by the consideration that patients affected by ND were affected by Al burden (responsible for the pathogenesis of the disease) in CNS before chelation. Moreover, the complexes formed by toxic metal with chelating agents are well removed by kidneys. Recent studies demonstrated that severe behavioural motor deficits and loss of the motor neurons through the nervous system resulted when an Al vaccine adjuvant was applied to an animal model. Indeed, mice injected with Al hydroxide showed a significant increase in cell death in the spinal cord and motor cortex, primarily affecting the motor neurons and inducing neuroinflammation. The effects closely resembled the damage seen in human ALS [30].

As recently reported, the immune system also appears to be sensitive to Al exposure [31]. Effects of Al on autoimmunity, oral tolerance, CD4+ and CD8+ expression, hypersensitivity, and erythrocyte immune function are suggestive of its immunotoxicologic activity. It has been suggested that many of the features of Al-induced neurotoxicity may arise in part from autoimmune reactions [30].

Finally, in a recent report by Exley C [32] Al is considered a potential contributor to the onset, progression, and aggressiveness of ND, even if it appears to be difficult to establish when it contributes to disease etiology. However, since Al represents a risk to human health, it is necessary to implement measures to reduce its body burden to the lowest practical limit.

Which strategy for common therapy of injury provoked by toxic metals can be proposed? Intracellular uptake of toxic metals would be adequately prevented by relevant inhibitors (chelators), whereas the ROS generation and ROS-mediated processes would be prevented or ameliorated by relevant antioxidant and scavengers of free radicals and Fe.

In our experience, as shown in previous studies and in the present, removal of toxic metals has induced beneficial effects by improving patient symptoms [29, 33, 34]. No adverse effects were observed from EDTA treatments. Metal removal appeared gradual in the time, and suggested many chelation therapies. In conclusion, in the present study we show that EDTA chelation therapy was able to reduce Al burden in patients affected by ND by ameliorating their clinical conditions. We hope that in the future such treatment will be considered as a useful tool to improve ND patient's symptoms.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Contact allergy to aluminium induced by commonly used pediatric vaccines

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We would like to complete the paragraph on Adjuvants (page 6) in the review Vaccination in children with allergies to non active vaccine components by Francheschini et al. [1] which was initiated by the Italian Pediatric Society of Allergy and Immunology in 2013 and published in Clinical and Translational Medicine in 2015.

As mentioned in the review, aluminium (Al) salts are widely used as adjuvants in diphtheria-tetanus-pertussis (DTP) and hepatitis A and B vaccines. The list can be completed with pneumococcal and meningococcal conjugate vaccines, which today are included in the national vaccination schedules in most countries in Europe and the Americas, and also in vaccines against human papilloma virus (HPV) and tick-bore encephalitis (TBE).

According to the authors, the most known and frequent reaction to Al salts is “a palpable nodule at the injection site”. This sounds harmless enough—but in typical cases the nodules are most annoying to the child due to severe pruritus for a very long time [2, 3]. Besides, most children with persistent itching vaccination granulomas become sensitized against Al [4].

Itching vaccination granulomas are described since 1960 [5] but considered very rare [6] until the 1990s when they were reported in 745 of 76,000 children participating in studies on a monocomponent acellular pertussis vaccine in Sweden [7]. Since then, another 102 children in Sweden who received commercial DTaP-polio-Hib-(HepB) combinations (Infanrix®, Pentavac®) and/or pneumococcal vaccines (Prevenar, Synflorix) are described [4, 8, 9]. The vaccines were given intramuscularly in three doses at 3, 5 and 12 months. In a prospective cohort study on 4758 toddlers the frequency of granulomas was 0.63% in those who received a DTaP combination vaccine alone and 1.18% in those who received an Al adsorbed pneumococcal vaccine at the same time. The risk for granulomas increased with the number of Al-containing vaccine doses [4].

The itching nodules appear remarkably late (months or even years) after the vaccination. Histopathological examination shows granuloma formations in which Al crystals can be demonstrated [10]. Clinically, pruritus is the dominating symptom with intense local itching in the vaccination area on the thigh, often causing skin alterations like eczema, hypertrichosis and hyperpigmentation. Intensified itching and swelling of the nodules is often reported when the child has a cold or another infection. After a duration of ½–12 years (median 3–4 years) the nodules eventually disappear and the pruritus ceases.

In some cases nodules were mistaken as tumours leading to unnecessary anxiety, investigations and surgery [11, 12].

Contact allergy to aluminium was verified in 77–95% of children with itching vaccination granulomas by epicutaneous testing with Al Chloride hexahydrate 2% and metallic Al (4, 7, 9). Sensitized individuals have reported contact dermatitis after the use of Al containing deodorants, pharmaceutics (ear drops, antiseptics), sun protectors, tattooing pigments and metallic aluminium [13]. Fortunately, and contrary to earlier belief, the sensitization to aluminium seems to vane with time [14].

The consequences of future vaccination with Al adsorbed vaccines in children who once reacted with itching granulomas and/or contact allergy to Al is only partially studied. Our clinical experience so far is that the risk for new granulomas diminishes with time and is very low when the original one has vanished and the itching ceased. In case of on-going severe pruritus the next dose may be postponed 6–12 months. The Al allergy is a delayed type IV reaction not associated with increased risk for anaphylaxis.

We want to point out that itching granulomas* are benign and self-limiting and no cause to refrain from vaccination in consideration of the risk for a serious infectious disease. They are poorly known but easy to recognize once you are aware of them. They should be familiar to all health care staff working with children to avoid mistrust and anxiety in the parents and unnecessary investigations of the child.

*see MMF studies under Adverse Reactions

Authors' contributions

EB participated in the pertussis vaccine study, organized the follow-up and testing of children with itching vaccination granulomas, performed the prospective cohort study and drafted the manuscript. BT organized and performed the clinical study on the monocomponent acellular pertussis vaccine in Göteborg and participated in the follow-up of the itching children. AI performed the testing of the children in the pertussis vaccine study. AGL performed the re-testing study where aluminium sensitization was showed to vane with time. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration.

Shaw CA[1], Petrik MS.

Author information

Abstract

Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS "cluster" represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. The demonstrated neurotoxicity of aluminum hydroxide and its relative ubiquity as an adjuvant suggest that greater scrutiny by the scientific community is warranted.

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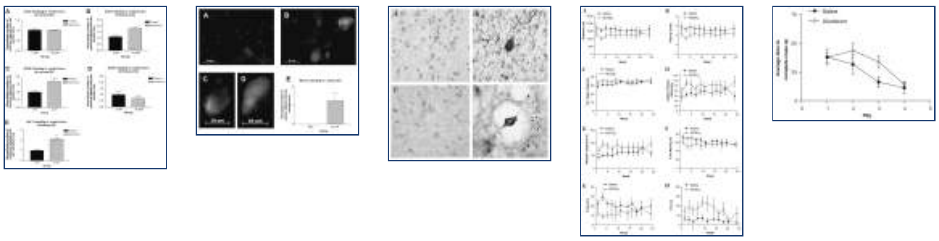

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Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes.

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Author information

Abstract

Our previous ecological studies of autism spectrum disorder (ASD) has demonstrated a correlation between increasing ASD rates and aluminium (Al) adjuvants in common use in paediatric vaccines in several Western countries. The correlation between ASD rate and Al adjuvant amounts appears to be dose-dependent and satisfies 8 of 9 Hill criteria for causality. We have now sought to provide an animal model to explore potential behavioural phenotypes and central nervous system (CNS) alterations using s.c. injections of Al hydroxide in early postnatal CD-1 mice of both sexes. Injections of a "high" and "low" Al adjuvant levels were designed to correlate to either the U.S. or Scandinavian paediatric vaccine schedules vs. control saline-injected mice. Both male and female mice in the "high Al" group showed significant weight gains following treatment up to sacrifice at 6 months of age. Male mice in the "high Al" group showed significant changes in light-dark box tests and in various measures of behaviour in an open field. Female mice showed significant changes in the light-dark box at both doses, but no significant changes in open field behaviours. These current data implicate Al injected in early postnatal life in some CNS alterations that may be relevant for a better understanding of the aetiology of ASD.

KEYWORDS: Adjuvants; Aluminium; Autism; Neurodevelopmental disorders; Neurotoxicity; Vaccines

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Biopersistence and brain translocation of aluminum adjuvants of vaccines

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Aluminum oxyhydroxide (alum) is a crystalline compound widely used as an immunological adjuvant of vaccines. Concerns linked to the use of alum particles emerged following recognition of their causative role in the so-called macrophagic myofasciitis (MMF) lesion detected in patients with myalgic encephalomyelitis/chronic fatigue/syndrome. MMF revealed an unexpectedly long-lasting biopersistence of alum within immune cells in presumably susceptible individuals, stressing the previous fundamental misconception of its biodisposition. We previously showed that poorly biodegradable aluminum-coated particles injected into muscle are promptly phagocytosed in muscle and the draining lymph nodes, and can disseminate within phagocytic cells throughout the body and slowly accumulate in brain. This strongly suggests that long-term adjuvant biopersistence within phagocytic cells is a prerequisite for slow brain translocation and delayed neurotoxicity. The understanding of basic mechanisms of particle biopersistence and brain translocation represents a major health challenge, since it could help to define susceptibility factors to develop chronic neurotoxic damage. Biopersistence of alum may be linked to its lysosome-destabilizing effect, which is likely due to direct crystal-induced rupture of phagolysosomal membranes. Macrophages that continuously perceive foreign particles in their cytosol will likely reiterate, with variable interindividual efficiency, a dedicated form of autophagy (xenophagy) until they dispose of alien materials. Successful compartmentalization of particles within double membrane autophagosomes and subsequent fusion with repaired and re-acidified lysosomes will expose alum to lysosomal acidic pH, the sole factor that can solubilize alum particles. Brain translocation of alum particles is linked to a Trojan horse mechanism previously described for infectious particles (HIV, HCV), that obeys to CCL2, signaling the major inflammatory monocyte chemoattractant.

Keywords: alum, vaccine adjuvants, macrophagic myofasciitis, neurotoxicity, genetics, monocytes, CCL2, MCP1

Billions of humans have been vaccinated and marked regression or eradication of several severe infectious diseases was observed. Nowadays, the potential applications of vaccines extend far beyond prevention of infectious diseases, and vaccination is considered to be a most promising weapon against a variety of different conditions. Vaccine safety has been regarded as excellent at the level of the population (1), but adverse effects have also been reported (2).

Concerns about the use of aluminum adjuvants have emerged following (i) recognition of their role at the origin of the so-called macrophagic myofasciitis (MMF) lesion in 2001 (3, 4), which revealed fundamental misconception of their adjuvant effect and pointed out their unexpectedly long-lasting biopersistence (4); and (ii) demonstration of their apparent capacity to migrate in lymphoid organs and then disseminate throughout the body within monocyte-lineage cells and progressively accumulate in the brain (5).

The present paper will review these emerging characteristics of alum adjuvant particles that raise concerns about innocuity of this widely used compound.

ALUM ADJUVANTS ARE LYSOSOME-DESTABILIZING PARTICULATE COMPOUNDS

Adjuvants have been used in vaccines for their ability to enhance the adaptive immune response to a co-administered antigen. Particulate aluminum salts (known as alum) have been the main approved adjuvants for use in human vaccines for more than 80 years (6). They are currently used in vaccines against tetanus, hepatitis A, hepatitis B, human papillomavirus, haemophilus influenzae B, pneumococcal and meningococcal infections, and anthrax. They mainly include aluminum oxyhydroxide, a crystalline compound, aluminum hydroxyphosphate, and amorphous aluminum phosphate. Alum is able to adsorb vaccine antigens on its surface. The strongest adsorption phenomenon results from ligand exchange, which involves the replacement of a surface hydroxyl on the adjuvant by a terminal phosphate group of the antigen (7).

Alum induces strong innate immune responses at the site of injection, as assessed by an influx of neutrophils, monocyte/macrophages, eosinophils, and MHC-II + antigen presenting cells, mainly dendritic cells (DCs) (8). Muscle-resident macrophages mainly located in fascias are among the first cells

to sense disturbance in muscle homeostasis (9). They alert the immune system through local production of chemokines, and recruit other myeloid cells, like neutrophils, and inflammatory monocytes that differentiate into inflammatory DCs (9). Specialized for antigen uptake, monocyte-derived inflammatory DCs have an immature phenotype in the muscle. However, they migrate to the lymph node T-cell paracortex upon contact with tissue debris or foreign material, and arrive there as mature cells expressing costimulatory molecules (10). Inflammatory DCs may be crucial for the alum adjuvant activity as assessed by selective depletion studies (11), but eosinophils also appear to play an important role (12).

Alum has been long believed to ensure a long-lasting immune response through formation of a depot slowly releasing the antigen under the influence of the interstitial fluid (13, 14). The view that the injected adjuvant remains extra-cellular has been challenged by muscle biopsy findings in immunized patients (4). In contrast to ancient belief, alum particles are avidly taken up by phagocytic cells (15). The strong binding of antigen to alum particles increases antigen uptake by DCs, reduces antigen degradation, and sustains antigen presentation *in vitro* (16). Macrophage survival may also be promoted by alum particle uptake (17). Alum injection induces *in vivo* the formation of persistent alum-induced granuloma at site of previous immunization (4, 18, 19). However, good immunization does not require local alum persistence, since no decrease of antigen-specific T- and B-cell responses were observed in case of removal of the injection site as early as 2 h after injection (20).

In spite of their long usage, the literature has pointed out that the adjuvanticity mechanisms of aluminum salts remain basically unknown despite most active investigation in the field in recent years (21, 22). Alum is deficient at initiating cell-mediated immunity and skews the immune response toward a T-helper type 2 (Th2) response associated with strong production of IL-4 and the IgG1 antibody subtype (23). Concerning the mechanisms of alum adjuvanticity, several explanations have been proposed, most of them being subsequently challenged (24). Notably, the NLRP3 inflammasome was shown to be strongly activated by alum (25, 26), but this finally appeared unessential to the adjuvant effect (27, 28). It remains true, however, that aluminum hydroxide and other crystals such as silica, urate sodium, and asbestos, strongly induce NLRP3 activation, IL1b release, and activation of the downstream inflammatory cascade. More recently, alternate models for alum-mediated immunity have been proposed on the basis of the link of alum adjuvant effects and the release of non-cytokine biomolecules, including uric acid (29), double-stranded DNA (30), and prostaglandin E2 (31). The specificity of crystal-induced signaling pathways has been proposed to explain why aluminum hydroxide particles exhibit a much more irritating effect than soluble aluminum (32). Consistently, alum crystals bind to and aggress the plasma membrane lipid bilayer (33), destabilizes lysosomes that degrade endocytosed, phagocytosed, or autophagocytosed materials (34, 35), and play important role in immunity. Highly controlled antigen processing functions of DCs use lysosomal proteases and pH changes optimal for the generation of peptides, rather than complete protein degradation (36). It is known that limitation of lysosomal proteolysis of antigenic proteins increases antigen presentation and immunogenicity (37), and that the stability of peptide:MHCII complexes allowing their accumulation on the DC surface is enhanced by lysosome activity inhibition (38). Alum adjuvant mechanisms may thus involve alum-induced blockade of lysosomes. Alum lysosomal destabilization remains still uncertain, but the physical rupture of the membrane may be directly caused by the crystalline structure of alum itself (39).

MMF IS A BIOMARKER ASSESSING LONG-TERM ALUM BIOPERSISTENCE IN A GIVEN INDIVIDUAL

In 1998, several French myopathologists described MMF as an emerging condition of unknown cause characterized by a pathognomonic lesion in muscle biopsy mixing large macrophages with submicron to micron-sized agglomerates of nanocrystals in their cytoplasm and lymphocytic infiltrates (3), distinct from other histiocytic diseases and always detected in the deltoid muscle of adults (40). Cytoplasmic inclusions were constantly found, surrounded or not by altered lysosomal membranes, and contained aluminum (4). Their crystalline structure was characteristic of aluminum hydroxide, and no exposure to aluminum other than that conferred by a prior immunization (100%) could be detected (4). It is now clear that the rapid emergence of MMF in France reflected the combination of (i) the replacement of the subcutaneous (s.c.) by the intramuscular (i.m.) route for vaccine injections in the early 1990s; (ii) the large-scale campaign of primo-vaccination of French adults against hepatitis B in the mid 1990s; and (iii) the preferential choice of the deltoid muscle for routine muscle biopsy in France, contrasting with the preferential use of the biceps brachialis and quadriceps muscles in other countries. Alum-containing vaccines may also induce skin pseudo-lymphoma in humans (41), and fibrosarcoma in cats (42).

Macrophagic myofasciitis has been reproduced experimentally by i.m. vaccination in mice, rats, and monkeys (4, 18, 19). The experimental lesion invariably shrinks over time (19), and, in monkeys, it begins to disappear completely from the muscle between 6 and 12 months after a DTP injection corresponding to 14- to 21-fold the human DTP-equivalent dose of alum (18).

Because of the unethical character of muscle biopsy in asymptomatic individuals, whether or not longstanding MMF may be commonly present in a hidden form in healthy individuals could not be directly determined. This seems very unlikely, however, as shown in a recent review of 130 consecutive deltoid muscle biopsies performed for diagnostic purposes in myalgic patients previously immunized with alum-containing vaccines. This study revealed that most alum receivers do not have long-lasting MMF. This could be reliably assessed whereas age, sex ratio, number of alum-adjuvanted injections, and delays elapsed from the last injection to deltoid muscle biopsy were similar in the MMF and non-MMF groups (43). This refutes non-documented belief that every vaccinee may have long-standing MMF lesions when biopsy is performed in the deltoid muscle (44). In addition, MMF and non-MMF patients had clinical differences as developed below.

In light of experimental models, it is important to check the individual vaccine record in each patient to assess the "unusually persistent" character of MMF. In a recent evaluation of 583 patients collected from 1994 to 2012 (45), the median time elapsed between the last alum administration and the biopsy was

65 months. Compared to our previous reports, this time had gradually increased from 36 months in 2001, i.e., shortly after the peak of French adult immunization, to 53 months in 2003 (46). An average number of 5.3 alum-containing shots had been administered during the 10 years prior to biopsy detecting MMF, mainly corresponding to vaccinations against hepatitis B (89.7%), tetanus (42.2%), and hepatitis A (8.8%). In practice, we consider that the MMF is unusually persistent when time elapsed from last immunization to the MMF detection exceeds 18 months. It is important to consider this point in young children who receive multiple vaccine injections in the first year of life, thus increasing the risk of coincidental association between a constitutive muscle disease and MMF detected in the quadriceps muscle used for pediatric immunizations. If the risk of such coincidental associations also potentially exists in adults, it is low in practice. For example, adult patients combining MMF and hereditary muscle disease is extremely rare, despite the intense immunization program of patients with muscular dystrophy.

Animal studies indicate that alum-induced granulomatous lesions considerably vary in size according to the genetic background (19), and the initial hypothesis made by WHO that MMF may reflect some individual inability to clear out alum from the body remains valid (47). In summary, the long-lasting MMF lesion should be considered as a biomarker assessing unusually long-term biopersistence of alum in affected individuals.

PATIENTS WITH MMF AT BIOPSY SUFFER MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

Macrophagic myofasciitis is typically detected in patients with diffuse myalgias and chronic fatigue, as shown in both the French series (46) and the recently published series of 16 patients (48).

In both series, most patients are women (70–80%) with a mean age of 45 years at the time of the biopsy, that typically complain of myalgias, with or without arthralgia, and disabling chronic fatigue. The onset of these symptoms is typically delayed from the immunization.

Strong statistical association between myalgias and MMF was detected by general survey in different French neuromuscular centers (myalgias in 90% of patients with MMF vs. 44% without MMF, $p < 0.0001$) (4). Onset of myalgia may follow exercise. They usually begin in the lower limbs, and not at the site of previous immunization from 0.5 to 84 months in the French patients and 3 to 192 months in Portuguese patients. They gradually extend toward the top of the body, affect the paravertebral muscles, and become diffuse (46). Myopathic electromyogram and elevation of creatine kinase (CK) are, respectively, observed in less than half of patients. Comparison of myalgic vaccinees with and without MMF at deltoid muscle biopsy showed significant differences: patients with MMF rarely had fibromyalgia (the required 11 tender points of the ACR 1990 criteria for fibromyalgia present in 16.6 vs. 55.5%, $p < 0.04$), and more often had delayed evoked potentials suggestive of CNS demyelination (38.5 vs. 5.7%, $p < 0.01$) (43), which does not support coincidental association.

Chronic fatigue is another important symptom (48, 49). A case–control study conducted under the aegis of the French regulatory agency AFSSAPS yielded chronic fatigue as both significantly more frequent and more severe in patients with MMF compared to those without MMF in the deltoid muscle (http://ansm.sante.fr/var/ansm_site/storage/original/application/030593fa4e393af7cec8ff7092832215.pdf).

Cognitive alterations further assess CNS involvement that are disabling though often not detected by routine examination. Patients complain of memory loss, foggy brain, and mood changes. Cognitive tests almost constantly show alterations suggestive of organic cortico-subcortical impairment, impacting visual memory, working memory, and dichotic listening (50). These deficits usually remain stable with time (51).

Taken together, chronic muscle pain, chronic fatigue, and cognitive dysfunction are consistent with the so-called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and about 50% of MMF patients meet international criteria for ME/CFS (48, 49). ME/CFS is a severe, complex, acquired illness classified as a neurological disorder in the WHO International Classification of Diseases since 1969 (ICD 10 G93.3), distinct from fibromyalgia and psychasthenia, which are classified as musculoskeletal (M79.7) and psychiatric (F48.8) disorders, respectively. International studies have estimated the prevalence of ME/CFS between 0.4 and 2.6% of the population, with a total annual cost burden to society of approximately $18.7–$24.0 billion in the USA (52). Symptoms of ME/CSF are closely similar to the post-infective chronic fatigue syndrome (53). The underlying cause of ME/CSF is currently unknown, but the illness is thought to be triggered by an abnormal immune response to an infectious or toxic agent, that results in chronic immune activation (54). Notably, ME/CFS patients have increased risk of developing diffuse large B-cell lymphoma and marginal zone B-cell lymphoma (55). Such a public health burden deserves continued efforts to investigate possible causes and to understand the pathological mechanisms of CFS.

PHAGOCYTES TRANSPORT ALUM PARTICLES TO THE LYMPHOID ORGANS AND THEN TO THE BRAIN

The conceptual link between long-term persistence of alum particles within macrophages at the site of previous immunization, and the occurrence of adverse systemic events, in particular neurological ones, has long remained an unsolved question. Aluminum has long been identified as a neurotoxic metal, affecting memory, cognition and psychomotor control, altering neurotransmission and synaptic activity, damaging the blood–brain barrier (BBB), exerting pro-oxidant effects, activating microglia and neuroinflammation, depressing the cerebral glucose metabolism and mitochondrial functions, interfering with transcriptional activity, and promoting beta-amyloid and neurofilament aggregation (56). In addition, alum particles impact the immune system through their adjuvant effect and by many other means. They adsorb vaccine antigens on their surface, which protect them from proteolysis thus forming a persistently immunogenic pseudo-pathogen (57). Alum particles may also bind undesirable residual products inherent to vaccine production procedures, as shown for HPV DNA sequences (58) or yeast proteins (59) that may be potentially hazardous (60). Finally, alum particles can directly induce allergy (61, 62) as other metals (63).

Concerns about long-term biopersistence of alum largely depend on the ability of alum particles to reach and exert toxicity in remote organs. This ability has been suggested by several

studies (64–67). The reference study on aluminum hydroxide biodisposition used isotopic ^{26}Al-enriched alum injected in the rabbit muscle: ^{26}Al was weakly eliminated in the urine (6% on day 28) and was detected in lymph nodes, spleen, liver, and brain (13). Whether ^{26}Al was still in particulate form or in soluble form was not explored. The fate of particulate material was explored in mice by our team. We successively performed i.m. injections of alum-containing vaccine, fluorescent latex beads, and fluorescent nanohybrids coated with precipitated alum (5). These materials were quickly captured by macrophages, a large proportion of which cleaved the injected muscle, mainly within immune cells, reaching the draining lymph nodes. Particle-laden cells then escaped the lymphatic system to reach the blood circulation, presumably via the thoracic duct. In so-doing, they were able to reach distant organs such as the spleen and liver and, much slowly, the brain. Recombinant chemokine injection and the use of genetically modified mice showed that systemic biodistribution of particles crucially depends on the monocyte chemoattractant MCP-1/CCL2. Into the brain, particles were mainly found in microglial cells. In accordance with good overall tolerance of alum, brain penetration was extremely low in normal conditions. However, brain translocation was significantly increased in case of altered BBB or after systemic and/or cerebral increase of the MCP-1/CCL2 signaling (5). Expression of this chemokine is subjected to significant interindividual variations related to age, genetic, and environmental factors. We have identified selective increase of circulating MCP-1/CCL2 in CFS/ME patients with MMF (45). The imbalance between the huge number of vaccinated individuals and the relatively low number of MMF cases suggests crucial involvement of individual susceptibility factors in intolerance to alum. Genetically driven MCP-1/CCL2 production might represent one of these factors (5).

Thus alum and other poorly biodegradable materials taken up at the periphery by phagocytes circulate in the lymphatic and blood circulation and can enter the brain using a Trojan horse mechanism similar to that used by infectious particles (68, 69). Previous experiments have shown that alum administration can cause CNS dysfunction and damage (70–72), casting doubts on the exact level of alum safety (73).

THE CONCEPT OF ASIA

Many CNS diseases likely result from gene–environment interactions. Some of them, such as idiopathic ME/SFC (74) and multiple sclerosis (MS) (75), have been previously associated with aluminum overload. An increased risk of developing MS in the long-term after alum-containing vaccine administration has been also reported (76, 77), and remains the subject of fierce debate.

Notably, about 10% of our MMF patients had concurrent MS-like disease (78), an additional 5–10% had another autoimmune disease, such as thyroiditis and diffuse inflammatory myopathies, and the remaining patients occasionally had low titers of various autoantibodies (46).

Yehuda Shoenfeld had delineated the "autoimmune (autoinflammatory) syndrome induced by adjuvants" (ASIA)(79), acknowledging that various combinations of (i) specific autoimmune diseases identified by well-established criteria, (ii) less-specific symptoms, such as myalgia, arthralgia, chronic fatigue, and cognitive impairment (the combination of which defines ME/CFS); and (iii) the appearance of circulating autoantibodies, can occur after exposure to a variety of chemical or natural products with immunological adjuvant properties. Discussion of the ASIA is very useful since it may alert physicians, when they encounter the above-mentioned symptoms, to check for prior vaccinations, and may help them to put a name on such conditions.

Symptoms associated with MMF are strikingly similar to those described as the Gulf war syndrome (GWS), a condition strongly associated with the administration of multiple vaccinations to soldiers (80, 81), especially the anthrax vaccine that contains alum, capable of inducing MMF (82), and possibly squalene (83). On these grounds, we proposed to delineate a vaccine adjuvant syndrome (84). Yehuda Shoenfeld reasoned similarly but added to GWS and MMF, his own experience on siliconosis, a disease complex observed in patients with leaky breast silicone implants attributed to deleterious adjuvanticity of silicone particles (85, 86). In so-doing, he enlarged the causal relationship to any compound with adjuvant properties. ASIA major and minor diagnostic criteria still need international validation but the ASIA concept already caught the attention of the international human and veterinary medical community, pointing out a need in the field (87, 88).

A LOT MUST BE DONE TO UNDERSTAND HOW, IN CERTAIN INDIVIDUALS, ALUM-CONTAINING VACCINES MAY BECOME INSIDIOUSLY UNSAFE

Alum has been used for decades to levels considered as an acceptable compromise between its role of adjuvant and its toxic effects by the industry and the regulatory agencies. However, the MMF story revealed several gaps in the knowledge on alum particles, including their exact mechanisms of action, their fate after injection, their systemic dissemination, and their safety on the long-term. Efforts have been done in the last years to develop novel adjuvants, but attempts to seriously examine safety concerns raised by the bio-persistent character and brain accumulation of alum particles have not been made.

The main questions that should be addressed concerning alum safety problems are listed in **Table 1**. It is important to look for genetic susceptibility factors that could explain why a given individual will appear intolerant to alum-containing vaccines whereas the vast majority of individuals vaccinated with the same vaccines remain healthy. Some patients with MMF are of the HLA-DRB1*01group, which is associated with an increased risk to develop autoimmune diseases (89). Genetic factors influencing alum biodistribution were also investigated. In keeping with experimental evidence that the CCL2/MCP-1 chemokine signaling governs brain translocation of phagocytosed particles (5), and that CCL2/MCP-1 serum levels are selectively increased in patients with MMF (45), genotyping of 252 symptomatic MMF patients and 516 healthy controls for 4 single nucleotide polymorphisms (SNPs) localized in the CCL2 gene showed that the AG haplotype of the SNP rs3760396C($-927G > C$) was associated with a slightly increased risk for disease (5). Interestingly, the rs 3760396 C allele is associated with a higher level of expression of CCL2 *in vitro* as assessed by transfection (90). These preliminary results deserve further investigations. Another axis of research consists in attempts to detect if subtle genetically determined defects in the

Table 1 | Main unsolved questions linked to alum adjuvants toxic effects.

WHAT IS THE MOST TOXIC?
Al^{3+} metal toxicity (or allergy to Al)
Particle toxicity due to elementary nanoparticles, e.g., mitochondrial toxicity, or to the micronic agglomerates they form, e.g., proinflammatory effects
Immune reactions against biopersistent biomolecules adsorbed on alum, and protected from degradation until complete particle solubilization (vaccine antigen or trace residual DNA sequences linked to vaccine production, or even self-antigens adsorbed on alum at time of injection-induced muscle necrosis)
WHAT FACTORS CONTRIBUTE TO BIOPERSISTENCE?
The quantity administered
Adsorbed molecules impeding extracellular solubilization and/or favoring phagocytosis of alum particles
Crystalline structure of the adjuvant damaging lipid bilayers (e.g., lysosomes)
WHAT FACTORS CONTRIBUTE TO BRAIN TRANSLOCATION?
Al^{3+} ion transport by transferrin (receptors present in CNS increase with iron deficiency)
Direct BBB damage by alum particles (proportion and kinetics in the circulation are unknown)
Monocyte cell transport of particles (the MCP1/CCL2-dependent Trojan horse mechanism is increased in case of altered BBB and/or neuroinflammation)
WHAT ARE THE SUSCEPTIBILITY FACTORS?
Individual environment (other exposures to Al, exposure to other metals, exposure to other particles, chronic viral infection)
Age of immunization, including early age (low body weight, immature BBB, early neurodevelopmental stage) and old age (increased MCP-1/CCL2 production, progressive BBB weakness, hidden neuropathological processes)
Genetic factors impacting either immunologic responses (e.g., HLA genotypes) or intracellular persistence of particles (xeno/autophagy genes), or neuromigration (chimiokines and other inflammation genes)

cell machinery used to clear out particles, namely autophagy (91), could contribute to the long-standing biopersistence of alum particles, as previously reported to explain intracellular persistence of intestinal pathogens in Crohn's disease (92). Cells coping with microbes use a dedicated form of autophagy termed "xenophagy" as a host defense mechanism to engulf and degrade intracellular pathogens. The same holds true for inert particles subjected to phagocytosis/endocytosis (93). As mentioned above, crystal particles are likely toxic to membranes, which may destabilize phagosomes and lysosomes, trigger inflammasome assembly, and impede the autophagy pathways (32–35, 39). However, crystal particles instead of killing macrophages promote their survival (17). Thus, macrophages will continuously perceive as foreign particles in their cytosol, just like senescent organelles or bacteria, and will likely reiterate the autophagic process until they dispose of alien materials. The process includes compartmentalization of particles within double membrane autophagosomes and subsequent fusion with repaired and re-acidified lysosomes, exposing antigen-bound alum particles to lysosomal acidic pH, the sole factor that can solubilize alum crystal and acid hydrolases that will degrade the antigen. The process involves a conserved pathway in which particles decorated by ubiquitinated proteins, recruit the adaptor protein p62/SQSTM1 (sequestosome 1), which targets the whole to the autophagosome through binding to the autophagosomal membrane protein LC3/Atg8 (94, 95). Autophagosomes formation also involves other Atg molecules, such as the high molecular weight complex (Atg12–Atg5–Atg16L), Atg7, and many others, and is regulated by IRGM (immunity-related GTPase family-M1). The autophagosome external membrane eventually fuses with lysosomes. Genes of all molecules of the autophagy pathway are subjected to variations that are currently screened in patients with MMF.

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Aluminum in Childhood Vaccines Is Unsafe

Neil Z. Miller

ABSTRACT

Aluminum is a neurotoxin, yet infants and young children are repeatedly injected with aluminum adjuvants from multiple vaccines during critical periods of brain development. Numerous studies provide credible evidence that aluminum adversely affects important biological functions and may contribute to neurodegenerative and autoimmune disorders. It is impossible to predetermine which vaccinated babies will succumb to aluminum poisoning. Aluminum-free health options are needed.

Introduction

From 1999 through 2002, several vaccines containing mercury were phased out of the childhood immunization schedule. Manufacturing of childhood vaccines with thimerosal ceased in 2001, but those that were not past their expiration date remained on the market for sale until January 2003.[1] They were replaced with low-mercury or "thimerosal-free" vaccines. In the years that followed, autism rates continued to rise, prompting health authorities to assert that autism is not linked to mercury in vaccines and that vaccination policies are safe and appropriate.[2-4] (If mercury in vaccines contributed to autism, then rates should have dropped after mercury was removed.) However, in 2002, during this so-called phase-out period, the Centers for Disease Control and Prevention (CDC) actually added two doses of mercury-containing influenza vaccines to the list of inoculations urged for all babies 6 to 23 months of age.[5] Two years later, the CDC also added *pregnant women in their first trimester* to the list of people officially recommended and actively encouraged to receive influenza vaccines, even though a majority of available doses contained mercury.[6]

In addition to these questionable actions during this highly publicized "phase-out" of mercury, four doses of a new vaccine with high *aluminum* content were added to the childhood immunization schedule in February 2000 (for pneumococcus) and two doses of another aluminum-containing vaccine (for hepatitis A) were added in 2005.[7,8] These changes to the vaccine schedule resulted in a substantial increase of aluminum-containing vaccine doses—from 10 to 16 injections—that babies are still mandated to receive by 18 months of age.

Prior to the mercury phase-out (pre-2000), babies received 3,925 micrograms (mcg) of aluminum in their first year-and-a-half of life. After pneumococcal and hepatitis A vaccines were added to the immunization schedule, babies began receiving 4,925 mcg of aluminum during the same age period—a 25% increase (Figure 1).[9,10] In 2011, CDC recommended that pregnant women receive a pertussis vaccine (Tdap), which also contains aluminum.[11] Studies show that aluminum crosses the placenta and accumulates in fetal tissue.[12] Thus, millions of babies in utero, infants, and young children were injected with, and continue to receive, unnaturally high doses of neurotoxic substances—mercury and aluminum—long after unsuspecting parents were led to believe that vaccines were purified and made safe.

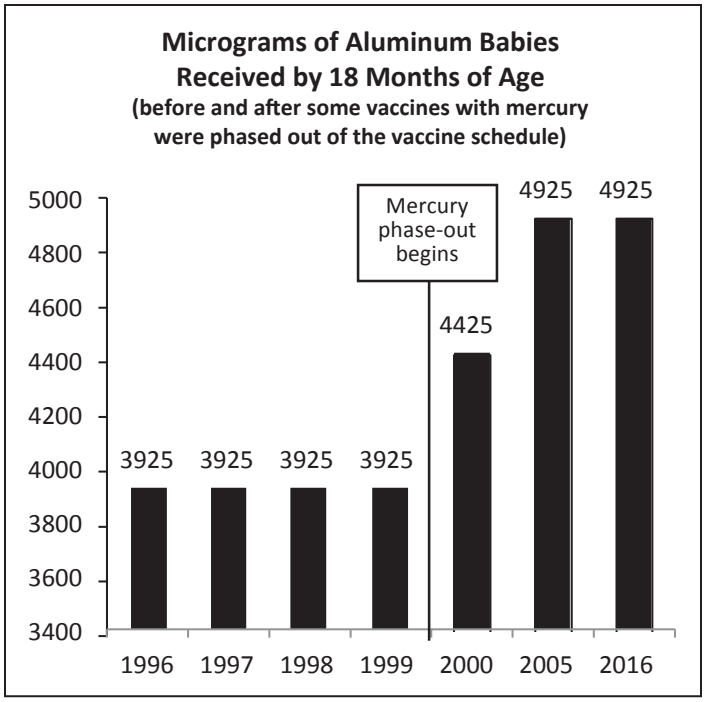

Figure 1. Aluminum Content from Childhood Vaccines

Vaccines containing aluminum were added to the childhood immunization schedule when some vaccines containing mercury were removed. Prior to the mercury phase-out (pre-2000), babies received 3,925 mcg of aluminum by 18 months of age. After pneumococcal and hepatitis A vaccines were added to the schedule, babies began receiving 4,925 mcg of aluminum during the same age period—a 25% increase.

Source: The vaccine manufacturers' product inserts and the CDC's annual childhood vaccination schedules.

Aluminum

Aluminum adjuvants are added to several vaccines to elicit a more robust immune response and increase vaccine efficacy. In the United States, Canada, Europe, Australia, and many other parts of the world, infants and young children receive high quantities of aluminum from multiple inoculations. For example, in the U.S. the hepatitis B, DTaP (for diphtheria, tetanus and pertussis), pneumococcal (PCV), *Haemophilus influenzae* type b (Hib), and hepatitis A vaccines are all administered during early childhood. Each of these

vaccines contains aluminum, and multiple doses (booster shots) are required (Table 1). Babies are injected with 1,225 mcg of aluminum instantaneously at age 2 months, and 4,925 mcg of accumulated aluminum by age 18 months (Figure 2).[9,10]

Table 1. Aluminum Exposures in Early Childhood from Recommended Vaccines

Vaccine	Aluminum Content	Vaccine Schedule
Hep B	250 mcg x 3 doses	Birth, 2, 6 months
DTaP	625 mcg x 4 doses	2, 4, 6, 15 months
PCV	125 mcg x 4 doses	2, 4, 6, 12 months
Hib	225 mcg x 3 doses	2, 4, 12 months
Hep A	250 mcg x 2 doses	12, 18 months

Source: The vaccine manufacturers' product inserts and the CDC's 2016 childhood vaccination schedule.

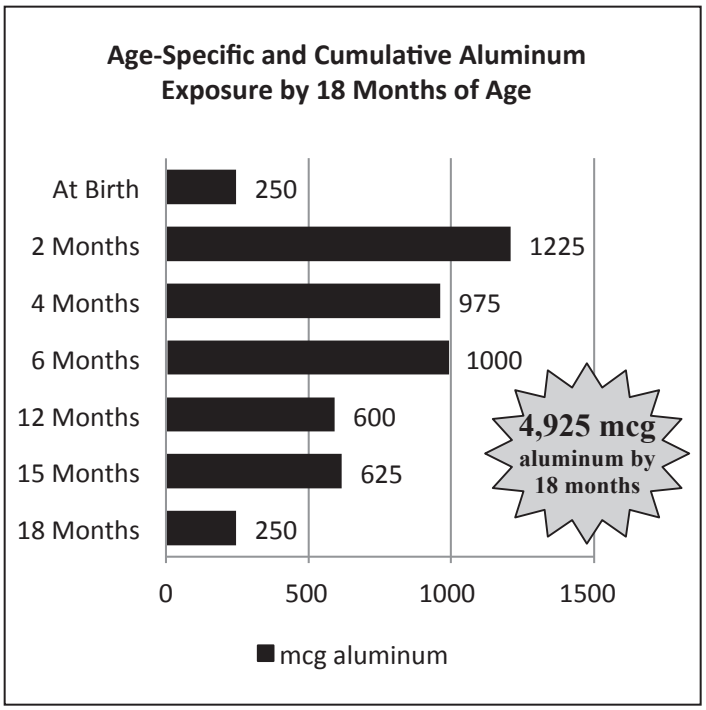

Figure 2. Cumulative Aluminum Exposure from Recommended Childhood Vaccines

Source: The vaccine manufacturers' product inserts and the CDC's 2016 childhood vaccination schedule.

Babies are not the only age group exposed to high quantities of aluminum from vaccines. The HPV vaccine (indicated for the prevention of cervical cancer and genital warts associated with some strains of human papillomavirus) is marketed to pre-teens and adolescents. Each dose in the three-dose series contains 500 mcg of aluminum. The Tdap vaccine (for tetanus, diphtheria, and pertussis) is given to pre-teens as well, and contains 390 mcg of aluminum.[13] Several adult vaccines also contain aluminum.

Aluminum is neurotoxic and has a long history of well-documented hazards.[14] For example, as early as 1921 The *Lancet* described a 46-year-old metal worker in whom "aluminium produced a rather slow intoxication. In this case it caused memory loss, tremor, jerky movements and incontinence of urine."[15] In 1927, Dr. Victor Vaughn, a toxicologist with the University of Michigan, testified before the Federal Trade Commission that "all salts of aluminum are poisonous when injected subcutaneously or intravenously."[16] By 1951, Chusid et al. showed that chronic epilepsy could be induced in monkeys through intra-cerebral administration of aluminum hydroxide cream.[17] In 1968, Driver et al. performed a similar experiment by placing aluminum hydroxide cream unilaterally on the posterior parietal cortex of six monkeys.[18] From 3 to 8 weeks after surgery, electrical abnormalities could be seen on an electroencephalogram and the monkeys exhibited "episodic twitching of the limbs and face." The animals were also impaired at learning new tasks and at re-learning tasks first learned prior to the intervention.

According to the American Academy of Pediatrics (AAP), "Aluminum is now being implicated as interfering with a variety of cellular and metabolic processes in the nervous system and in other tissues."[19] Bishop et al. published data showing that "aluminum accumulates in the body when protective gastrointestinal mechanisms are bypassed, renal function is impaired, and exposure is high."[20] For example, in premature infants, "prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development" by 18 months of age. More recently, Kawahara et al. published research confirming that "aluminum can cause severe health problems in particular populations, including infants."[21] The authors of this paper also declared that "whilst being environmentally abundant, aluminum is not essential for life. On the contrary, aluminum is a widely recognized neurotoxin that inhibits more than 200 biologically important functions and causes various adverse effects in plants, animals, and humans."

Neurologic and Autoimmune Disorders

Numerous studies provide compelling evidence that injected aluminum is detrimental to health. For example, a recent paper by Tomljenovic and Shaw affirmed that aluminum is a neurotoxin and may be a co-factor in several neurodegenerative disorders and diseases, including Alzheimer's, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis (ALS), autism, and epilepsy.[22] According to the authors, "The continued use of aluminum adjuvants in various vaccines for children as well as the general public may be of significant concern. In particular, aluminum presented in this form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences."

Recent data by Perricone et al. showed that aluminum adjuvants in vaccines have been linked to multiple sclerosis, systemic lupus erythematosus, chronic fatigue syndrome, Gulf War syndrome, macrophagic myofasciitis, arthritis, and autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), an autoimmune disease with neurological and cognitive manifestations.[23] Clinical symptoms associated with vaccine-induced autoimmunity can take months or years to manifest, much longer than the time intervals utilized in most vaccine safety studies.

Although aluminum is a neurotoxin, pre-school children are repeatedly injected with aluminum adjuvants from multiple vaccines during critical periods of brain development. A recent paper published in the journal *Lupus* found that this may lead to neuro-developmental and autoimmune disorders.[24] During early development, the child's blood-brain barrier is more permeable to toxins, and the kidneys are less able to eliminate them. Thus, children have a greater risk than adults of adverse reactions to aluminum adjuvants in vaccines. The authors of this paper issued the following warning: "Because children may be most at risk of vaccine-induced complications, a rigorous evaluation of the vaccine-related adverse health impacts in the pediatric population is urgently needed."

Macrophagic Myofasciitis (MMF)

Some people develop macrophagic myofasciitis (MMF) after receiving an aluminum-containing vaccine.[25-39] MMF is characterized by an aluminum-filled lesion (wound) at the site of an earlier vaccination. MMF lesions occur when the aluminum adjuvant from a vaccine remains embedded in the muscle tissue and causes a continuous immune reaction. The lesions are persistent, long-term granulomas (or inflammatory tumors) found in the quadriceps in children and deltoid muscles of adults, common vaccination sites. Several vaccines contain aluminum hydroxide, which has been identified as the causal factor of MMF lesions.[25]

Although MMF is associated with a macrophagic lesion at the site of vaccination, it is a systemic ailment. Symptoms include chronic fatigue, chronic diffuse myalgia (muscle weakness), arthralgia (joint pain), and disabling headaches. Aluminum's toxic effects can also manifest as impaired psychomotor control, repetitive behavior, speech disorders, sleep disturbances, seizures, confusion, and anxiety, as well as deficits of concentration, learning, and memory. Nearly 20% of patients with MMF develop an autoimmune disease, including neuromuscular and multiple sclerosis-like demyelinating disorders.[26-28]

Several descriptive studies document MMF in pediatric populations. For example, Spanish scientists presented data on seven children younger than 3 years of age with lesions of macrophages on muscle biopsies at the site of vaccination.[29] In three of four cases tested, elevated levels of aluminum in muscle were detected (indicative of a reaction to aluminum adjuvants in vaccines). All of the children developed hypotonia (a lack of normal muscle tone) and motor or psychomotor delay. Six of the children also had abnormal neuro-imaging, associated with neurological anomalies, including atrophy and abnormal myelination.

In the U.S., Gruis et al. evaluated four cases of MMF in young children with hypotonia, motor delay and failure to thrive, likely due to intramuscular injections of aluminum-containing vaccines.[30] Another team of American physicians evaluated MMF in two fully vaccinated children. Both showed typical aluminum-filled macrophages at muscle biopsies.[31] One child had abnormal pupillary reflexes and urinary retention suggesting dysautonomia while the other child had developmental delay and hypotonia.

Israeli researchers documented MMF in six Arab children.[32] Reactions included hypotonia, seizures, motor delay, and developmental delay. The authors of this paper believe that genetic predisposition is a factor in determining the prevalence of MMF in different populations.

German researchers documented MMF in a 3-month-old East Indian child following his hepatitis B vaccine at birth, "after which he developed generalized hypotonia, and central nervous system and peripheral nervous system manifestations at one month of age."[33] The child also had respiratory failure, decreased spontaneous movements, apnea spells, and generalized seizures. Aluminum was detected in the muscle biopsy macrophages. The authors recommend that "after vaccination, children should be closely followed to detect these complications at early stages."

Italian researchers believe that MMF in children "is probably more common than reported. Diagnosis requires a high index of suspicion and can be missed if biopsy is performed outside the vaccination site."[34] According to Canadian MMF researchers, "aluminum has been demonstrated to impact the central nervous system at every level, including by changing gene expression. These outcomes should raise concerns about the increasing use of aluminum salts as vaccine adjuvants." Moreover, "based on the current and emerging literature, it seems unlikely that in the future aluminum will be considered safe for human use in any of the current medicinal applications."[28]

Animal Studies

A recent paper by Luján et al. found that sheep developed a new type of autoimmune and inflammatory disorder—ovine autoimmune/inflammatory syndrome induced by adjuvants (ASIA)—after receiving vaccines containing aluminum adjuvants.[40] The condition appears in some sheep two to six days after they are vaccinated. Symptoms of the acute phase include poor response to external stimuli and acute meningoencephalitis. The chronic phase causes muscular atrophy, neurodegeneration of the gray matter of the spinal cord, and death.

Khan et al. conducted several mouse experiments to determine the long-term biological distribution of vaccine-related aluminum nanoparticles.[41] They discovered that aluminum travels from the injection site to distant organs such as the spleen and brain, where aluminum deposits could still be detected one year later. Aluminum remains in monocyte-lineage cells long after vaccination and may cause neurologic and autoimmune disorders. According to these scientists, "Alum has high neurotoxic potential, and administration of continuously escalating doses of this poorly biodegradable adjuvant in the population should be carefully evaluated by regulatory agencies since the compound may be insidiously unsafe."

Scientists also looked at whether Gulf War Syndrome, which afflicted many veterans of Western militaries with cognitive and behavioral deficits similar to ALS (a progressive neurodegenerative disease that destroys nerve cells), could be related to the aluminum-containing anthrax vaccines they received. In a series of studies, mice were injected with adjuvants at doses equivalent to those given to vaccinated U.S. Gulf War veterans.[42,43] The aluminum-injected mice exhibited significant deficits in memory and motor functions. Testing showed motor neuron loss and progressive deficiencies in strength. The mice also had pathological abnormalities that are characteristic of neurological diseases such as Alzheimer's and dementia. According to the authors of these studies, "The demonstrated neurotoxicity of aluminum hydroxide and its relative ubiquity as an adjuvant suggest that greater scrutiny by the scientific community is warranted."[43]

Israeli scientists recently evaluated an aluminum adjuvant and the HPV vaccine Gardasil to determine behavioral and inflammatory effects.[44] Female mice were injected with either aluminum or Gardasil in amounts equivalent to human exposure, or they received a true placebo. (Vaccine safety trials for the HPV vaccine did not provide the control group with an inert substance or true placebo; the "control" group was injected with aluminum.) The Gardasil and aluminum-injected mice spent significantly more time exhibiting depressive behavior when compared to the placebo-injected mice. In addition, anti-HPV antibodies from the sera of Gardasil-injected mice showed cross-reactivity with the mouse brain protein extract. Analysis revealed microglial activation in the hippocampi of Gardasil-injected mice. According to the authors, "It appears that Gardasil via its aluminum adjuvant and HPV antigens has the ability to trigger neuroinflammation and autoimmune reactions, further leading to behavioral changes."

Autism

There is evidence that aluminum in vaccines may be linked to autism. For example, the *Journal of Inorganic Biochemistry* published data showing a highly significant positive linear correlation between the amount of aluminum infants receive from their vaccines and the rates of autism in several developed nations (Pearson r = 0.89-0.94).[45] The authors of this ecological study commented on their findings: "Our results...suggest that a causal relationship may exist between the amount of aluminum administered to preschool children at various ages through vaccination and the rising prevalence of autism spectrum disorders."

In another recently published paper, Shaw et al. found that genetic predispositions may sensitize some children to central nervous system damage induced by aluminum-containing pediatric vaccines.[46] Moreover, vaccines with aluminum adjuvants are *injected* into the body, bypassing protective barriers of the gastrointestinal tract and skin. Absorption of aluminum by this mode is more efficient than through ingestion, increasing the likelihood of a toxic outcome. The authors summarized their findings: "Evidence has now emerged showing that autism may in part result from early-life immune insults induced by environmental xenobiotics. One of the most common xenobiotic with immuno-stimulating as well as neurotoxic properties to which infants under two years of age are routinely exposed worldwide is the aluminum vaccine adjuvant."

Recent research published in the *Journal of Toxicology* found that aluminum exposure produces adverse effects in living organisms and is especially damaging to the central nervous system.[47] Aluminum from vaccine adjuvants crosses the blood-brain and blood-cerebrospinal fluid barriers, provoking harmful immuno-inflammatory responses in neural tissues. Yet, clinical studies on vaccine safety often give aluminum-containing injections to a "control" group as a harmless "placebo" despite evidence that aluminum is toxic to humans and animals. The use of aluminum as a placebo cannot be justified. According to the authors of this paper, "Studies on animal models and humans have shown that aluminum adjuvants by themselves cause autoimmune and inflammatory conditions. These findings plausibly implicate aluminum adjuvants in pediatric vaccines as causal factors contributing to increased rates of autism spectrum disorders in countries where multiple doses are almost universally administered."

In another recent animal study, young mice were injected with either high or low levels of aluminum adjuvants (designed to correlate with U.S. or Scandinavian childhood vaccine schedules).[48] Significant changes in the mice were observed, affirming the role of aluminum adjuvants in adversely altering the central nervous system. The authors commented on their findings: "These current data implicate aluminum injected in early postnatal life in some central nervous system alterations that may be relevant for a better understanding of the etiology of autism spectrum disorders."

Vaccine Industry Conferences and Concerns

In May 2000—3 months *after* the CDC added the aluminum-containing pneumococcal vaccine to the recommended immunization schedule for children—the U.S.

Department of Health and Human Services (HHS) sponsored a Workshop on Aluminum in Vaccines.[49,50] The workshop, given in San Juan, Puerto Rico, was attended by members of the vaccine industry, including government officials, immunologists, pathologists, vaccine manufacturers, metal ion specialists, and other interested people. It was organized to increase knowledge about aluminum as an adjuvant in vaccines, investigate potential adverse reactions associated with aluminum in vaccines, and develop a research agenda on the effect of aluminum in the human body. Experts from around the world were invited to give their presentations on vaccines and aluminum.

Dr. Romain Gherardi, a specialist in neuromuscular disease and professor at the Mondor Institute of Biomedical Research, showed that MMF without vaccination does not occur. In fact, it often begins after receiving a hepatitis B vaccine. Myalgia was present in 94% of patients with MMF, and 85% of these people were disabled. Although 30% of patients had their first myalgias within 3 months after their last vaccination, 20% of patients' symptoms took longer than 2 years to manifest. These myalgias begin in the calves and legs, then progress to diffuse myalgia. Fatigue was present in 93% of patients with MMF, and 87% of these people were disabled. In addition, 34% of MMF patients had autoimmune disease, including multiple sclerosis and arthritis.[50, pp 48-74]

In June 2000, the CDC sponsored a conference on thimerosal (mercury) in vaccines, although aluminum was discussed as well.[51] CDC scientists analyzed the agency's Vaccine Safety Datalink (VSD) database containing thousands of medical records of vaccinated children and found statistically significant relationships between mercury in vaccines and developmental delay, tics, and attention deficit disorder.[51, pp 40-41] However, Dr. Tom Verstraeten, CDC epidemiologist, analyzed the data and determined that the injuries could have been caused by aluminum in the vaccines.[51, p 77] It is also possible that the neurological damage was due to the synergistic effects of both aluminum and mercury in the vaccines given to the affected children.

Although millions of children every year are required to receive vaccines containing aluminum and mercury, evidence supporting the safety of this practice is lacking. For example, according to Dr. Richard Johnston, immunologist and professor of pediatrics at the University of Colorado School of Medicine, "Aluminum and mercury are often simultaneously administered to infants, both at the same site and at different sites. However...there is absolutely no data, including animal data, about the potential for synergy, additivity or antagonism, all of which can occur in binary metal mixtures."[51, p 20] Dr. Alison Maule, who attended the Workshop on Aluminum in Vaccines, voiced similar concerns: "We need to bear in mind that we are not only putting aluminum in here, we are putting in mercury.... Often these effects are additive but there is always the possibility of synergy. We know nothing about that."[50, p 106] Dr. Vito Caserta, chief medical officer for the Vaccine Injury Compensation Program, had this to say: "One of the things I learned at the aluminum conference in Puerto Rico…that I never really understood before, is the interactive effect of different metals when they are together in the same organism. It is not the same as when they are alone, and I think it would be foolish for us not to include aluminum as part of our thinking with this."[51, p 234] Dr. William Weil, pediatrician, former member of the National Institutes of Health, and representative for the AAP Committee on Environmental Health, was also present at the CDC conference and made his concerns known: "In relationship to aluminum, being a nephrologist for a long time, the potential for aluminum and central nervous system toxicity was well established by dialysis data. To think there isn't some possible problem here is unreal."[51, pp 24-25]

Some health authorities who oversee federal vaccine initiatives candidly acknowledge their limited understanding of metals—aluminum and mercury—that are added to several vaccines. For example, Dr. Martin Myers, director of the National Vaccine Program Office and host of the HHS-sponsored Workshop on Aluminum in Vaccines, made a frank admission: "Perhaps the most important thing that I took away from the last meeting was that those of us who deal with vaccines have really very little applicable background with metals and toxicological research."[49, pp 1-2] Dr. Neal Halsey, director of the Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, and former member of the CDC's Advisory Committee on Immunization Practices (ACIP), was also present at the workshop on aluminum. He had concerns regarding missing data: "We do not seem to have information on the age-related toxicity of aluminum, especially when we are dealing with very young infants…. We do not know whether or not there is a difference in susceptibility by age, as there [is] with other metals."[50, pp 83-84]

Some health authorities seemed to admit that even if aluminum is dangerous, it would be burdensome to remove it. For example, according to Dr. John Clements with the World Health Organization's Expanded Programme on Immunization, "There are not easy and obvious substitutes to aluminum adjuvants…. The existing vaccines, if they change the adjuvant for any reason, would need to be resubmitted for clinical trials for safety and efficacy and it would take a great deal of time to do that."[50, p 75] Furthermore, "Aluminum is not perceived, I believe, by the public as a dangerous metal. Therefore, we are in a much more comfortable wicket in terms of defending its presence in vaccines."[49, p 64]

Note: In 2005, 5 years after conference attendees spoke out about a lack of data on the effects of mixing different metals in childhood vaccines, Dr. Boyd Haley, former professor of medicinal chemistry and chairman of the chemistry department at the University of Kentucky, published a study in which he investigated the effect of combining aluminum hydroxide with thimerosal.[52] In this study, cultured neurons showed no significant cell death six hours after they were exposed to just aluminum; more than 90% survived. Thimerosal alone also caused few neurons

to die after six hours of exposure. Again, more than 90% survived. However, when cultured neurons were exposed to aluminum and thimerosal, only about 40% survived after six hours, clearly demonstrating synergistic toxicity (Figure 3).

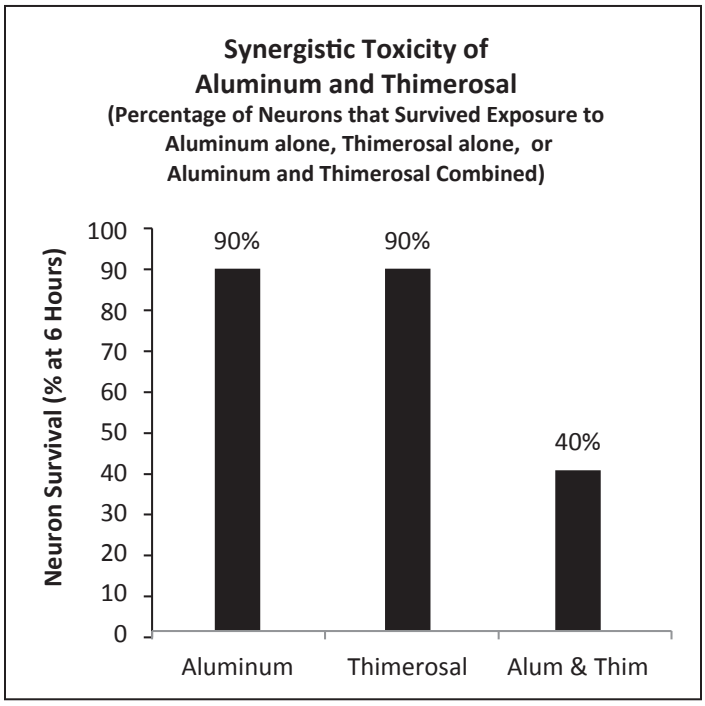

Figure 3. Survival of Neurons Exposed to Aluminum, Thimerosal, or Both

Unconvincing Evidence of Adjuvant Safety

Although several high-level representatives of the CDC, World Health Organization (WHO), American Academy of Pediatrics, Institute for Vaccine Safety, National Vaccine Program Office, and Vaccine Injury Compensation Program who attended the conferences on aluminum and thimerosal had serious concerns about the potential hazards associated with aluminum in vaccines, a conference report and workshop summary published in the journal *Vaccine* 2 years later declared that "the message from this conference for the global public should stress the safety of both these adjuvants and these vaccines," despite acknowledging that "we don't know" how aluminum adjuvants interact with the immune system and how it is processed by infants and children.[53] The conference report minimized risks by claiming that aluminum has been used as a vaccine adjuvant for more than 70 years and "has an established safety record with low incidence of reported adverse events." However, no one is warning vaccine recipients to consider the possibility that their adverse event could be related to aluminum in their vaccines nor encouraging them to report it to health authorities. Furthermore, research indicates that many people who have adverse reactions to aluminum-containing vaccines won't exhibit symptoms for several weeks, months, or years, so it's very difficult for vaccine recipients to recognize that the vaccines they received some time ago may be related to their current disabling autoimmune ailments.

A few years later, the FDA published a study, Mitkus et al., in which the authors concluded that "the benefits of using vaccines containing aluminum adjuvant outweigh any theoretical concerns."[54] This study is often cited as a confirmation that injecting babies with multiple doses of aluminum-containing vaccines is safe. However, there are major flaws in the FDA's analysis:

1. To determine an aluminum intake "minimal risk level" (MRL) for humans, a single animal study was used.[55] This study found that mice could receive up to 26 milligrams of aluminum per kilogram of body weight per day (26 mg/kg/day) with no adverse effects. After considering differences between mice and humans (and other factors), this number was reduced to create a margin of safety, and an MRL of 1 mg/kg/day was established for humans, including infants.[56] But there is a problem: 26 mg/kg/day is not a safe amount of aluminum for animals. Several studies confirm that animals are harmed by much lower quantities of aluminum—3.4 to 6.1 mg/kg/day—and at least three of these studies were published before the FDA paper in 2011, so the FDA study was fallacious at its inception.[57-60] Rats that were given just 6.1 mg/kg/day aluminum (30 mg/kg/day $AlCl_3$) needed significantly more repetitions to learn a maze when compared to a control group.[57] Rats that were given just 5.6 mg/kg/day aluminum (50 mg/kg/day $AlCl_3$-$6H_2O$) had significantly impaired spatial learning and memory abilities when compared to a control group. They also had cellular shrinking, plus behavioral, biochemical, and histological alterations.[58] Rats that were given just 3.4 mg/kg/day aluminum (17 mg/kg/day $AlCl_3$) "showed behavioral, biochemical, and histological changes similar to those associated with Alzheimer's disease."[60]

2. The MRL for humans is derived from dietary aluminum *fed* to mice. But infants are *injected* with aluminum. Injected aluminum bypasses the gastrointestinal tract and has unique toxic properties compared to aluminum that is ingested. To determine the safety of injected aluminum, scientists must conduct experiments with injected—not ingested—aluminum.

3. After vaccines containing aluminum adjuvants are injected into the body, aluminum nanoparticles can be transported by monocyte-lineage cells to draining lymph nodes, blood and spleen—and may also penetrate the brain.[41] Aluminum is unsafe even in trace quantities. For example, just 50 nanomolars of aluminum are sufficient to generate reactive oxygen species (ROS), or oxidative stress, in human primary neuronal-glial cell cultures and induce inflammatory gene expression.[61] In another study, just 10 nanomolars of aluminum increased C-reactive protein (CRP) levels four-fold, causing inflammation in human brain microvessel endothelial cells.[62] But the FDA assumes, without evidence, that these poorly biodegradable aluminum nanoparticles,

which have been detected in body organs up to a year after vaccination, are harmless, and they are not calculated by the FDA as part of the aluminum "body burden" until they dissolve.

4. The "retention function for aluminum," a mathematical equation that the FDA used to help estimate levels of aluminum in infants, was derived from data on only one person, an adult (rather than from numerous infants), and an estimate on the rate of absorption of aluminum hydroxide following injection was based on data from just two rabbits.

The FDA paper also falsely claimed that "occasional irritation (dermal) at the site of injection is the only adverse effect that has been reported in the published literature" following injections of aluminum-containing vaccines. And the clinical symptoms in patients diagnosed with MMF "are considered to be due to separate, coincidental immune or neurological disorders that are unrelated to the presence of aluminum in vaccines."[54] The Global Advisory Committee on Vaccine Safety, established by WHO, welcomed the FDA's analysis endorsing the safety of aluminum in vaccines.[63] The CDC vigorously defends the presence of aluminum in vaccines as well.[64] Clearly, FDA, CDC, and WHO agree on continuing indefinitely with their current policies of injecting babies with multiple doses of aluminum-containing vaccines.

Aluminum Toxicity Acknowledged for Parenteral Nutrition

Although the FDA's recent paper advocates the continued use of aluminum in childhood vaccines, FDA has known for many years that aluminum can be dangerous. For example, some infants require parenteral nourishment (administered by intravenous injection). All parenteral nutritional formulas contain aluminum. According to the FDA, "when medication and nutrition are administered orally, the gastrointestinal tract acts as an efficient barrier to the absorption of aluminum, and relatively little ingested aluminum actually reaches body tissues. However, parenterally administered drug products containing aluminum bypass the protective mechanism of the gastrointestinal tract and aluminum circulates and is deposited in human tissues."[65]

In a 1997 study published in the *New England Journal of Medicine*, scientists assessed 182 infants who received intravenous injections of nutritional formula that contained differing quantities of aluminum.[20] They calculated that infants who received aluminum at greater than 4 to 5 mcg/kg/day would lose 1 point per day on the Bayley Mental Development Index ($p = 0.03$). Babies who score low on this test are at risk for subsequent developmental and educational problems. This study contributed to FDA's decision to set limits on aluminum content in parenteral drug products and require warning labels on the package inserts—safety measures that were never required with aluminum-containing vaccines. In the Code of Federal Regulations, Title 21, published in the Federal Register, aluminum toxicity levels are revealed:

> WARNING: This product contains aluminum that may be toxic.... Research indicates that patients with impaired kidney function, including premature neonates, who receive [injections] of aluminum at greater than 4 to 5 mcg per kilogram of body weight per day, accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates.[66]

This means that for a 6-pound baby with impaired kidney function, 11-14 mcg of injected aluminum would be toxic. The hepatitis B vaccine given at birth contains 250 mcg of aluminum—20 times higher than safety levels indicated for preemies. Babies weigh about 12 pounds at two months of age when they are injected with 1,225 mcg of aluminum from their CDC-recommended vaccines—50 times higher than safety levels for preemies.

Healthy babies may be able to handle quantities of aluminum above FDA toxicity levels indicated for patients with impaired kidney function. However, no one knows how much more aluminum is safe because adequate studies were never conducted. In addition, babies are not screened for renal function prior to vaccination. Therefore, it is impossible to know ahead of time which babies will succumb to aluminum poisoning. Instead, parents are expected to play Russian roulette with their children.

Summary

Aluminum adjuvants are added to several vaccines to elicit a more robust immune response and increase vaccine efficacy. Infants and young children throughout the world receive high quantities of aluminum from multiple inoculations. Incremental changes to the vaccination schedule during the past several years significantly increased the quantity of aluminum in childhood shots. Numerous studies provide compelling evidence that injected aluminum can be detrimental to health. Aluminum is capable of remaining in cells long after vaccination and may cause neurologic and autoimmune disorders. During early development, the child's brain is more susceptible to toxins and the kidneys are less able to eliminate them. Thus, children have a greater risk than adults of adverse reactions to aluminum in vaccines.

Millions of children every year are injected with vaccines containing mercury and aluminum despite well-established experimental evidence of the potential for additive or synergistic toxicity when an organism is exposed to two or more toxic metals. Dr. Haley's study in which cultured neurons died at an accelerated rate following concurrent exposure to aluminum and thimerosal provides evidence of an enhanced detrimental effect. In addition, aluminum toxicity levels published by FDA indicate that two-month-old babies who are vaccinated according to CDC guidelines may

be receiving quantities of aluminum that are significantly higher than safety levels.

Conclusion

Toxic metals such as aluminum do not belong in prophylactic medications administered to children, teenagers, or adults. Vaccines are normally recommended for healthy people, so safety (and efficacy) standards must be impeccable. Parents, especially, should not be compelled to permit their loved ones to receive multiple injections of toxic metals that could increase their risk of neurodevelopmental and autoimmune ailments. Safe alternatives to current disease prevention technologies are urgently needed.

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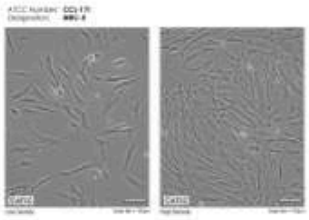
MRC-5 (ATCC® CCL-171™)

Organism: ***Homo sapiens*, human** / Cell Type: **fibroblast** / Tissue: **lung** / Disease: **Normal**

Karyotype

Chromosome Frequency Distribution 50 Cells: 2n = 46. This is a normal diploid human cell line with 46,XY karyotype. The modal chromosome number was 46, occurring in 70% of cells. The rate of polyploidy was 3.6%. Both X and Y chromosomes were normal. Note: Cytogenetic information is based on initial seed stock at ATCC. Cytogenetic instability has been reported in the literature for some cell lines.

Images



Derivation

The MRC-5 cell line was derived from normal lung tissue of a 14-week-old male fetus by J.P. Jacobs in September of 1966.

Clinical Data

Caucasian
male
14 weeks gestation

Virus Susceptibility

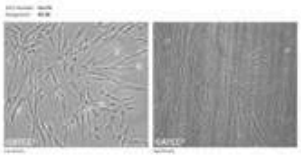
Human poliovirus 1
Herpes simplex virus
Vesicular stomatitis, Glasgow (Indiana)
Vesicular stomatitis, Orsay (Indiana)

Comments

The cells are capable of 42 to 46 population doublings before the onset of senescence.

WI-38 (ATCC® CCL-75™)

Organism: ***Homo sapiens*, human** / Cell Type: **fibroblast** / Tissue: **lung** / Disease: **normal**

Karyotype	normal diploid
Images	
Derivation	The WI-38 human diploid cell line was derived by Leonard Hayflick from normal embryonic (3 months gestation) lung tissue.
Clinical Data	3 months gestation fetus Caucasian female
Virus Susceptibility	Vesicular stomatitis, Glasgow (Indiana) Herpes simplex virus Pseudorabies virus Human poliovirus 1
Comments	WI-38 cells have a finite lifetime of 50 plus or minus 10 population doublings with a doubling time of 24 hours. This line was the first human diploid cell line to be used in human vaccine preparation. The 8th passage ampule from which this freeze was derived was found to contain a bacterial contaminant (a micrococcus). The cell line was subsequently cured by several passages in the presence of antibiotics. Growth of the cells is enhanced by addition of tumor necrosis factor alpha (TNF alpha) to the medium. This cell line is negative for reverse transcriptase.

Title: Spontaneous Integration of Hun

K. Koyama,
Sound Choice Pharmaceu

Introduction

A trio of recent publications in the journal NEURON reports the presence of hundreds of diverse de novo gene mutations indicating that autism spectrum disorder (ASD) may be a disease of genomic instability, with a significant environmental component. Altered double strand break formation and repair pathways (DSB) may be a commonality among the diverse genetic mutations that have been documented in ASD. US birth year change points in AD are apparent in 1980, 1988 and 1996, coinciding with the switch to or introduction of childhood vaccines contaminated with human endogenous retrovirus K (HERVK) and human fetal DNA fragments (6). We hypothesize that the HERVK and human fetal DNA contaminants could contribute to the genomic instability of ASD as demonstrated by de novo mutations.

Cell free DNA can be taken up by healthy cells via receptor mediated uptake or may spontaneously penetrate cell membranes that have altered permeability, for instance, during inflammatory reactions. Nuclear uptake of cell free DNA fragments is thought to provide a source for maintenance of DNA integrity during rescue of collapsed replication forks or base lesion repair. Spontaneous extracellular DNA uptake has also been exploited for gene therapy as well as for cellular gene correction (2,4,5,7,8, and 9). While free DNA uptake has been used advantageously, the process has also been associated with generation of mutations and chromosomal aberrations (3).

Vaccines manufactured using human fetal cells contain residual DNA fragments (50-500 bp) (Table I). It is possible that these contaminating fragments could be incorporated into a child's genome and disrupt normal gene function, leading to autistic phenotypes. In this study we demonstrate foreign DNA uptake in human cells and genomic integration by incubating the cells with Cy3-labeled human Cot1 (placental) DNA fragments which represents contaminating residual human fetal DNA in vaccines.

Table 1. Levels of residual human double stranded DNA (Picogreen assay) and human single stranded DNA (Oligreen assay) in Rubella vaccine (MeruvaxII) and Hepatitis A vaccine (HAVRIX).

Vaccine name	Double Stranded DNA (ng/vial)	Single Stranded DNA (ng/vial)	Length (bps)
Meruvax II (Rubella)	142.05	35.00	240
HAVRIX (Hepatitis A)	276.00	35.74	Not measurable

Methods and

Materials and Methods: Human Cot1 DNA (Invitrogen) was labeled with Mirus *Label* IT Cy^{TM}3 *Labeling Kit* (Mirus).

U937 cells (monocytes) were grown in Dublecco's Mofication of Eagle's Medium (DMEM) supplemented with 15% fetal bovine serum (FBS) and 1% antibiotic-antimycotic solution at 37°C under a humidified atmosphere containing 5% CO^2/95% air. HL-60 cells (myeloblast) were grown in Iscove's Modified Dulbecco's Medium (IMDM) supplemented with 20% FBS and 1% antibiotic-antimycotic solution at 37°C under the same condition. 750ng of Cy3 labeled Human Cot1 DNA was incubated per1.0×10^7 cells for 24 hours and 48 hours.
Cellular and nuclear DNA uptake was analyzed under fluorescent microscope. Genomic DNA of U937 cells was purified by ethanol precipitation removing short fragment of nucleic acids including unincorporated Cy3 labeled Human Cot1 DNA. The amount of Cy3 labeled human Cot1 DNA incorporated into U937 chromosomes was calculated with relative fluorescent unit (RFU) measured by a fluorimeter.

Loosely adherent NCCIT (teratocarcinoma) cells were grown with a cell density 3×10^4 per well of a 24-well plate which a German glass cover slips was placed in each well at 37°C under a humidified atmosphere containing 5% CO^2/95% air. HFF1 (Human Foreskin Fibroblast 1) cells were grown with the same condition except DMEM supplemented with 15% fetal bovine serum (FBS) and 1% antibiotic-antimycotic solution was used as a medium.

BE (2)-C (neuroblastoma) cells were grown in the same condition except medium used was a 1:1mixture of Eagle's Minimum Essential Medium (EMEM) and F12 Medium supplemented with 10%FBS and 1% antibiotic-antimycotic solution. M059K (Glioblastoma-Double Stranded Break repair proficient) and M059J (Glioblastoma-Double Stranded Break repair deficient) were also grown with the same condition except the medium used was a 1:1 mixture of DMEM and Ham's F12 Medium supplemented with 10% FBS, 0.05mM non-essential amino acids, and 1% antibiotic-antimycotic solution. After cells were cultured in each condition for 2 to 3 days 500ng Cy3 labeled Human Cot1 DNA was added and incubated at 37°C under a humidified atmosphere containing 5% CO^2/95% air by gently shaking for 24 hours and 48 hours. After incubation nucleus was stained with Hoechst, German glass cover slips were placed on glass slides, and cellular and nuclear DNA uptake was analyzed under fluorescent microscope.

To model inflammation, all adherent cell lines were activated with lipopolysaccharide (LPS). And, saponin permeabilization was also tested for HFF1 cells . Three concentrations of LPS, 1ng/10^4cells, 10ng/10^4cells, and 100ng/10^4cells were tested in the wells of each cell line previously mentioned. Cells were incubated with Cy3 labeled Human Cot1 DNA and LPS at 37°C under a humidified atmosphere containing 5% CO^2/95% air by gently shaking for 24 hours and 48 hours. As well as cells incubated without LPS, these cells were also stained with Hoechst before cellular and nuclear DNA uptake was analyzed under fluorescent microscope.
HFF1 cells were incubated with 0.02% saponin , 300ng DAPI, and 500ng Cy3 labeled human Cot 1 DNA for 24 hours, 48 hours, and 72 hours. Cells were viewed under fluorescent microscope as well.

Results (Table 2):

Spontaneous cellular and nuclear DNA uptake was evident in HFF1, NCCIT and U937 (Fig1, 3, 7 and 8). DNA uptake in BE (2)-C and M059K was not measurable because of high auto fluorescence of the cells. No Cy3 signal was observed in HL-60. With inflammation caused by LPS cellular DNA uptake was observed in HFF1, NCCIT, M059J, and U937 (Fig 2, 4, 5 and 6).

The amount of labeled Cy3 human Cot1 DNA incorporation in U937 genomic DNA was 0.0111 +/- 0.0034pg (n=12) per cell in 24 hours, which was approximately 0.167% of total U937 genomic DNA. DNA incorporation in NCCIT cells was 0.0026pg/cell in 24 hours and 0.04pg/cell in 48 hours which is 0.6% of total NCCIT genomic DNA.

Table 2: DNA uptake in Various Cell lines

	Spontaneous Cellular uptake	Spontaneous Nuclear uptake	Incorporation in Genomic DNA	Cellular /Nuclear Uptake with LPS or saponin
HFF1	Yes	Yes	Not Done	Increase/Increase
NCCIT	Yes	Yes (variable)	0.0026pg per cell 24 hrs 0.04pg per cell 48 hrs	Same/Same
BE(2)-C	No	No	Not Done	No/No
M059K	No	No	No	No/No
M059J	No	No	Not Done	Yes/No
U937	Yes	Yes	0.011 +/- 0.003pg per cell 24 hrs	Same/Same
HL60	No	No	No	No

nan DNA Fragments into Host Genome

T. A. Deisher
utical Institute, Seattle, WA

Results

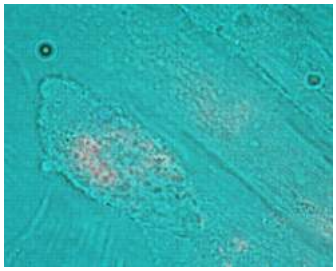


Fig 1. HFF1 spontaneous cellular and nuclear DNA uptake (bright field & Cy3 red combined).

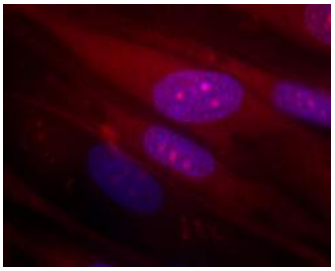


Fig 2. HFF1 cellular and nuclear DNA uptake after permeabilization with saponin. (Cy3 red & nucleus blue combined)

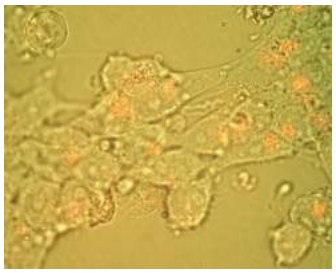


Fig 3. NCCIT spontaneous cellular DNA uptake (bright field & Cy3 red combined)

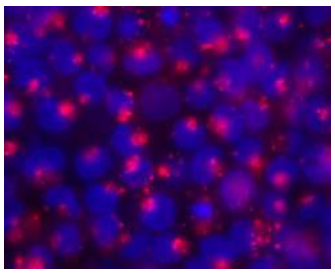


Fig 4. NCCIT cellular DNA uptake after lipopolysaccharide activation (Cy3 red & nucleus blue combined)

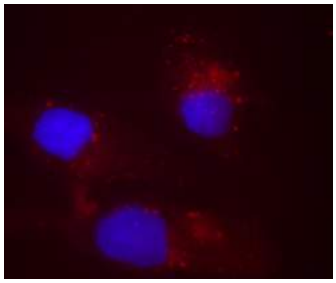


Fig 5. M059J cellular DNA uptake after lipopolysaccharide activation (10ng/10^4 cells).
(Cy3 red & nucleus blue combined).

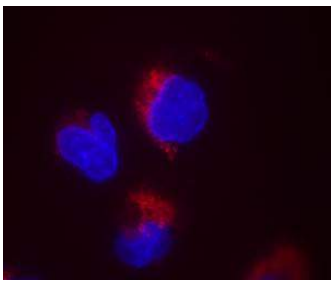


Fig 6. M059J cellular DNA uptake after lipopolysaccharide activation (100ng/10^4 cells).
(Cy3 red & nucleus blue combined).

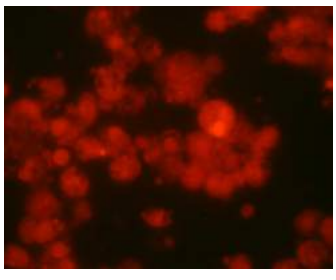


Fig 7. U937 spontaneous cellular/nuclear DNA uptake (Cy3 red)

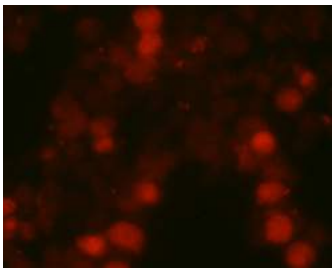


Fig 8. Purified U937 **nuclei** containing Cy3 labeled DNA before DNA purification (Cy3 Red)

Discussion

Our measured genomic incorporation (0.003 to 0.04 pgs) of 0.2% - 0.6% of the whole genome in 24 to 48 hours seems high at first glance. However, our numbers are consistent with previous reports showing that exogenous DNA replaced up to 1% of the whole genome within 30 minutes (6). Although HL-60 cells did not spontaneously take up exogenous DNA in our experiments, the cell line has been used in the past as a model for spontaneous DNA uptake (8).

Cellular and nuclear DNA uptake in human foreskin fibroblast (HFF1) cells and in NCCIT cells suggests that embryonic and neonatal cell are more susceptible to DNA uptake than cells from a more mature source. These results indicate the need for further study of DNA incorporation from exogenous sources to compare the susceptibility of infants and toddlers versus teens and adults.

Increased DNA uptake after LPS activation suggests that systemic inflammation or immune responses could increase susceptibility for exogenous DNA uptake. Human diploid cell produced vaccines are contaminated by exogenous DNA fragments and a retrovirus, and vaccines elicit systemic inflammation and immune activation. Our future research goals are to localize the sites of DNA integration, to demonstrate phenotype changes caused by foreign DNA integration in factor dependent cell lines, and to determine the biological and/or pathological activities of Human Endogenous Retrovirus K (HERVK) fragments in vaccines.

Table3: Cell Description

Cells	Source	Morphology	Transfection host
U937	Histocytic Lymphoma	Monocyte	Yes
HL60	Leukemia	Myeloblast	Yes
BE(2)C	Neuroblastoma	Neuroblast	No
M059K	Glioblastoma	Fibroblast	No
M059J	Glioblastoma	Fibroblast	No
HFF1	Foreskin	Fibroblast	No

Conclusion

Not only damaged human cells, but also healthy human cells can take up foreign DNA spontaneously. Foreign human DNA taken up by human cells will be transported into nuclei and be integrated into host genome, which will cause phenotype change. Hence, residual human fetal DNA fragments in vaccine can be one of causes of autism spectrum disorder in children through vaccination. Vaccine must be safe without any human DNA contaminations or reactivated viruses, and must be produced in ethically approved manufacturing processes.

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RESEARCH PAPER

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Characteristics and viral propagation properties of a new human diploid cell line, walvax-2, and its suitability as a candidate cell substrate for vaccine production

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Keywords: biological characteristics, cell substrate, human diploid cell strain (HDCSs), human diploid cell vaccines (HDCVs), viral sensitivities

Abbreviations: ATCC, American Type Culture Collection; CCID50, 50% cell culture infectious dose; CCTCC, China Center for Type Culture Collection; CPE, cytopathogenic effect; ELISA, enzyme-linked immuno sorbent Assay; FFU, fluorescent focus units; G6PD, glucose 6 phosphate dehydrogenase; GM, growth medium; HAV, hepatitis A virus; HDCSs, human diploid cell strains; HDCV, human diploid cell vaccine; LD, lactate dehydrogenase; MCB, master cell bank; MDCK, Madin–Darby canine kidney; MOI, multiplicity of infection; NIFDC, National Institute for Food and Drug Control; PAGE, polyacrylamide gelelectrophoresis; PCB, primary cell bank; PFU, plaque forming units; PPLO; pleuropneumonia-Like organisms; STR, Short tandem repeats; VZV, varicella zoster virus; WCB, Working cell bank

Human diploid cell strains (HDCSs), possessing identical chromosome sets known to be free of all known adventitious agents, are of great use in developing human vaccines. However it is extremely difficult to obtain qualified HDCSs that can satisfy the requirements for the mass production of vaccines. We have developed a new HDCS, Walvax-2, which we derived from the lung tissue of a 3-month-old fetus. We established primary, master and working cell banks successfully from reconstituted frozen cells. Observations during the concurrent propagation of Walvax-2 and MRC-5 cells revealed differences in terms of growth rate, cell viability and viral sensitivities. Specifically, Walvax-2 cells replicated more rapidly than MRC-5 cells, with Walvax-2 cells attaining the same degree of confluence in 48 hours as was reached by MRC-5 cells in 72 hours. Moreover, Walvax-2 cells attained 58 passages of cell doublings whereas MRC-5 reached 48 passages during this period. We also assessed the susceptibility of these cells to rabies, hepatitis A, and Varicella viruses. Analysis of virus titers showed the Walvax-2 cells to be equal or superior to MRC-5 cells for cultivating these viruses. Furthermore, in order to characterize the Walvax-2 cell banks, a series of tests including cell identification, chromosomal characterization, tumorigenicity, as well as tests for the presence of microbial agents, exogenous viruses, and retroviruses, were conducted according to standard international protocols. In conclusion, results from this study show that Walvax-2 cell banks are a promising cell substrate and could potentially be used for the manufacturing of HDCVs.

Introduction

The replication of viruses occurs only when the virus enters into host cells, often resulting in diseases that are difficult to treat. Currently, there are no widely accepted therapeutics available to treat such diseases, therefore prophylactic vaccines play an imperative role in the fight against viral diseases. Antibodies produced for most kinds of viral diseases when the immune system is stimulated by intact viral particles,.[1,2] Owing to this property, the vast majority of viral vaccines still adopt the traditional cell substrate culture method. Three cell substrates, human diploid cells, continuous cell lines and primary cell lines, are always used for developing vaccines.[3] However, continuous and primary cell lines used for vaccine production suffer from the limitation of

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being potentially strongly tumorigenic. Four Additionally the primary cell lines, which are obtained from animals, introduce potentially risky exogenous agents.[4] In contrast, human diploid cell strains (HDCSs), acquired from embryos or other tissue cells of human origin, possess identical chromosome sets that are free of all known adventitious agents.[5] These unique properties explain the value of such materials and the current interest in their use in the development of human viral vaccines.[6,7,8] Human diploid cell vaccines (HDCVs) have been licensed all over the world. Many studies have demonstrated superior immunogenicity and safety of HDCVs relative to those using any other tissue culture, such as hamster kidney cells or vero cell vaccines.[9] The WHO recommends HDCS as the safest cell culture substrate for the production of viral vaccines[10] and consequently they have become the preferred cell substrate for vaccine production worldwide.

Hayflick in 1961[8] and Jacobs in 1967[7] developed the 2 most well known HDCSs, Wistar Institute (WI)-38 and Medical Research Council (MRC)-5, respectively, that currently serve as international standardized cell strains. Since then, there has been continuing interest in the development of HDCSs. Eleven,[12] However, it is extremely hard to obtain human fetal tissue from which to derive qualified human diploid cell strains. This is due to issues that include the requirement for strict ethical review, the possibility of environmental degradation, and food safety hazards, all of which may lead to chromosomal aberrations such as the presence of aneuploidy and polyploidy for the karyotype.[13] Most importantly, strict requirements regarding the methods for obtaining suitable tissues from which to derive HDCS via abortion render the acquisition of appropriate material difficulty. Even if a new HDCS is derived successfully, it might not satisfy requirements for industrial production due to its inability to sustain multiple passages, the IMR-9 cell line being an example.[14,15] Due to the diminishing supply of WI-38[10] cells, the MRC-5 line has become the most widely used cell strain in the production of HDCS-derived human vaccines. China consequently confronts 2 key challenges for the production of viral vaccines from MRC-5 cells (which are mainly obtained from abroad): concerns about influences of limited passages, and the policies of the countries from which the cells are imported. More specifically, the numbers of passages of the imported MRC-5 cells are generally higher, generally later than the 20th passage, resulting in restricted mass production due to decreased growth vitality. Additionally, according to the standard for the Pharmacopoeia of the People's Republic of China (2010), Volume III, the use of the HDCSs is limited to generations within 2-thirds of the primary cell lifespan for the manufacture of vaccines. Due to the scarce HDCSs resources, the research and production of viral HDCVs in China are substantially restricted. For example, human diploid cell rabies vaccine, which is considered to be the gold standard for rabies vaccines, is not currently available in China.[16] Furthermore, the productive cell generations for the OKA-HDC on the Chinese market from 3 manufactures are MRC-5 cells in the 32nd and 33rd passages,[17] which have therefore already reached the limit required as described above in Chinese Pharmacopeia (the 33rd passage is the last cell doubling that could be used in the production for the MRC-5). Relying on imported HDCSs, may lead to unstable supply as well as unpredictable costs. Therefore the intention of this study is to develop a completely new HDCS of Chinese origin that could be used in manufacturing viral vaccines.

This study, therefore, aims to (i) establish and characterize Walvax-2, a totally new HDCS; and (ii) evaluate the susceptibility to 3 kinds of viral vaccine strains, namely the CTN-V/PV strain of rabies, the YN-5 strain of hepatitis A, and the Oka strain of Varicella virus in Walvax-2, thereby preparing for the industrial development of HDCVs in China.

Results

Source tissue material

We obtained 9 fetuses through rigorous screening based on carefully specified inclusion criteria (see Methods section). The Walvax-2 strain of cells met all of these criteria and proved to be the best cell line following careful evaluation. Therefore it was used for establishing a human diploid cell strain. Walvax-2 was derived from a fetal lung tissue, similar to WI-38 and MRC-5, and was obtained from a 3-month old female fetus aborted because of the presence of a uterine scar from a previous caesarean birth by a 27-year old healthy woman.

Primary cell stock and cell bank system

After incubation for 48 h, a confluent cell monolayer formed and then increased in density over the following 48 hours. After a series of successful cultures, these cells were specified as the primary cell seeds of the Walvax-2 human diploid cell line. Thereafter, a 3-tiered cell bank consisting of pre-master cell bank (PCB，P6), master cell bank (MCB, P14), and working cell bank (WCB, P20) was established.

Figure 1 shows a gradual growing procedure for cells after propagation. Initially, round cells with clear and relatively dark edges were observed; as time went by, the cells elongated to become spindle shaped and translucent fibroblasts (**Fig. 1A**). Over a period of 24 hours during which the cells divided and proliferated, the cells grew into flame shaped, typical plump diploid fibroblasts with good refractive properties, and rearranged into highly polarized areas with curling patterns (**Fig. 1B**). Finally, the cells formed a dense confluent monolayer after 48 hours (**Fig. 1C**).

Walvax-2 cells maintained excellent capabilities for growth and proliferation until the 50th passage, after which these abilities degraded. At passage 58, cells exhibited blurred edges and could not form a confluent monolayer after being cultured for 72 h. Also noted were increasing black spots in cells, as well as dead cells in the media. (**Fig. 1D**). Cell death was eventually observed after 20 d

Cryopreservation stability and recovery viability

The Walvax-2 3-tiered cell bank, composed of PCB (P6), MCB (P14), and WCB (P20), exhibited a homogeneous growth

pattern and attained identical population doublings (58) when compared with the primary cell seed. All the cells restored from frozen stock reached adherent growth in 2–8 h and formed a confluent monolayer in 24 h, with the percentage of viable cells in the range of 80–90% (**Fig. 2**). Each of the curves in **Figure 2** demonstrates the growth features for the Walvax-2 primary cell seed as well as the cell banks. Generally speaking, the typical diploid cell with limited replicative lifespan follows a "slow-logarithmic-slow" model. However, Walvax-2 cells show strong cell proliferation, with the missing "slow" pattern at the beginning for each curve, until the 50th passage, after which the viability of the cells decreases dramatically. Furthermore, comparative cell doubling times are summarized in **Table 1**. The results confirm that the Walvax-2 cells reconstituted from the frozen state do not alter their stability and viability, and could potentially be used as a cell substrate due to these crucial properties.

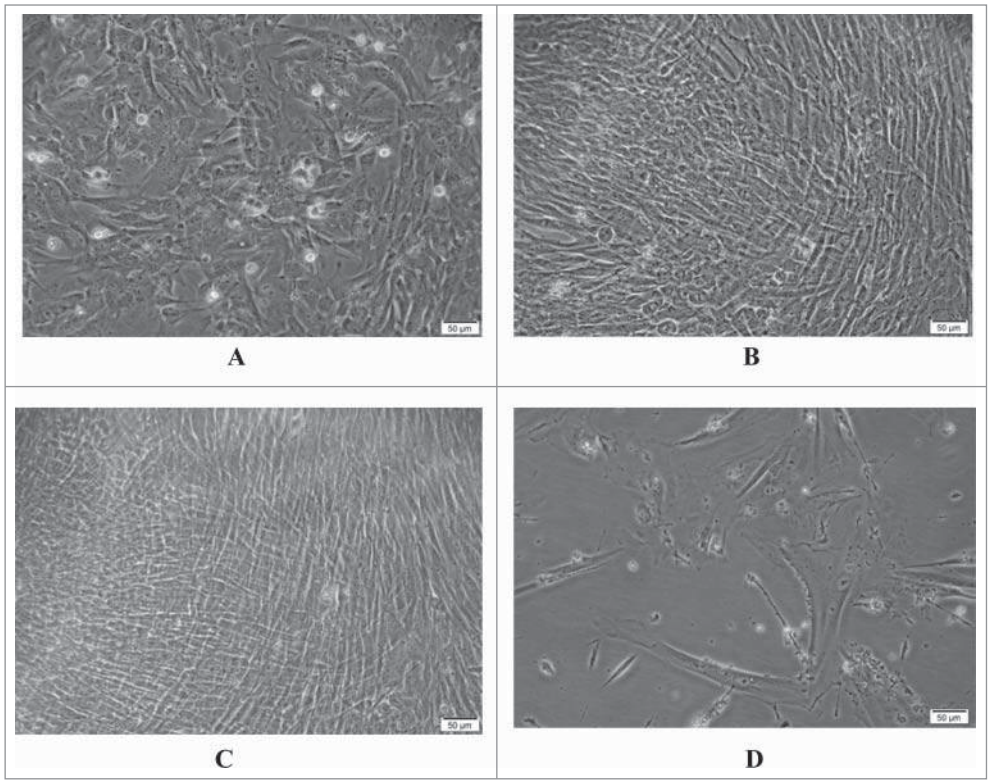

Figure 1. Morphology of the Walvax-2 cells. The cells were cultured and incubated at 37 °C. The photos were taken at 4 h (**A**), 24 h (**B**) and 48 h (**C**) and at 72 h post-subculture for the 58th passage (**D**).

Cell identification

As shown in **Figure 3**, the isozyme patterns of the Walvax-2 cells, using LD and G6PD as indicators, are identical to those of human diploid cells (MRC-5) and the human cervical cancer cell line (Hela) preserved in China Center for Type Culture Collection (CCTCC), whereas the mouse fibroblast cell line (L929) exhibits entirely different results. These findings confirm the fact that the Walvax-2 cell banks behave in a manner similar to other human-derived cell lines.

STR profiles of 16 DNA fragments of gene locus for Walvax-2 cells are shown in **Figure 4**, from which we see that they match the targeted alleles as expected. In **Table 2** the data from this study are compared with those of STR databases in ATCC of USA and DSMZ of Germany. Three qualified laboratories, CCTCC, NIFDC (National Institutes for Food and Drug Control) and Law School of Kunming Medical University, draw the

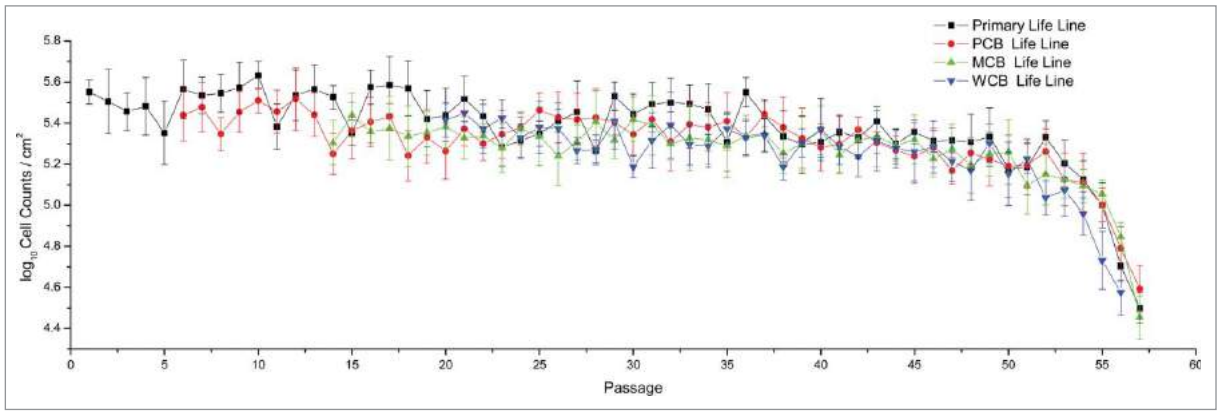

Figure 2. The growth patterns of Walvax-2 cell banks. Primary cells were isolated from fetal lung tissue, frozen at the 6th, 14th and 20th passages, and then recovered and subcultured continuously until cell senescence occurred.

Table 1. Population doubling times of the Walvax-2 cells with and without being subjected to freezing

Passage number	Without being subjected to freezing	Reconstituted from the frozen state	
	Population doubling time(h)	Cell origin	Population doubling time(h)
P 10	18–20	PCB,P6	18–20
P 20	29–31	MCB, P14	30–32
P25	30–32	WCB, P20	30–32
P32	38–40	The 28th passage from the WCB	39–41
P43	39–41	The 38th passage from the WCB	40–42
P55	55–60	The 48th passage from the WCB	57–62

same conclusions that the Walvax-2 cell line displays its own specific DNA profile of human individual origin distinct from the MRC-5 and the Hela cell lines.

Chromosomal characterization

The chromosomal characterization for PCB (P6), MCB (P14), WCB (P20) from the 38th passage, which is the last passage that could be used for producing viral vaccines according to the requirements of Chinese Pharmacopeia, are illustrated in **Figure 5**. They show clearly that the Walvax-2 cells are 46/XX, typical diploid type of human origin. The chromosomal analysis of the Walvax-2 cells as summarized in **Table 3** demonstrate that the karyological properties of Walvax-2 cells satisfy the requirements of diploid cells of human origin to be used for producing viral vaccines, with the frequencies of abnormalities being considerably lower than the corresponding national standards.

Microbial agent tests

No cultivable bacteria or fungi were found in broth and agar cultures. Mycoplasma tests using both the culture method and DNA staining technique, also met the corresponding requirements.

Exogenous virus agent tests

Results for the testing of general (non-specific) as well as specific adventitious viral agents were negative for all tested viruses as described in detail in the "materials and methods" section.

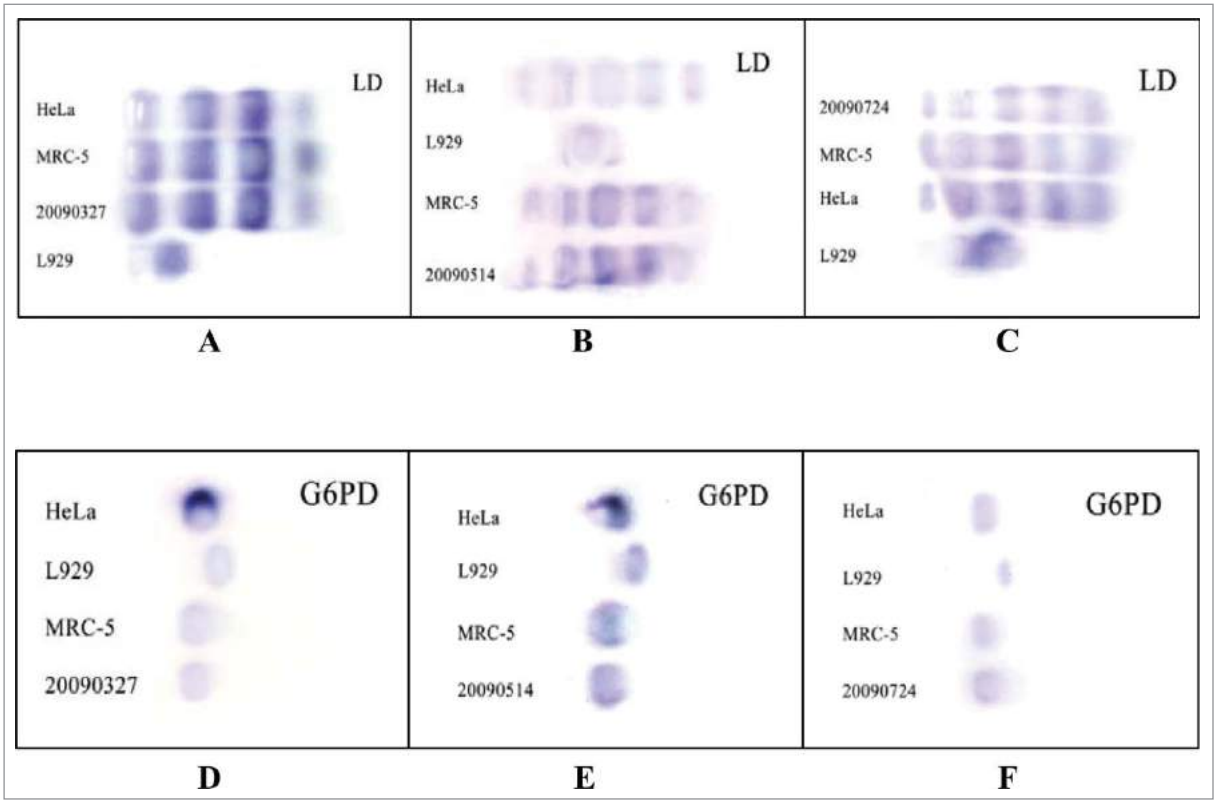

Figure 3. Isoenzyme tests for the Walvax-2 cells. Firstly, LD and G6PD, 2 isoenzymes used as indicators, were isolated from HeLa, L929, MRC-5 and Walvax-2 cells, and then subjected to PAGE and stained. The numbers of 20090327, 20090514 and 20090724 illustrated in the pictures represent Walvax-2 cells for the 18th, 30th and 50th passages.

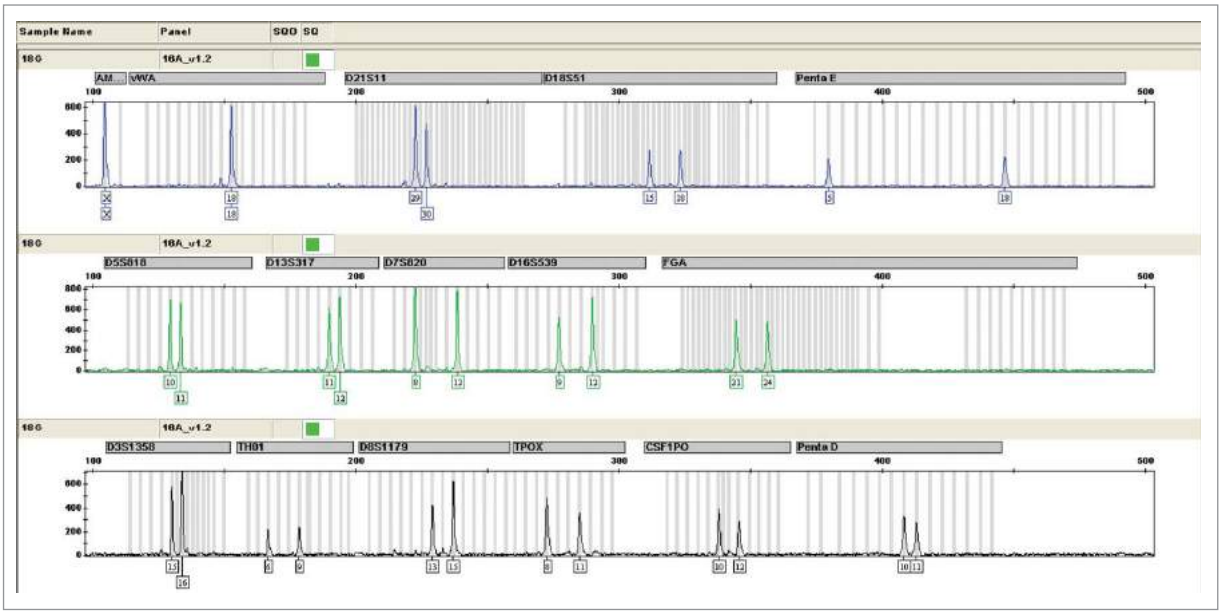

Figure 4. The Short Tandem Repeat （STR） map of Walvax-2 cells for the 18th passage. According to the instructions supplied with the Goldeneye 16A identification kit (people spot), the DNA of Walvax-2 cells at the 18th passage were isolated and amplified by multiplex PCR with primers of 16 STR sites. Then the STR map was obtained by analyzing the samples of PCR by capillary electrophoresis (CE). The STR maps of Walvax-2 cells at the 30th and 50th passages (not shown) were the same as shown.

Retrovirus test

The results in **Figure 6** make it clear that no retroviruses were found in the Walvax-2 cells, as well as the system control cells of MRC-5. However obvious retroviruses were found in the Sp2/0-Ag14 cells of the positive control group, seen as tiny black dots in the figure.

Tumorigenicity test

Tumorigenicity tests were conducted at 2 points following the inoculation of cells into the nude mice, 21 and 84 d All mice survived in all study groups. During the animal tests, no pathological abnormalities of nodule growths were found in the experimental as well as the parallel negative control group (MRC-5), and for both groups there was no pathological heterogeneous cell growth observed at the inoculating site or other sites including heart, liver, spleen, lung, kidney, brain and mesenteric lymph nodes after autopsy. In contrast, nodule and heterogeneous cell growth were easily found in the inoculating site in the positive control group (Hela). These results show that the Walvax-2 cells can be used for the production of vaccines with little risk of potential carcinogenesis.

Susceptibility to viruse tests

Infectivity titers of the CTN-1V strain for the rabies virus are presented in **Table 4**. CTN-1V virus was well adapted in Walvax-2 relative to MRC-5. Maximum infectivity titers of CTN-1V virus for Walvax-2 and MRC-5 were 8.14 and 7.41 FFU/ml, respectively. During the period for virus propagation, the titers in Walvax-2 cells were consistently higher than those of MRC-5 cells, although the differences were not always statistically significant. However, analysis of the overall situation of the adaptation of the CTN-1V in Walvax-2 cells relative to MRC-5 cells yielded a significant difference ($P < 0.001$) by a 2-tailed t-test. Similarly, the results for the PV strain adaptation in both human diploid cells demonstrated a consistent trend, which exhibited distinct differences for the titers.

Table 2. The STR mapping of the Walvax-2 cells

gene locus	Walvax-2	MRC-5*	HeLa*	gene locus	Walvax-2	MRC-5*	HeLa*
Amelogenin	X	X,Y	X	D16S539	09,12	9,11	9,10
vWA	18	15	16,18	FGA	21,24	—	—
D21S11	29,30	—	—	D3S1358	15,16	—	—
D18S51	15,18	—	—	THO1	06,09	8	7
PentaE	05,18	—	—	D8S1179	13,15	—	—
D5S818	10,11	11,12	11,12	TPOX	08,11	8	8,12
D13S317	11,12	11,14	12.13.3	CSF1PO	10,12	11,12	9,10
D7S820	08,12	10,11	8,12	PentaD	10,11	—	—

*Data from ATCC and DSMZ

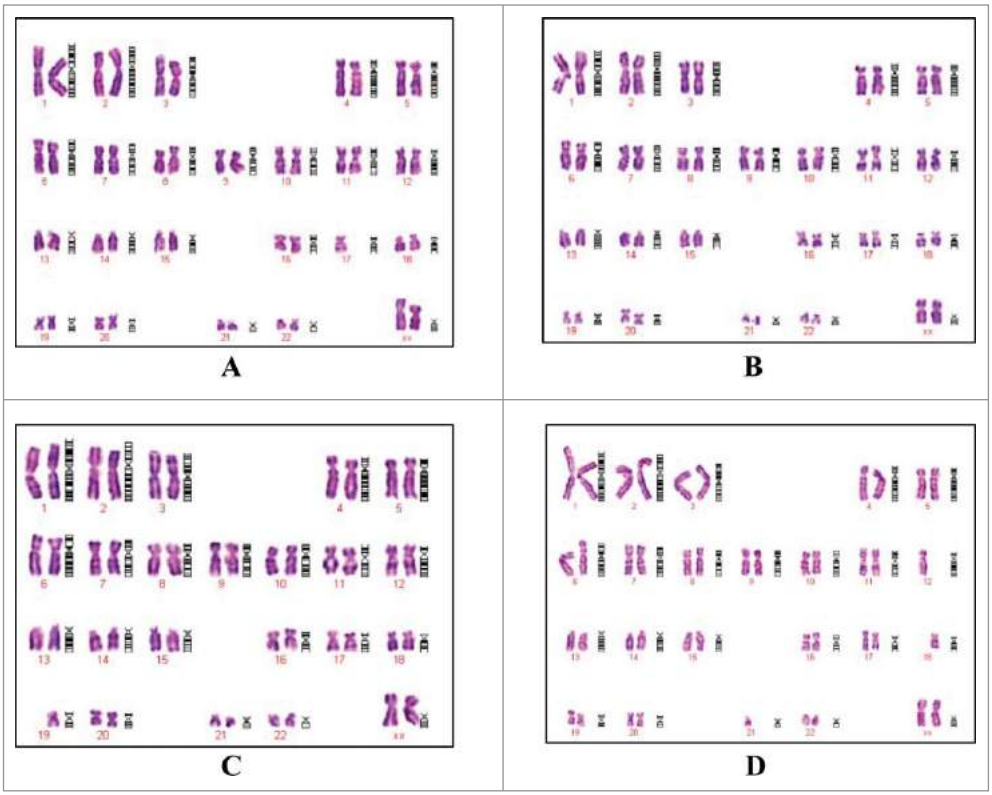

Figure 5. Chromosomes from Walvax-2 cell banks. Walvax-2 cells were incubated 1 day post-subculture, after which the colcemid and then Giemsa banded karyotype analyses were carried out. Pictures were the karyotype of Walvax-2 cells at the 6th (**A**), 14th (**B**), 20th (**C**) and 38th (**D**) passages

Discussion

HDCS, deemed as the safest cell substrate, play a vital role in the production of viral human vaccines. However, it is extremely hard to obtain qualified HDCSs that meet the requirements for mass production. It took us 4 y to successfully establish Walvax-2 cell lines and a 3-tiered cell bank, namely PCB, MCB and WCB. Complete records for the cell bank establishment, cell culture conditions, and tests are available. The criteria used for characterizing the Walvax-2 cell banks are those recommended internationally[18,19] and concurrent titrations were set up using MRC-5 cells (the most widely used human diploid cell substrate as a parallel control. Walvax-2 cells have received qualification test reports from the NIFDC and CCTCC, an important step in their use for the production of human viral vaccines in China. Given that the availability of HDCSs, and therefore the production of HDCVs, is currently subject to external forces, the development of an HDCS of Chinese origin has great implications for improving the stability of the supply of HDCVs in China.

Data for the VZV virus propagating in Walvax-2 and MRC-5 cells is given in **Table 5**. In Walvax-2 cells the virus titer grew rapidly to 6.28 log PFU/ml, and reached a peak of 6.59 log PFU/ml at passage 41. In contrast, the virus titers in MRC-5 were much lower, with the overall numbers less than 6.0 log PFU/ml. All comparisons except that of the earliest generation were all statistically significant, indicating strong adaptation of the VZV strain for Walvax-2 cells relative to MRC-5 cells.

The comparative results for YN5 adaptability are listed in **Table 6**. The titer after one generation in Walvax-2 reached 7.32 log CCID50/ml, even higher than the value in the original cells (passage 23). During the course of 8 passages propagated continuously in the Walvax-2 cells, the infectious virus titers increased from 7.32 to 7.65 log CCID50/ml, which was marginally higher than those of MRC-5 cells (7.0 to 7.36 log CCID50/ml).

Walvax-2 cells displayed a fibroblastic morphology similar to that of MRC-5 cells. However, observations during the concurrent propagation of Walvax-2 and MRC-5 cells revealed differences in terms of growth rates and cell viability. The Walvax-2 cells replicated more rapidly than MRC-5 –they attained the same degree of confluence in 48 hours as was reached by MRC-5 in 72 hours, and the results are in line with measured cell doubling times as listed in **Table 1**. After freezing and recovering, the growth characteristics and patterns of the 3 life lines (PCB, MCB, and WCB) are similar to those of the primary life line, and attained 58 passages of cell doublings whereas MRC-5 reached 48 passages, with the difference decreasing gradually

Table 3. The accumulated results of chromosomal analysis of Walvax-2 cells

Passage	Structural abnormalities	Aneuploidy	Polyploidy	Hyperdiploidy	Breaks or gaps
Standard*	≤2 %	≤18 %	≤4 %	≤2 %	≤8 %
10—19	0/3500	265/3500 (7.57%)	1/3500 (0.03%)	22/3500 (0.63%)	0/3500
20—29	0/6000	538/6000 (8.97%)	3/6000 (0.05%)	49/6000 (0.82%)	1/6000 (0.17%)
30—39	0/4500	423/4500 (9.4%)	1/4500 (0.02%)	40/4500 (0.89%)	1/4500 (0.02%)
40—50	0/9000	945/9000 (10.5%)	7/9000 (0.08%)	113/9000 (1.26%)	7/9000 (0.08%)

*Chinese pharmacopeia, volume III, 2010 edition

with increasing hours of freezing.[8] In conclusion, these results may indicate that Walvax-2 is a cell line with superior characteristic of high growth ability, as well as strong viability compared to MRC-5. It could be used as a host for the cultivation and inoculation of viruses, although different schedules for inoculation and propagation should be further studied based on the growth characteristics of particular viruses. Furthermore, the stability of the karyotype is another crucial issue when using the HDCS in the manufacture of vaccines. The results for karyological data on Walvax-2 cells, as summarized in **Table 3**, demonstrate increases of aneuploidy and hyperdiploidy with age. However, this is not a concern on the grounds that the 2 "middle groups," which are directly related to those to be used in the manufacture of vaccines according to the requirements of Chinese Pharmacopeia, have frequencies of aneuploidy and hyperdiploidy of 9.4% and 0.89% respectively, which are substantially lower than the national standards of 18% and 2%, respectively.

The susceptibility of the human fetal cell strain MRC-5 to viruses infectious in man has

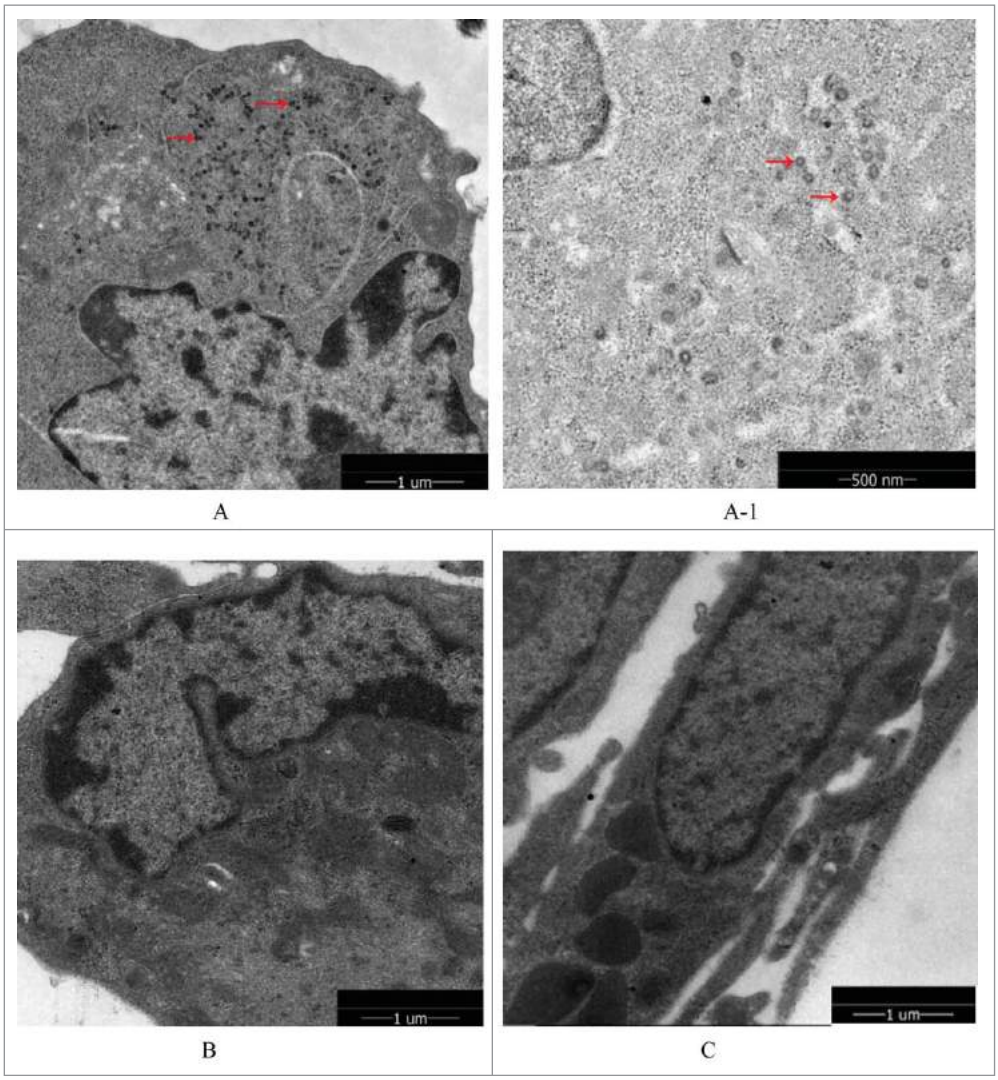

Figure 6. Retrovirus tests of Walvax-2. The results were observed by mirror electron microscopy(200Kv 5000x/160Kv 7800x). The arrows point to virus particles detected as shown in the picture. (**A**) and (**A-1**) were represented positive controls (Sp2/0-Ag14), (**A-1**) was partial enlarged detail of (**A**). (**B**) was represented negative control (MRC-5). (**C**) was represented the cells of Walvax-2 of the 24th passage.

Table 4. Propagation of CTN-1V or PM virus in the Walvax-2 or MRC-5 cells

Virus Passage NO.	CTN-1V virus (log FFU/ml)[a]			PVvirus (log FFU/ml)[a]		
	Walvax-2 cells	MRC-5 cells	P[b]	Walvax-2 cells	MRC-5 cells	P[b]
original	7.50	7.50	/	7.50	7.50	/
1	4.84 ± 0.62	4.58 ± 0.40	>0.05	4.40 ± 0.27	3.62 ± 0.23	>0.05
2	5.40 ± 0.21	5.02 ±0.34	<0.05	5.04 ±0.18	4.75 ± 0.24	<0.05
3	6.10 ± 0.37	5.41 ± 0.24	<0.05	5.30 ± 0.33	4.83 ± 0.25	<0.05
4	6.530.31	6.09 ± 0.17	<0.05	5.86 ± 0.10	5.02 ± 0.13	<0.05
5	6.78 ± 0.40	6.14 ± 0.16	<0.05	6.21 ± 0.21	5.63 ± 0.05	<0.05
6	7.08 ± 0.15	6.57 ± 0.42	>0.05	6.57 ± 0.53	6.02 ± 0.18	>0.05
7	7.34 ± 0.22	6.89 ± 0.21	<0.05	7.01 ± 0.70	6.00 ± 0.23	>0.05
8	7.51 ± 0.21	7.16 ± 0.08	>0.05	6.93 ± 0.19	6.28 ± 0.25	<0.05
9	7.67 ± 0.18	7.09 ± 0.10	<0.05	7.23 ± 0.23	6.59 ± 0.26	<0.05
10	8.14 ± 0.31	7.41 ± 0.35	<0.05	8.02 ± 0.19	7.11 ± 0.38	<0.05

Passages the 1th to 4th, subculture; Passages the 5th to 8th, cell-mixing; Passages the 9th to 10th, cell-free medium;
[a] ±SD.
[b] Significance of difference (P value) determined by 2-tailed t-test

Table 5. Propagation of VZV strain in the Walvax-2 or MRC-5 cells

Virus Passage No.	Virus Titer in Walvax-2 cell (log PFU/ml)[a]	Virus Titer in MRC-5 cell(log PFU/ml) [a]	P^b
31(original)	5.0	5.0	
33	6.28 ± 0.28	5.42 ± 0.19	>0.05
35	6.13 ± 0.12	5.56 ± 0.11	<0.05
37	6.31 ± 0.28	5.52 ± 0.08	<0.05
39	6.27 ± 0.14	5.58 ± 0.12	<0.05
41	6.59 ± 0.06	5.74 ± 0.13	<0.05

[a] ±SD.
[b] Significance of difference (P value) determined by 2-tailed t-test

been well demonstrated over the past 10 years, indicating the value of such material for the isolation of viruses and the development of vaccines. In this study, the Walvax-2 cell line served as a host for the cultivation of the CTN-V/PV strain of rabies, the YN-5 strain of hepatitis A, the Oka strain of Varicella virus, with results that demonstrate good sensitivity to these viruses. Compared to the MRC-5 cells, titers for viruses in the Walvax-2 cells are higher, with the overall numbers achieving statistical significance. These discrepancies elucidate that Walvax-2, as a new human diploid cell line, is equal or superior to MRC-5 for the propagation of viruses. Generally speaking, as the cell passage number increases the viral titers will experience an initial decrease, and then increase gradually as the cell substrate adapts to the virus. This trend is observed for the propagation of rabies virus in our study. However, the results are not the same for the propagation of VZV and HAV strains in HDCSs, which exhibit increased titers after only one generation. To the best of our knowledge, this may be attributed to the fact that these 2 virus strains are quite sensitive to HDCSs, and particularly to the Walvax-2 cells. Alternatively, the higher titers for Walvax-2 may relate to the characteristics of high growth ability as well as strong viability compared with MRC-5, as described in the "Results" section. Nevertheless, more research needs to be done to investigate the susceptibility of Walvax-2 cells to a greater variety of viruses, and to develop fully the potential of Walvax-2 cells as a cell substrate platform for producing viral vaccines for human use in China.

Table 6. The titers of HAV (YN5) adapted in human diploid cells

Virus Passage NO.	Infectivity titer in Walvax-2 cells (log $CCID_{50}$/ml)[a]	Infectivity titer in MRC-5 cells (log $CCID_{50}$/ml) [a]	P^b
23(original)	7.0	7.0	
24	7.32 ± 0.28	6.27 ± 0.27	<0.05
25	7.47 ± 0.09	7.01 ± 0.23	>0.05
26	7.50 ±0.17	7.35 ± 0.14	>0.05
27	7.62 ± 0.06	7.18 ± 0.38	>0.05
28	7.97 ± 0.09	7.50 ± 0.23	>0.05
29	8.21 ± 0.29	7.54 ± 0.24	<0.05
30	7.81 ± 0.17	7.35 ± 0.14	<0.05
31	7.65 ± 0.14	7.36 ± 0.34	>0.05

[a] ±SD.
[b] Significance of difference (P value) determined by 2-tailed t-test

The sensitivity to rabies virus of Walvax-2 has important implications for China. Human diploid cell rabies vaccine, which is free of complications but is highly immunogenic,[20] is considered to be the gold standard for rabies vaccine.[16] According to the report by the WHO, there are roughly 55000 human deaths caused by rabies annually.[21] Following India, China ranks in second place for the highest number of human cases in the world.[22] However, there is no such gold standard rabies vaccine on the Chinese market, where the disease burden is remarkably high. Possible reasons are as follows: the vaccine, regarded as liquid gold by the general public, represents a financial burden and hence has lower usage in developing countries. To minimize costs as well as make it affordable for Indians, the Serum Institute of India indigenously developed Ravivax (Pitman-Moore strain, MRC-5), decreasing the cost for the vaccine dramatically (from US $40 dropped to $7).[20] This is also one of the motivations for this study, to develop a totally new HDCS that could be used as a culture medium in manufacturing viral vaccines in China. Recently, a document from the Chinese pharmacopeia commission indicates that the current 2 kinds of cell substrate rabies vaccine presently on the international market, PVRV and PHK, may not be included in the updated Chinese pharmacopeia (2015).[23] The explanations for the removed vaccines are that they will no longer be manufactured or will be replaced by others. Human diploid cell rabies vaccine is gaining increased national attention in China. We tested the susceptibility of 2 rabies strains concurrently in our study, CTN-V and PV. We found that the titers of CTN-1V strain are higher than those of PV strain, independent of the effects of adaptation by the cell substrates. Both strains have been used for production in China over the years, and the safety and immunogenicity of the vaccines have been verified.[24] Consequently, considering the impact on future production, CTN-1V will be the preferred rabies strain for research and production in the future. Although we have reported results of the susceptibility of 3 viruses in this study, we prepared rabies vaccines using the preferred CTN-1V-HDC (Walvax-2) viral strain (15^{th} passage) and determined the potency to be higher than 6.0IU/dose, which was significantly greater than the WHO-recommended standard of 2.5 IU/ dose[16] (described in detail in another study[25]). The efficacies of the diploid rabies vaccines on animal tests would further confirm the use of the Walvax-2 cells in human viral vaccine production.

There are several limitations to this study. More work is required regarding the adaptation of a greater variety of viruses on the Walvax-2 cells and the possibility for the industrial development of appropriate vaccines. In recent years, a large number of research papers have reported the application of Gene chip technology and high-throughput sequencing PCR technology for detecting potential contaminations of viruses. Thus, further screening of human-derived viruses needs to be conducted, especially for tumorigenic DNA viruses, retroviruses et al. Currently, we have been conducting tests for the human

herpes simplex virus 6 and 7, and further screening will be carried out soon.

In conclusion, we have successfully established and characterized a new human diploid cell line designated Walvax-2, and evaluated its susceptibility to 3 kinds of viral vaccine strains. The Walvax-2 cells are equally susceptible, and in some cases superior to, the MRC-5 line for the cultivation of viruses. Results from this study suggest that the Walvax-2 cell banks are a promising cell substrate and could potentially be used for the manufacturing of HDCVs.

Materials and Methods

Cells and viruses

HeLa, MRC-5, L929, MDCK, VeroandSp2/0-Ag14 cells were obtained from the America Center for Type Culture Collection (CCL-2, CCL-171, CCL-1, CCL-34, CCL-81, andCRL-158). Rabies fixed virus CTN-1Vstrain[26,27] and Pasteur strain were provided by the National Institute for Food and Drug Control (NIFDC, P.R. China) and Jiangsu Simcere Vaxtec Bio-Pharmaceutical Co., Ltd, respectively. The Varicella zoster virus Oka strain[28] was provided by American Type Culture Collection (ATCC). The hepatitis A virus (HAV) YN5 strain was isolated in 2003 from a hepatitis A patient in Kunming, China.[29]

Laboratory animals

Kunming mice, guinea pigs and rabbits were supplied by Guangdong Medical Laboratory Animal Center (Guangdong Province, P.R. China). Specific-pathogen-free (SPF) eggs were purchased from Beijing Merial Vital Laboratory Animal Technology Co., Ltd. Nude mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd.

The care and use of laboratory animals were approved by the Animal Care and Use Committee of Yunnan Walvax Biotechnology Co., Ltd. All animals were treated humanely and euthanized by cervical dislocation at the end of the experimental period.

Culture medium and other reagents

The growth medium (GM) for all cells was Eagle's minimum essential medium (M0769; Sigma) supplemented with 10 percent calf serum, 2 percent 2 M Glutamine (G8540; Sigma) and 2 percent 0.83 M $NaHCO_3$. The cryopreservation solution was GM added with 10 percent DMSO (D8418, sigma). Inorganic salts were purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai, P.R. China).

Source tissue material

The fetal material was provided by the Department of Obstetrics and Gynecology of Yunnan Hospital, with legal and ethical agreements from the donator. Before the study, we made strict and comprehensive inclusion criteria in order to guarantee a high quality cell strain: 1) gestational age 2 to 4 months; 2) induction of labor with the water bag method; 3) the parents career should not involve contact with chemicals and radiation; 4) both parents are in good health without neoplastic and genetic diseases, and with no history of human tissue or organ transplantation in the families traced for 3 generations; and 5) no infectious diseases. The tissues from the freshly aborted fetuses were immediately sent to the laboratory for the preparation of the cells.

Preparation of primary cell stock and cell banks

The preparations of the primary cell stock and serial propagation of cells were carried out according to the methods of Jacobs in 1970[8] and Hayflick in 1961.[30] The selected primary Walvax-2 cell seed was used for passaging, with the inoculation concentration of 5×10^5 cells /ml. Subsequent subculture was conducted at a 1:2 split ratio immediately subsequent to the formation of a dense cell monolayer. When the cells reached the 6^{th}, 14^{th}, and 29^{th} cell doublings, cultures were harvested and frozen to form a pre-master cell bank (PCB), master cell bank (MCB) and working cell bank (WCB).

Cryopreservation stability and recovery viability

Cryopreservation was performed 6 times for Walvax-2 cells with the cell lines designated as P6, P14, P20, P28, P38 and P48. These particular cell lines were chosen on the grounds that they represented the corresponding cell banks of PCB, MCB, WCB, the major working passages, and the entire lifecycle of the Walvax-2 cells. The cells were centrifuged and re-suspended in cryopreservation solution, and the cell concentration was adjusted to $6\sim10\times10^6$ cells /ml. The suspension was dispensed in 1.0 ml to 2.0 ml Cryogenic Vials (#430659，Corning). Following the manufacturer's instructions for the use of programmed cooling boxes (Nalgene Mr. Frosty，Thermo Fisher), the cryogenic vials were then sealed and put into the boxes at −70C overnight. Then cryogenic vials were placed directly into liquid nitrogen for long term cryopreservation. The frozen cells were recovered according to the procedures given by Jacobs in 1970[8] and Hayflick in 1961.[30]

Cells reconstituted from the frozen state were taken immediately for the calculation of population doubling times by cell counting. The three-tiered banks were propagated serially for doubling time assessments. The experiments were repeated 8 times, and the doubling times were compared with that of cells that had not been frozen.

Cell identification

The cell identification was evaluated by a 2-step procedure: Firstly isoenzyme analysis was performed using lactate dehydrogenase (LD) and Glucose 6 phosphate dehydrogenase (G6PD) as indicators to confirm Walvax-2 cell banks were human-derived cells. Then, Short Tandem Repeat (STR) analysis was conducted using MRC-5 as a parallel control by 3 qualified laboratories: China Center for Type Culture Collection (CCTCC), National Institutes for Food and Drug Control (NIFDC), and Law School of Kunming Medical University to assure that the cells were derived from the tissue of a specific human individual and different from any other established human diploid cell lines.

Chromosomal characterization

Chromosome examinations were conducted for every 10 passages by counting percentages for 5 types of chromosomal aberrations, including structural abnormalities, aneuploidy, polyploidy, hyperploidy and breaks or gaps. Chromosome specimen slides were obtained using the method of Coburn and Leykauf,[31] and then stained with Giemsa. Giemsa-banded karyotypes were recorded by Applied Imaging Software—Karyotyping 3.0 (England).

Microbial agents tests

The presence of bacterium, fungus and mycoplasmas for Walvax-2 cells were tested according to the requirements of ATCC and WHO.[18,19] Bacillus subtilis (CMCC(B)63501), Clostridium sporogenes (CMCC(B)64941) and Candida albicans (CMCC(F)98001) were used as positive controls for the tests of bacteria and fungi. A total of 19 cell passages were tested for sterility. The cell samples were tested under different temperatures for 2 weeks to confirm that no bacterial and fungal contamination was present. The mycoplasma test was conducted as per requirement in Volume III of Chinese Pharmacopeia, using the culture method and DNA staining technique, and B6yh4 cells were used as a positive control. All positive controls were provided by the National Institute for Food and Drug Control (NIFDC, P.R. China).

Exogenous virus agents tests

Tests for adventitious viral agents of Walvax-2 cells were conducted as per requirements for Preparation and Control of Animal Cell Substrates Used for Production and Testing of Biologics in Volume III of Chinese Pharmacopeia, including testing for general adventitious viral agents (non-specific virus) and specific adventitious viral agents.

General adventitious agents included embryonated egg inoculation by the yolk sac, allantoic cavity; i.c. and i.p. inoculation of adult and suckling mice, i.p. inoculation of guinea pigs; monolayer cell culture using MRC-5, and vero cells for detection of various human viruses.

Tests for specific adventitious agents consisted of human derived virus, bovine derived virus and porcine virus. For the human derived virus test, 6 viruses including HBV, HCV, HIV, Human cytomegalovirus, human nasopharyngeal virus and human parvovirus B19, were carried out based on per testing kit, using ELISA and PCR methods, respectively. For the bovine derived virus test, 3 methods were used: (i) the microscopic CPE observation method; (ii) different cell culture conditions for hemadsorption activity, and (iii) fluorescence quantitative RT-PCR method (bovine adenovirus, bovine parvovirus, bovine diarrhea virus, bovine influenza virus, bovine parainfluenza virus, rabies virus and retrovirus). The possible swine viral contamination was examined using RT-PCR and PCR methods for classical swine fever virus, Japanese encephalitis virus and Pseudorabies virus.

Retrovirus test

The retrovirus test was performed according to procedures described in " Reverse transcriptase activity assay in attenuated live vaccine"(Yan Kong et al)[32] and "Development of an improved product enhanced reverse transcriptase assay" (Audrey Chang, et al).[33] More specifically, the testing methods included product-enhanced reverse transcriptase (PERT) assay, infection test and direct observation by transmission electron microscopy. The mouse bone marrow cell line Sp2/0-Ag14 served as a positive control while MRC-5 cells were used for the system control.

Tumorigenicity test

To ascertain whether the cells had any neoplastic properties, P10, P20, P28, P38 and P48 Walvax-2 cells were implanted into 10 nude mice aged 4–6 weeks, in the thigh of the right hind leg of each mouse according to the requirements of Chinese Pharmacopeia. MRC-5 cells served as the negative control, and Hela cells served as the positive control. All animals were examined after 21 and 84 d following the inoculation of the cells. Animals not surviving the full period were examined post mortem, and observations for neoplastic growth were conducted for all tested animals.

Susceptibility to viruses test

Particular cell generations that would potentially be used for producing viral vaccines, were used to determine susceptibility to viruses after 25 to 30 cell doublings. Three kinds of viral vaccine strains (rabies, Varicella zoster and Hepatitis A) were used for the assays. To determine the susceptibility of Walvax-2 cells relative to MRC-5 cells, concurrent titrations were compared for the same cell doublings.

Rabies Virus

Virus propagation

The CTN-1V and Pasteur strains were propagated in Walvax-2 and MRC-5 cells by the method of Wiktor et al.[34] The virus maintenance medium was consistent with GM with the addition of 2% (v/v) fetal calf serum. A multiplicity of infection (MOI) of 0.01 was used. The viruses were incubated at 34–35°C.

Virus titration

The rabies virus was titrated using a modified test as described by Smith et al.[35] Virus titer was expressed in fluorescent focus units (FFU)/ml. Briefly, a monolayer of BSR cells in 96-well plates was incubated with serial fold5- virus dilutions at 37°C in a 5% CO_2 humidified incubator for 24 h. The cells were then fixed with 80% cold acetone at -20°C for 30 minutes, and then stained with the Rabies DFA Reagent (5100; Millipore). The plates were examined by fluorescence microscopy (Olympus Corp., Tokyo, Japan), and the numbers of fluorescent foci presented in the wells were recorded. The highest dilutions with fluorescent foci less than 30 were defined as endpoints, and virus titers were calculated by the following formula: virus titer (FFU/ml) = (the mean foci number in the endpoint wells × 5 + the mean foci number in the wells with lower dilutions next to the

endpoint well) ÷2 × the dilution factor of the lower dilutions ÷ the volume of virus dilution inoculated into each well.

Varicella Zoster Virus (VZV)

Virus propagation

The Oka strain at passage 31 was inoculated into Walvax-2 and MRC-5 cells and grown into a confluent monolayer at an MOI of 0.01.[36] Infected cells were incubated at 36 °C for 48–52 hrs till the cytopathogenic effect (CPE) was estimated to be approximately 75% to 100%. The cells were then trypsinized and resuspended in cryopreservation solution and stored at -196°C. The virus was serially propagated 8 times as described above for Walvax-2 and MRC-5 cells.

Virus titration

A plaque assay[37,38] was used and virus titer was expressed in plaque forming units (PFU)/ml. When Walvax-2 and MRC-5 cells in 6-well plates grew to a near confluent monolayer, the old medium was poured off and the monolayer was infected with cell-associated virus in fresh medium (with 2% fetal calf serum and 1% penicillin-streptomycin). Infections were allowed to proceed for 8–9 days, at which point the first signs of CPE was visible, the cells were stained and plaques counted.

Hepatitis A Virus

Virus propagation

According to the method of Wang et al,[39] the HAV YN5 strain was propagated in Walvax-2 cells and MRC-5. Briefly, Walvax-2 cells were trypsinized and inoculated with HAV at a MOI of 0.01 and stirred gently with a magnetic stirrer for 2 h at 37°C. The cells were then seeded in T225 flasks filled with GM at 37°C for 3–4 d until a confluent monolayer was formed. The GM was replaced by virus maintenance medium, consisting of MEM supplemented with 2% (v/v) fetal calf serum, 0.35% (m/v) $NaHCO_3$, 2% (v/v) and 2 M Glutamine; Cells were incubated at 35°C for 25 d Afterwards the cells were harvested and stored at −80°C.

Virus titration

An enzyme-linked immunosorbent assay (ELISA) was used to determine the virus infectivity titer of HAV.[40] The monolayers of Walvax-2 and MRC-5 were inoculated with serial fold5- cell-associated virus dilutions and incubated at 37°C for 1 h. Each dilution was assayed in quadruplicate. Then the inoculums were removed and replaced with a 1 ml nutrient MEM overlay containing 2 % fetal calf serum and incubated at 35°C for 25 d. The infected cells were harvested and sonicated. The presence of HAV-Ag was tested by ELISA. The $CCID_{50}$ value was calculated by a modified Reed-Muench's method.[41]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ORIGINAL ARTICLE

Effect of thimerosal, methylmercury, and mercuric chloride in Jurkat T Cell Line

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ABSTRACT

Mercury is a ubiquitous environmental toxicant that causes a wide range of adverse health effects in humans. Three forms of mercury exist: elemental, inorganic and organic. Each of them has its own profile of toxicity. The aim of the present study was to determine the effect of thimerosal, a topical antiseptic and preservative in vaccines routinely given to children, methyl mercury, and mercuric chloride on cellular viability measured by MTT in Jurkat T cells, a human T leukemia cell line. The treatment of Jurkat T cells with thimerosal caused a significant decrease in cellular viability at 1 μM (25%, $p<0.05$; IC50: 10 μM). Methyl mercury exhibited a significant decrease in cellular viability at 50 μM (33%, $p<0.01$; IC50: 65 μM). Mercuric chloride ($HgCl_2$) did not show any significant change in cellular survival. Our findings showed that contrary to thimerosal and methyl mercury, mercuric chloride did not modify Jurkat T cell viability.

KEY WORDS: Cell Survival/drug effects; organic mercury compounds; mitochondrial membranes/drug effects; MTT; T-Lymphocytes/drug effects; Cell Death/drug effects

Introduction

Mercury, one of the most widely diffused and hazardous organ-specific environmental contaminants, exists in a wide variety of physical and chemical states, each with unique characteristics of target organ specificity (Aleo *et al.*, 2002). Mercury occurs in three forms: the elemental or metallic form, inorganic salts, and organic compounds. The toxicity of mercury is complex and depends on the form of mercury, route of entry, dosage, and age at exposure (Clarkson, 1997). The organic form of mercury, mainly methyl mercury, is known to be more toxic than the inorganic form (Shenker *et al.*, 1992). Chronic exposure to low levels of methyl mercury can modulate T- and B-cell functions (cytokine production, cell growth, and proliferation) and different cellular processes leading to apoptotic cell death (Makani *et al.*, 2002; Shenker *et al.*, 1992). Ethyl mercury is an organic mercury compound, and in the form of thimerosal has been used as a topical antiseptic and as a preservative in vaccines routinely given to children, including diphtheria-tetanus-acellular pertussis (DTP), hepatitis B, and some Haemophilus influenzae type B (Goldman & Shannon, 2001; Halsey, 1999; Pichichero *et al.*, 2002). Thimerosal (as sodium ethylmercuric thiosalicylate) contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. The normal dose of a pediatric vaccine contains about 12.5–25 μg of mercury per 0.5 ml. (No authors listed, AAP, 1999). Massive overdoses from inappropriate use of products containing thimerosal have resulted in toxic effects (Axton, 1972; Fagan *et al.*, 1977; Lowell *et al.*, 1996; Matheson *et al.*, 1980; Pelassy *et al.*, 1994; Pfab *et al.*, 1996). Inorganic mercury (I-Hg) compounds (as mercury salts) are also a significant source of mercury overexposure in both adults and children in some countries (Clarkson, 2002). Inorganic mercury compounds have been used for many years in numerous products, including various medications, germicidal soaps, teething powders, and skin lightening cream containing mercury (Clarkson, 2002). Many of these mercury-based products are still in use today (Geier *et al.*, 2010; Goldman & Shannon, 2001). In the present study, we evaluated the effect of thimerosal, methyl mercury and mercuric chloride ($HgCl_2$) on the viability of Jurkat T cells

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by (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

Methods

Cell culture

Human T leukemic Jurkat cells were purchased from American Type Culture Center (ATCC no. TIB-152) (Rockville, MD, USA) and maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum, 1% glutamine, and 1% antibiotics/antimicotics (pen./strep.). The cells were grown at 37 °C in a humidified atmosphere of 5% CO_2.

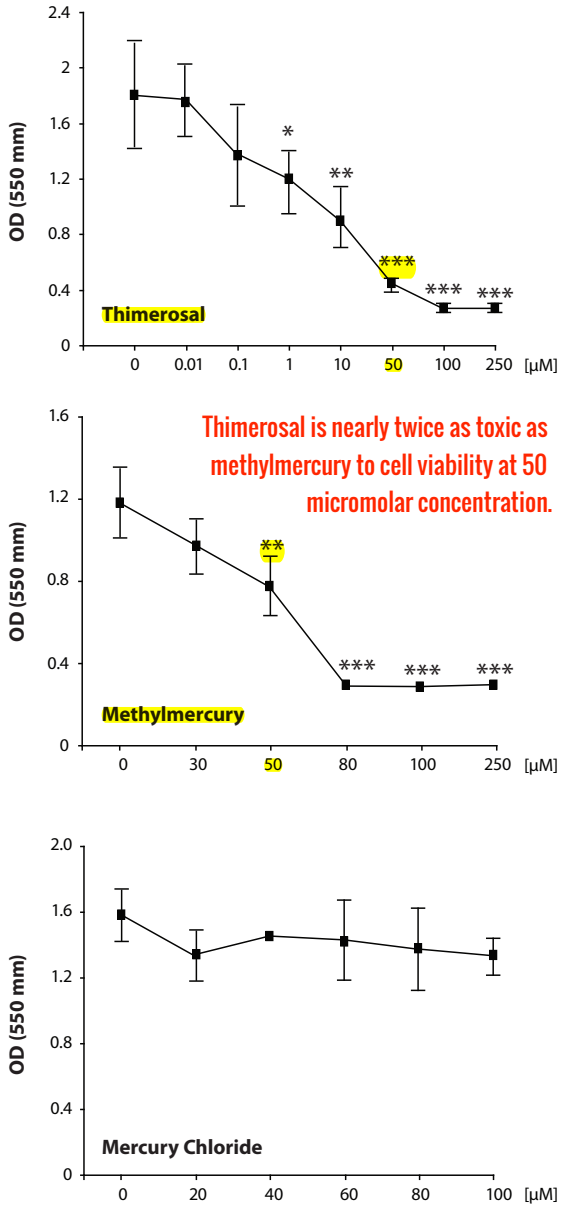

Figure 1. Viability of Jurkat cells determined by MTT-assay after exposure to thimerosal, methylmercury and mercury chloride. The data are expressed as mean ± SEM. Asterisks indicate significant differences from control cells without treatment (n=3, *p<0.05;**p<0.01;***p<0.001). Note, the x-axis is not a linear scale.

Mercury and its chemical compounds

Thimerosal (EtHg), methyl mercury (MeHg) and mercuric chloride [(mercuric (II) chloride ($HgCl_2$) also termed 'mercury two')] were purchased from Sigma. PBS and water were used to dilute mercuric chloride ($HgCl_2$) and thimerosal, respectively. Cells treated only with vehicles were used as controls.

Cytotoxicity assay (MTT)

The principle behind this technique depends on the capacity of living cells to reduce tetrazolium salt [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to a formazan crystal in their metabolizing mitochondria. The number of 1×10^4 cells/well Jurkat T cells (ATCC no. TIB-152) were seeded into 96 well plates and exposed to thimerosal, methyl mercury, and mercuric chloride ($HgCl_2$) at concentrations of thimerosal (0.01-0.1-1-10-50-100-250 µM), methyl mercury (30-50-80-100-250 µM), and mercuric chloride ($HgCl_2$ (20-40-60-80-100 µM). The plates were incubated at 37 °C in a humidified atmosphere containing 5% CO_2. After 48 hours, the medium was discarded and 20 µl/well of MTT solution (5 mg/ml) was added and incubated for 3 hours at 37 °C (5% CO_2). Finally, 20µl/well of isopropanol was added and the color intensity was read spectrophotometrically at 590 nm using a Microplate Reader (Bio-Rad Model 550, California, USA).

Statistical analysis

The ANOVA one-way test was used to determine statistical significance. A p-value of less than 0.05 was considered to be statistically significant.

Results

We exposed Jurkat T cells to thimerosal, methyl mercury and mercuric chloride in the concentrations reported in Figure 1 for 48 hours. Upon exposure to thimerosal, methyl mercury and mercuric chloride ($HgCl_2$), the viability of cells was measured with MTT assay. As shown in Figure 1, the treatment of Jurkat T cells with thimerosal caused a significant decrease in cellular viability at 1µM (25%, p<0.05; IC50: 10 µM). Methyl mercury exhibited a significant decrease in cellular viability at 50 µM (33%, p<0.01; IC50: 65 µM). Finally, at all concentrations analyzed, mercuric chloride ($HgCl_2$), did not show any significant change in cellular survival (Figure 1).

Discussion

Mercury is ubiquitous in the environment and exposure occurs from the use of mercury-containing dental

amalgam, vaccine preservatives, and ingestion of fish containing high levels of methyl mercury (Counter & Buchanan, 2004; Krantz & Dorevitch, 2004; Ratcliffe *et al.*, 1996). In the literature, however, there are few data showing the effect of organic and inorganic mercury on cell viability. Considerable concern has been expressed recently over the cumulative dose of ethyl mercury given to children through routine immunizations (Geier *et al.*, 2010; Hornig *et al.*, 2004). The source of mercury in vaccines is the antimicrobial preservative thimerosal, containing 49.9% mercury by weight. Our findings demonstrate that thimerosal at the concentration usually found in vaccines, affects significantly cellular viability. A recent paper showed that after thimerosal exposure at the same concentration as tested in the present study, a human glioblastoma cell line displayed a similar effect (James *et al.*, 2005). On the other hand, the form of mercury that accumulates in the food chain is methyl mercury. Some people may be exposed to higher levels of mercury in the form of methyl mercury if they have a diet high in fish, shellfish, or marine mammals that come from mercury-contaminated waters. Colombo *et al.* (2004) determined the sensitivity of Jurkat T cells to up to 1μM of methyl mercury after 48 hours of exposure (Colombo *et al.*, 2004). They found that cellular viability determined by MTT assay showed no toxic effects during the first 48 hours, yet exposure for up to 72 hours caused a significant decrease in cellular viability at the higher dose of mercury (1 μM) (Pelassy *et al.*, 1994). Our findings are in accordance with these data and show that organic mercury, such as methyl mercury and thimerosal, are more cytotoxic than inorganic mercury (as $HgCl_2$). Experiments are in progress to ascertain the underlying mechanisms of ethyl mercury induced cell death. It has been proposed to induce depletion of thiol reserves (*e.g.*: GSH) and ROS damage, activating death-signaling pathways (Makani *et al.*, 2002). A previous study showed that thimerosal was able to induce apoptosis and G2/M phase in human leukemia U937 cells (Woo *et al.*, 2006). Finally, according to other authors (Bahia *et al.*, 1999; Ogura *et al.*, 1996), methyl mercury showed a higher toxicity compared to mercuric chloride ($HgCl_2$). Recently, mercuric chloride ($HgCl_2$) was reported to affect the differentiative capacity instead of proliferation in neural stem cells (Cedrola *et al.*, 2003). Further studies will attempt to assess the possible effect of thimerosal as preservative in vaccines. Our data showed an effect of organic mercury on the viability of Jurkat T cells, suggesting a possible toxic effect of these compounds of mercury *in vivo*.

Conflict of interest statement

We have no conflicts of interest connected with this work.

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Low-dose mercury exposure in early life: relevance of thimerosal to fetuses, newborns and infants.

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Author information

Abstract

This review explores the different aspects of constitutional factors in early life that modulate toxicokinetics and toxicodynamics of low-dose mercury resulting from acute ethylmercury (etHg) exposure in Thimerosal-containing vaccines (TCV). Major databases were searched for human and experimental studies that addressed issues related to early life exposure to TCV. It can be concluded that: a) mercury load in fetuses, neonates, and infants resulting from TCVs remains in blood of neonates and infants at sufficient concentration and for enough time to penetrate the brain and to exert a neurologic impact and a probable influence on neurodevelopment of susceptible infants; b) etHg metabolism related to neurodevelopmental delays has been demonstrated experimentally and observed in population studies; c) unlike chronic Hg exposure during pregnancy, neurodevelopmental effects caused by acute (repeated/cumulative) early life exposure to TCV-etHg remain unrecognized; and d) the uncertainty surrounding low-dose toxicity of etHg is challenging but recent evidence indicates that avoiding cumulative insults by alkyl-mercury forms (which include Thimerosal) is warranted. It is important to a) maintain trust in vaccines while reinforcing current public health policies to abate mercury exposure in infancy; b) generally support WHO policies that recommend vaccination to prevent and control existing and impending infectious diseases; and c) not confuse the 'need' to use a specific 'product' (TCV) by accepting as 'innocuous' (or without consequences) the presence of a proven 'toxic alkyl-mercury' (etHg) at levels that have not been proven to be toxicologically safe.

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Thimerosal Induces DNA Breaks, Caspase-3 Activation, Membrane Damage, and Cell Death in Cultured Human Neurons and Fibroblasts

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Abstract

Thimerosal is an organic mercurial compound used as a preservative in biomedical preparations. Little is known about the reactions of human neuronal and skin cells to its micro- and nanomo-lar concentrations, which can occur after using thimerosal-containing products. A useful combination of fluorescent techniques for the assessment of thimerosal toxicity is introduced. Short-term thimerosal toxicity was investigated in cultured human cerebral cortical neurons and in normal human fibroblasts. Cells were incubated with 125-nM to 250-μM concentrations of thimer-osal for 45 min to 24 h. A 4′, 6-diamidino-2-phenylindole dihy-drochloride (DAPI) dye exclusion test was used to identify non-viable cells and terminal transferase-based nick-end labeling (TUNEL) to label DNA damage. Detection of active caspase-3 was performed in live cell cultures using a cell-permeable fluorescent caspase inhibitor. The morphology of fluorescently labeled nuclei was analyzed. After 6 h of incubation, the thimerosal toxicity was observed at 2 μM based on the manual detection of the fluorescent attached cells and at a 1-μM level with the more sensitive GENios Plus Multi-Detection Microplate Reader with Enhanced Fluorescence. The lower limit did not change after 24 h of incubation. Cortical neurons demonstrated higher sensitivity to thimerosal compared to fibroblasts. The first sign of toxicity was an increase in membrane permeability to DAPI after 2 h of incubation with 250 μM thimerosal. A 6-h incubation resulted in failure to exclude DAPI, generation of DNA breaks, caspase-3 activation, and development of morphological signs of apoptosis. We demonstrate that thimerosal in micromolar concentrations rapidly induce membrane and DNA damage and initiate caspase-3– dependent apoptosis in human neurons and fibroblasts. We conclude that a proposed combination of fluorescent techniques can be useful in analyzing the toxicity of thimerosal.

Keywords

thimerosal; active caspase-3; apoptosis; toxicity; neurons; fibroblasts; DNA breaks; membrane damage; DAPI

Thimerosal (sodium ethylmercury-thiosalicylate) is an antibacterial and antifungal mercurial compound used as a preservative in biological products and vaccines, in concentrations ranging from 0.003 to 0.01% (30 –100 μg/ml) (Ball *et al*., 2001). Thimerosal contains 49.6 % mercury by weight and releases ethylmercury as a metabolite. In the body, ethylmer-cury can be converted to inorganic mercury, which then preferentially accumulates in the kidneys and brain (Blair *et al*., 1975). Inorganic mercury is known to induce membrane and DNA damage (Ferrat *et al*., 2002;Ben-Ozer *et al*., 2000), and in cell culture conditions it was shown to be mutagenic and generate DNA breaks in concentrations below 500 nM (Schurz *et al*., 2000). Ethylmercury

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can significantly increase the concentration of inorganic mercury in many organs (Magos *et al*., 1985). After *in vivo* administration, ethylmercury passes through cellular membranes and concentrates in cells in vital organs, including the brain, where it releases inorganic mercury, raising its concentrations higher than equimolar doses of its close and highly toxic relative methylmercury (Magos *et al*., 1985).

However, little is known about acute reactions of various types of human cells following short-time exposure to thimer-osal in micro- and nanomolar concentrations.

In this paper we used a convenient and easily reproducible combination of fluorescent techniques analyzing various markers of DNA and membrane damage, and investigated the toxicity of micromolar and nanomolar concentrations of thimerosal (125 nM–250 μM) occurring in the first 24 h of exposure in cultures of human cortical neuronal cells and in human fibroblasts.

We found that thimerosal in micromolar concentrations rapidly decreased cellular viability. Within several h after thimer-osal administration, cells lost their capability to exclude the fluorescent dye 4′,6-diamidino-2-phenylindole dihydrochlo-ride (DAPI) and developed multiple DNA breaks accompanied by caspase-3 activation and apoptotic morphology. Neuronal cell cultures demonstrated a higher sensitivity to thimerosal compared with fibroblasts.

MATERIALS AND METHODS

Cell cultures

HCN-1A Human cerebral cortical neurons (CRL-10442) were purchased from American Type Culture Collection (ATCC, Manassas, VA) and were cultured according to ATCC recommendations. The line was derived from cortical tissue removed from a patient undergoing hemispherec-tomy for intractable seizures. As recommended by ATCC, the cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) with 4 mM L-glutamine, modified to contain 4.5g/l glucose and 1.5g/l sodium bicarbonate, supplemented with 10% fetal bovine serum, and the pH adjusted to 7.35 prior to filtration.

Normal neonatal human foreskin HCA 2 fibroblasts (PD32) were obtained from the laboratory of Dr. Olivia Smith-Pereira, Ph.D. The cells were grown in DMEM supplemented with 10% fetal bovine serum medium, and the pH was adjusted to 7.4 prior to filtration. For the experiments, all cells were subcultured in 24-well cell culture plates (Fisher, Pittsburgh, PA). All experiments were reproduced in triplicates. Each of the parallel series yielded identical results.

Thimerosal

Thimerosal (minimum 97% HPLC), SigmaUltra (Sigma, St. Louis, MO) was added to cell cultures in 30 μl of double-distilled water to final concentrations of 250 μM, 50 μM, 10 μM, 2 μM, 1 μM, 500 nM, 250 nM, and 125 nM. Concentrations of 1 μM–125 nM were used with neuronal cells only. Control cell cultures received 30 μl of water without thimerosal.

Dye exclusion test using DAPI

DAPI is a nonintercalating DNA-specific dye with an emission maximum in the blue spectrum (Shapiro, 1985). It is widely used for counterstaining cellular nuclei in fixed sections and has been demonstrated to be useful for the detection of nonviable cells with compromised membranes in live cell cultures (Boutonnat *et al*., 1999;McCarthy and Hale, 1988).

The DAPI exclusion test was performed as described (Boutonnat *et al*., 1999). Briefly, cells were incubated with DAPI (Sigma, St. Louis, MO) diluted in a cell culture medium at a final concentration of 100 ng/ml for 30 min at 20°C (Boutonnat *et al*., 1999). A fluorescent signal was monitored and representative images were taken at 45 min and 2, 4, 6, and 24 h after the addition of thimerosal, The DAPI incubation started 30 min before each observation was made (at 15 min, 90 min, etc). Images were acquired using an Olympus IX-70 fluorescent microscope equipped with a MicroMax digital camera system (Princeton Instruments, Inc., Trenton, NJ) containing an RTE/CCD-1300-Y/HS array cooled by a Peltier device. Image acquisition was performed using the *MetaMorph* 4.1 program (Advanced Scientific, Inc., Meraux, LA). The micrographs were taken at central parts of the wells, where cellular density was most uniform.

Terminal transferase-based nick-end labeling (TUNEL)

Cells were fixed in ice cold methanol, and TUNEL staining for detection of DNA breaks was performed using the ApoTaq Fluorescein and ApoTaq Rhodamine kits for indirect immunofluorescence (Serologicals, Gaithersburg, MD), employing the standard technique recommended by the manufacturer. Following washing, the cells were counterstained with the DNA binding dye DAPI (1 μg/ml) for visualization of all cellular nuclei and were mounted in Vectashield (Vector Laboratories, Burlingame, CA) for observation by fluorescence microscopy.

Caspase-3 detection

Detection of active caspase-3 in live cell cultures was performed using an APO LOGIX™ carboxyfluorescein (FAM) caspase detection kit (Cell Technology, Minneapolis, MN). The kit detects active caspases in living cells through the use of a FAM-labeled DEVD fluoromethyl ketone (FMK) caspase inhibitor, which irreversibly binds to active caspase-3 (Amstad *et al*., 2000;Bedner *et al*., 2000;Smolewski *et al*., 2001). The inhibitor is cell permeable and noncytotoxic. With lesser affinity, FAM-DEVD-FMK binds to the other caspases participating in apoptosis: caspase-8 >caspase-7 >caspase-10 >caspase-6 in the order of decreasing binding affinity (Carcia-Calvo *et al*., 1998).

The kit was used as recommended by the manufacturer. Briefly, 10 μl of 30X Working Dilution FAM-Peptide-FMK was added to 300 μl of cell culture medium/per well, directly in 24-well cell culture plates after 5 h or 23 h of incubation with thimerosal. Cells were incubated for 1 h at 37°C under 5% CO_2, protected from light. Then the medium was carefully removed, and the cells were washed twice with 2 ml/per well of 1X Working Dilution Wash Buffer. The fluorescent signal was observed under an Olympus IX-70 fluores-cence microscope equipped with a MicroMax digital camera system (Princeton Instruments, Inc.) containing an RTE/CCD-1300-Y/HS array cooled by a Peltier device. Caspase-positive cells appeared fluorescing green. Representative images were taken at 6 h and 24 h after the addition of thimerosal. Image acquisition was performed using the *MetaMorph* 4.1 program (Advanced Scientific, Inc.). Positive controls included cultures of cortical neurons treated with 0.5 μM staurosporin to induce caspase-3 activation. In several series of experiments, we added DAPI to cell cultures to the concentration of 100 ng/ml for 30 min immediately after 1 h of incubation with the FAM-Peptide-FMK solution. This made the co-localization of active caspase-3 and DAPI signals possible.

Fluorescence measurements using a microplate reader

In a separate set of experiments, we measured both active caspase-3 and DAPI signals in co-localization experiments using a GENios Plus Multi-Detection Microplate Reader with Enhanced Fluorescence (Tecan Inc., Research Triangle Park, NC). Neuronal cells were incubated with 1–250 μM concentrations of thimerosal for 6 h and processed as described for simultaneous DAPI and active caspase-3 detection. Both FITC and DAPI fluorescence were

measured directly in 24-well plates using a Chroma Technology bandpass filter set: FITC excitation D490/40, emission 520/10; DAPI excitation D360/40, emission 460/20. The reactions were repeated twice and yielded the same dose-dependent increase in thimerosal toxicity. Background fluorescence was subtracted from the experimental series, and the results were represented as graphs of average values using Microsoft Excel.

RESULTS

Thimerosal-Induced Changes in Membrane Permeability and Cell Viability

Changes in cell viability rapidly occurred after administration of thimerosal in all cell cultures and were detected by the loss of ability to exclude the fluorescent dye DAPI. DAPI is classified as a semipermeant dye, which requires a relatively short (30-min) exposure time of cell cultures to the dye prior to the signal observation in a DAPI exclusion test (Boutonnat *et al*., 1999). Under these conditions, the dye has been shown to be useful for the detection of nonviable cells and can be utilized as a selective marker of membrane integrity. Indeed, it is a less toxic alternative to propidium iodide (PI) (Boutonnat *et al*., 1999).

The results of the experiments show a dose- and time-dependent increase of membrane permeability to DAPI, first detected after 2 h of incubation with thimerosal and resulting in the penetration of the dye into the nuclei and DNA staining (Figs. 1 and 2). Figure 1 presents experiments performed on human cultured cortical neurons (HCN-1A) and shows that, after 2 h of incubation with thimerosal at a concentration of 250 μM, the DAPI penetrated through cellular membranes and stained the cellular nuclei. The inability to exclude the dye indicates the loss of cellular membrane integrity and cell death (Boutonnat *et al*., 1999;McCarthy and Hale, 1988). After 4 h of incubation, thimerosal-induced membrane permeability and DNA staining were observed at a concentration of 10 μM. After 6 h of incubation with thimerosal, changes in membrane permeability were detected at concentrations as low as 2 μM, based on the appearance of DAPI-stained cells attached to the bottom of the wells. In control cell cultures, which were treated with DAPI alone, only sporadic dead cells were detected, and their numbers stayed the same 2, 4, and 6 h after the addition of DAPI (Fig. 1). There was no change in cell membrane permeability for DAPI for up to 24 h if no thimerosal was added.

We performed direct counts of DAPI-positive cells for the initial quantitative assessment of our results. We counted all DAPI-positive cells in two ×40 fields of view for each of the thimerosal concentrations after 6 h of incubation. All counts were taken in central parts of the wells, where the cellular density was most uniform. The comparison with the average density of cells in these areas revealed that, at 2-μM thimer-osal, 11% were DAPI-positive; at 10-μM thimerosal, 58% were DAPI-positive; at 50-μM thimerosal, 61% of the cells were DAPI-positive; and at 250-μM thimerosal, 100% of the neurons had compromised cellular membranes. In controls, less than 1% of the cells were DAPI positive, due to cell death naturally occurring in the cell cultures.

No changes in membrane permeability and DAPI staining were observed with thimerosal concentrations lower than 2 μM at times of incubation up to 24 h.

Since dying cells disattach from the bottom shortly after death and float in the media, they cannot be counted. This explains the similar numbers of DAPI-positive cells counted after 10- and 50-μM thimerosal treatments, and it could have some affect on the sensitivity of the lower limit of toxicity measurements. To address this issue and to take into consideration all DAPI-stained cells, we used a fluorescent microplate reader, which detects the fluorescence of both attached and floating dead cells (see Fig. 3). Using a GENios Plus Microplate Reader, we detected the lower limit of thimerosal toxicity for neuronal cells after 6 h of incubation to be at 1-μM concentration of thimerosal.

Experiments with cultured human fibroblasts produced similar results, although, when compared with neuronal cells, the fibroblasts demonstrated a slightly lower sensitivity to thimer-osal toxicity by the DAPI exclusion test in terms of the number of DAPI-stained cells (Fig. 2).

Similar to neuronal cells, significant numbers of DAPI-stained nuclei were first observed after 2 h of incubation with thimerosal at 250 μM concentration in the fibroblast culture experiments (Fig. 2). After 4 h of incubation, nuclear staining was detected at 10-μM concentration of thimerosal. However, unlike the neuronal cells, the human fibroblasts did not show toxicity at 2-μM concentration of thimerosal after 6 h of incubation.

Detection of Thimerosal-Induced DNA Damage

We used TUNEL to detect DNA breaks generated in neurons and fibroblasts after 6 h of incubation with thimerosal. Following incubation, the cells were fixed, labeled by TUNEL, and counterstained by DAPI, which in these experiments was employed as a fluorescent DNA marker to visualize all cell nuclei in fixed cell cultures.

The results of these experiments are presented in Figure 4. The figure demonstrates that TUNEL-positive cells were detected in all cell cultures after 6 h of incubation, up to the concentration of 2 μM of thimerosal.

To determine if extending the time of incubation with thimerosal at concentrations below 2μM would result in the generation of DNA breaks, we extended the time of incubation to 24 h in a separate series of experiments. After 24 h, a TUNEL signal was detected in neuronal cells at 1-μM concentration of thimerosal (versus 2 μM at 6 h) (not shown). Incubation of neuronal cells for 24 h with concentrations of thimerosal below 1 μM (125, 250, and 500 nM) did not produce a TUNEL signal.

Detection of Apoptotic Morphology in Thimerosal-Treated Cells

We performed a morphological evaluation of the fixed and fluorescently stained cell cultures after thimerosal treatment for the purpose of identifying apoptotic cells. To identify apoptotic morphology, the cells were fixed and then stained by DAPI. In this experiment, DAPI was employed not as a vital dye, as in our previous study, but rather as a fluorescent histological nuclear stain. Although DAPI is an important marker used in live cell cultures to selectively label nonviable cells (Boutonnat *et al*., 1999;McCarthy and Hale, 1988), it is also frequently used in fixed cells to visualize nuclear morphology and apo-ptotic bodies. We used it for this purpose in these tests.

Apoptotic morphology was detected in thimerosal-treated cells. Figure 5 demonstrates that, after 6 h of incubation, both fibroblasts and neurons showed morphological signs of apo-ptosis, which included chromatin condensation on the nuclear membrane, the appearance of characteristic doughnut-shaped nuclei, different stages of apoptotic body formation, and freely positioned apoptotic bodies. After 6 h of incubation, apoptotic morphology was observed at concentrations as low as 2 μM of thimerosal (Fig. 5), whereas, at 24 h after incubation, similar apoptotic morphology was observed at concentrations as low as 1 μM.

To further confirm the apoptotic nature of cell death induced by thimerosal, we performed detection of active caspase-3, which is a sensitive and specific indicator of apoptosis.

Active Caspase-3 in Thimerosal-Treated Cells

Caspase-3 activation serves as a sensitive marker of ap-optosis, developing through caspase-3–dependent mechanisms, which constitutes one of the most frequent apoptotic pathways. We

employed visualization of active caspase-3 directly in living cells through the use of a FAM-labeled peptide caspase inhibitor (FAM-Peptide-FMK) (see Materials and Methods).

We detected caspase-3–positive neuronal cells after 6 h of incubation with thimerosal at concentrations ranging from 250 to 2 μM. The intensity of the signal was dose-dependent and much lower at the 2-μM concentration, compared to higher concentrations, probably due to an earlier stage of caspase-3 activation (Fig. 6).

Assessment of 200 cells per well randomly, using the fluo-rescent microscope, revealed that active caspase-3 was expressed in 20% of the cells at 2-μM thimerosal, 26% at 10-μM thimerosal, 83% at 50-μM thimerosal, and 97% of the neurons at 250-μM thimerosal concentration. In the controls, less than 1% of the cells was caspase-3–positive, due to cell death naturally occurring in the cell cultures.

At 2-μM thimerosal, the active caspase-3 signal was predominantly observed in the cytoplasm, which represents the early stage of its activation, whereas, at higher concentrations of thimerosal, the signal was detected in both the cytoplasm and the nuclei (Fig. 6). (Nuclear localization of active caspase-3 is characteristic for later stages of the apoptotic process.)

When we used a fluorescent microplate reader, which detects signals from the detached cells, we detected active caspase-3 activation at 1-μM concentration of thimerosal after 6-h incubation, probably due to the added contribution from floating dead cells (Fig. 3).

When we extended the incubation time with thimerosal from 6 to 24 h, detectable numbers of attached cells with active caspase-3 were observed at 1-μM concentration of thimerosal (Fig. 7). An active caspase-3 signal at 1-μM concentration was cytoplasmic, demonstrating an earlier stage of caspase-3 activation. Interestingly, after 24 h of incubation, the neurons treated with 2-μM thimerosal showed the migration of caspase-3 from the cytoplasm to the nuclei (Fig. 7). The majority of caspase-3–positive cells were also DAPI-positive, which indicates membrane damage occurring simultaneously with apoptotic response. However, at the higher 250-μM concentration of thimerosal, a number of cells were only DAPI-positive without caspase-3 activation, demonstrating necrotic death (Fig. 7). We did not detect active caspase-3 at 24 h of incubation in untreated neurons, or in neuronal cultures treated with lower concentrations of thimerosal (500, 250, and 125 nM).

DISCUSSION

Our data indicate that thimerosal is toxic to human neurons and fibroblasts if applied in micromolar concentrations (1–250 μM). An early sign of thimerosal toxicity is a change in cellular membrane permeability to the vital dye DAPI, which is associated with the loss of cell viability (Boutonnat *et al*., 1999;McCarthy and Hale, 1988). This can be detected as early as 2 h after incubation.

DAPI proved to be useful for analyzing thimerosal toxicity, because it is a sensitive marker of membrane integrity. It is employed as a propidium iodide substitute in cell viability assays and labels nuclei of dying cells, which lack an intact plasma membrane (Boutonnat *et al*., 1999;Castro-Hermida *et al*., 2000;McCarthy and Hale, 1988;Robertson *et al.*, 1998). Dual staining experiments using propidium iodide and DAPI co-staining with FACS analysis demonstrated that DAPI stains only dead cells (McCarthy and Hale, 1988). Viable cells that are not stained by PI also exclude DAPI (McCarthy and Hale, 1988).

The nature of cell death labeled by DAPI in the case of thimerosal treatment deserves additional discussion. The DAPI exclusion method relies on the fact that this dye is largely impermeable to cells with an intact plasma membrane. However, when cell membrane integrity becomes

compromised, DAPI gains access to the nucleus, where it complexes with DNA and renders the nucleus highly fluorescent. Early compromised integrity of plasma membranes is a characteristic feature of necrotic cell death, whereas, in apoptosis, cellular membranes are compromised at later times. This is why intra-cellular staining by DAPI (and also by its more toxic substitute propidium iodide) is regularly interpreted as a sign of necrosis (Boutonnat *et al.*, 1999). However, in the case of thimerosal, the changes in membrane permeability coincided with the activation of apoptosis-specific caspase-3 (Fig. 3). In our opinion, this indicates a separate direct membrane damaging effect of thimerosal that developed simultaneously with apoptotic changes, such as caspase-3 activation.

In many cases, the importance of caspase-3 activation is related to its connection to specific and extensive apoptotic DNA cleavage (Porter and Janicke, 1999). This DNA fragmentation can be labeled by the TUNEL technique and is widely used for the visualization of apoptotic cells. A caspase-activated deoxyribonuclease (CAD, or DFF 40) is implicated as a direct executioner of the cleavage (Liu *et al*., 1997;Mukae *et al.*, 1998). Most of the time, the enzyme is kept inactive by the binding of an inhibitor (ICAD, or DFF 45). Activation of the nuclease occurs when the inhibitor is cleaved by activated caspase-3 (Enari *et al*., 1998;Sakahira *et al*., 1998). However, the exact sequence of events in case of a human brain is likely different from this scheme. In human CNS neurons, other caspase-3–related pathways and possibly the other DNA cleaving enzymes are more important, and the role of the CAD-mediated mechanism is likely limited, because no expression of CAD mRNA was detected in human brain cells (Mukae *et al*., 1998).

Similar to our results, high cellular toxicity of thimerosal in low micromolar concentrations was recently reported using another cell culture model (Makani *et al*., 2002). The effects of different concentrations of thimerosal were examined in Jurkat cells. The cells were incubated with 5- to 0.5-μM concentrations of thimerosal for 24 h. Concentration-dependent apopto-sis was detected and measured by TUNEL. Caspase-3 activation was also detected after 4 and 6 h of incubation with thimerosal. The study concluded that thimerosal induced caspase-3–dependent apoptosis in Jurkat cells. This apoptosis was associated with the depolarization of the mitochondrial membrane and release of cytochrome c. In this same study, a significantly enhanced generation of reactive oxygen species was also detected, as a result of incubation with thimerosal (Makani *et al*., 2002). We hypothesize that these elevated levels of free radicals and the subsequent oxidation may play role in apoptosis induction and might also be involved in the direct membrane-damaging effects of thimerosal identified in our study.

We showed that the concentrations of thimerosal that induced toxic effects in human cortical neurons ranged from 1 to 250 μM. However, comparisons of the nuclear morphology of dying cells after incubation with higher versus lower concentrations of thimerosal demonstrate important differences. Although caspase-3 activation was detected in both high and low concentrations of thimerosal, the morphology of dying cells was different in these two situations. The cell bodies of neurons treated with higher concentrations of thimerosal (50 – 250 μM) were swollen, which is more characteristic of necrotic cell death, whereas cells treated with low concentrations (2–10 μM) were shrunken, as is typical for apoptosis (Fig. 7). Similarly, the nuclei of dying neurons treated with 250-μM thimer-osal were larger in size and swollen, in contrast to the shrunken nuclei of cells treated with 2-μM thimerosal (Fig. 7). Thus, cell death occurring after incubation of neuronal cells with higher concentrations of thimerosal has features of both apoptosis (caspase-3 activation) and necrosis (cell edema and nuclei swelling). This can be explained by a direct membrane-damaging effect of thimerosal, which rapidly leads to the loss of membrane integrity and cell swelling. This process likely occurs simultaneously with apoptosis induction, the initiation of the caspase cascade, and the activation of caspase-3. At lower concentrations of thimerosal, direct membrane-damaging effects are weaker, and no swelling is observed.

Investigation of thimerosal toxicity is especially important at the present time, because this compound is used in biological products and can be administered in toxic doses either accidentally or intentionally (Ball *et al*., 2001).

In our study, the concentrations of thimerosal that induced toxic effects ranged from 1 μM (405 μg/l) to 250 μM (101 mg/l), which is equivalent to the levels of inorganic mercury from 201 μg/l to 50 mg/l. In clinical cases of accidental or intentional usage in high concentrations, thimerosal was administered in doses from 3 mg/kg to several hundred mg/kg (Ball *et al*., 2001). Such doses resulted in local necrosis at the application site and severe central nervous system and kidney injury.

Much lower concentrations are reached during normal vaccination, when thimerosal-containing vaccines are used. In the case of a full series of vaccinations containing thimerosal, up to 403 μg of thimerosal (equivalent to 200 μg of mercury) are received by 6 months of age (calculated from Ball *et al*., 2001). This results in the administration of 200/3.81 = 52 μg/kg, 200/5.22 = 38 μg/kg, and 200/6.27 = 32 μg/kg of mercury. These calculations utilize averages of the 5th, 50th, and 95th% weight for females at birth (2.36 kg, 3.23 kg, 3.81 kg) and at 6 months (5.25 kg, 7.21 kg, 8.73 kg) = 3.81 kg, 5.22 kg, 6.27 kg, reported by (Ball *et al*., 2001) when used in calculating exposure limits for mercury in comparisons of various agencies guidelines.

The lowest toxic concentration of mercury contained in the thimerosal doses in our present study (201 μg/l) is less than four times higher than some of these estimated concentrations. The rapidly developing toxicity of thimerosal in low micro-molar concentrations over short time frames is of concern and suggests that additional research is necessary to estimate the effects of prolonged exposure to thimerosal in lower doses.

In this paper we demonstrated that extending the time of incubation with thimerosal from 2 to 6 h is associated with toxicity that was not seen after a shorter time of exposure. For this reason, further studies of lower concentrations and longer exposure times appear to be warranted. These results indicate that additional research is needed to more fully delineate the dose- and time-dependent toxicity of thimerosal in sub-micro-molar concentrations and suggests that toxicity may occur at even lower doses than those utilized in these experiments, with longer times of exposure. Because mercury can be retained in body organs for months to years, the study of longer incubation times is warranted. We also conclude that a proposed combination of fluorescent techniques combining the assessment of DNA, membrane damage, and active caspase-3 is useful in studying thimerosal toxicity.

Acknowledgements

We are grateful to Katie Fewell and Dr. Benxiao Zhang for valuable technical assistance in experiments and in manuscript preparation. This research was supported by grant R01 CA78912-01 from the National Cancer Institute, National Institutes of Health (D.S.B.); by grant 004949-054 from the Texas Higher Education Coordinating Board (D.S.B. and V.V.D.); and by grants from DeBakey Medical Foundation (V.V.D.), Baylor College of Medicine (V.V.D.), the Taub Foundation (D.S.B.), the Henry J. N. Taub Fund for Neurosurgical Research (D.S.B.), the George A. Robinson IV Foundation (D.S.B.), the Blanche Greene Estate Fund of the Pauline Sterne Wolff Memorial Foundation (D.S.B.), and the Seigo Arai and Koppelman Funds of the Neurological Research Foundation (D.S.B.).

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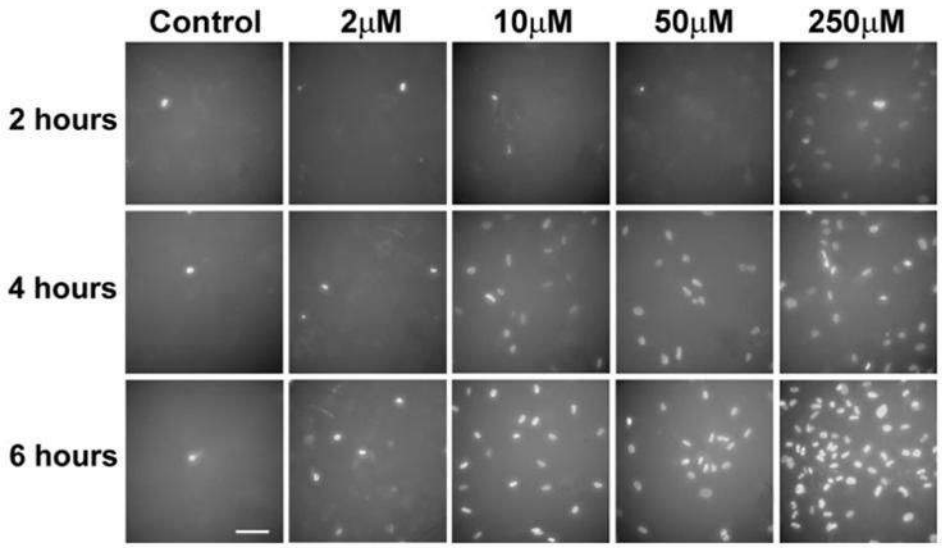

FIG 1.

Nonviable human cortical neurons in cell culture detected by a DAPI exclusion test after incubation with various concentrations of thimerosal. All panels have the same density of cells plated on a dish. Only nonviable cells are visualized by nuclear staining with DAPI, when cellular membranes are compromised and cells are either dead or dying. Solitary dying cells can be seen in controls, whereas the majority of cells incubated with thimerosal have compromised membranes. (Bar = 100 μm).

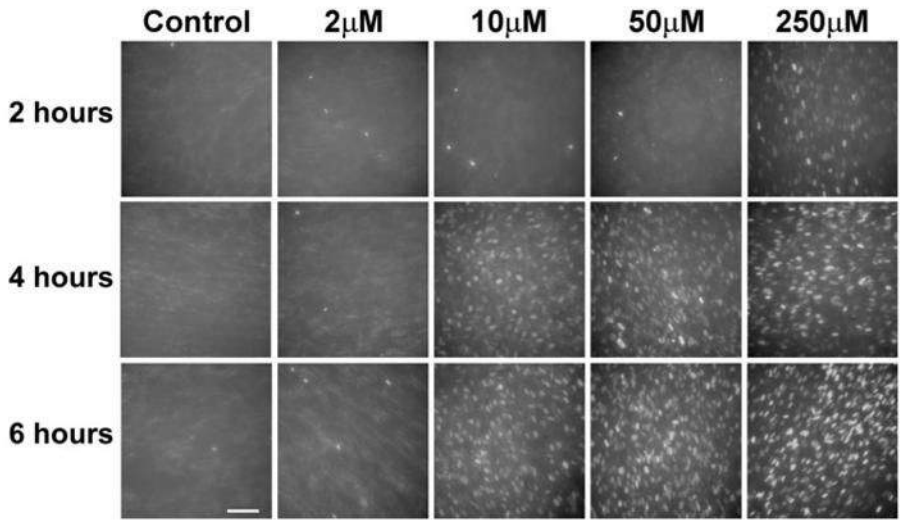

FIG 2.

Nonviable human skin fibro-blasts (PD 32) in cell culture detected by a DAPI exclusion test after incubation with various concentrations of thimero-sal. All panels have the same density of cells plated on a dish and represent young fibroblasts that underwent only 32 population doublings in cell culture conditions. Exclusively nonviable cells are visualized by nuclear staining with DAPI, when cellular membranes are compromised and cells are either dead or dying. (Bar = 100 μm).

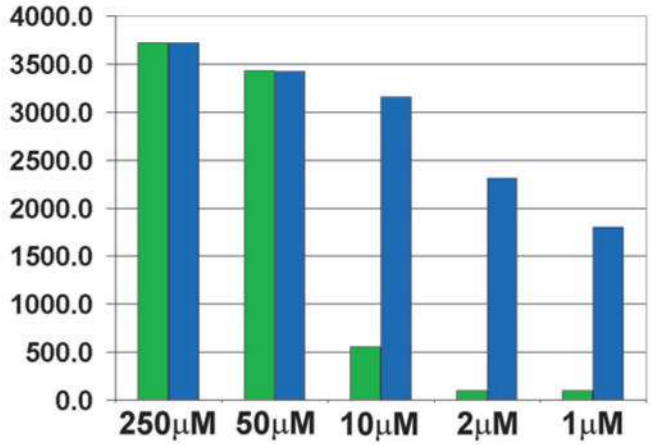

FIG 3.

Simultaneous detection of caspase-3 activation and nonviable cells (DAPI test) in cultured human cortical neurons after 6-h incubation with various concentrations of thimerosal. A GENios Plus Multi-Detection Micro-plate Reader with Enhanced Fluorescence was used for the detection. Labeling of active caspase-3 was performed in live cell cultures using a FAM-labeled DEVD fluoromethyl ketone caspase inhibitor (green) with the simultaneously performed DAPI exclusion test (blue), showing dead or dying cells. Fluorescence from both floating and attached nonviable cells was recorded. A Chroma Technology bandpass filter set was used to acquire single-color images: FITC excitation D490/40, emission 520/10; DAPI excitation D360/40, emission 460/20. The reactions were repeated twice, and averages are shown. For the easier comparisons, the caspase-3 signal at 250 μM was equalized (multiplied 6.71 times) with DAPI signal. *Y*-axis – arbitrary GENios Plus readings of fluorescence. Note that the DAPI exclusion test reveals the early appearance of cells with compromised membranes and a stronger DAPI signal compared to the caspase-3 signal.

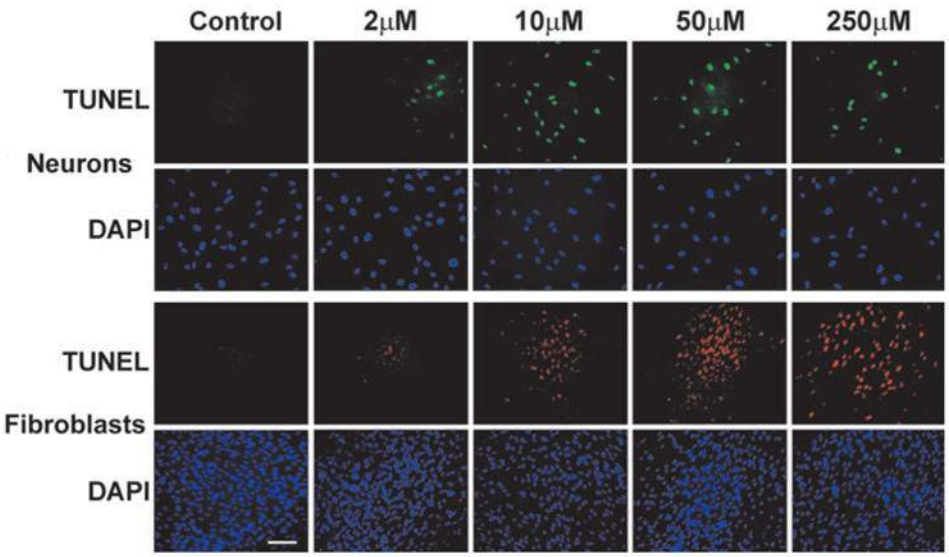

FIG 4.

Detection of DNA breaks by TUNEL in cultures of human cortical neurons (green fluorescence) and human fibroblasts (PD32) (red fluorescence) after 6 h of incubation with various concentrations of thimerosal. Blue fluores-cence – DAPI counterstaining was performed on fixed cells to visualize all cellular nuclei. (Bar = 100 μm).

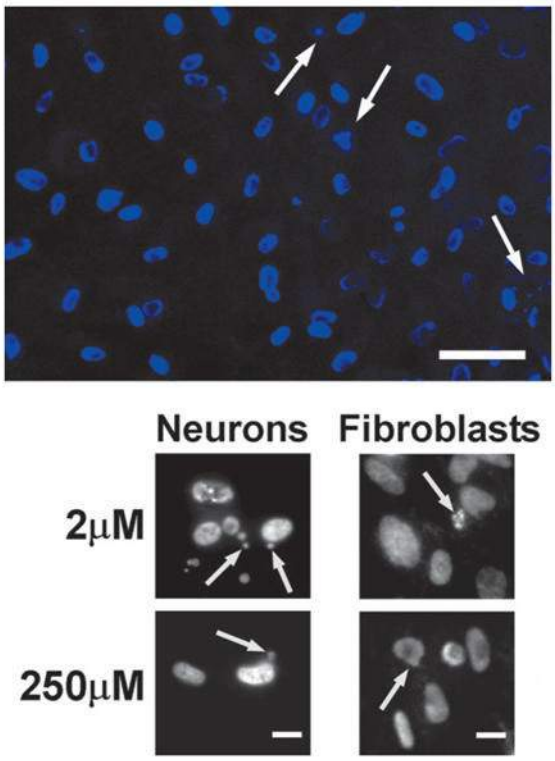

FIG 5.

Apoptotic morphology in human neurons and fibroblasts after 6 h of incubation with 2- and 250-μM concentrations of thimerosal. Cell were fixed and stained by DAPI (1 μg/ml) to visualize nuclear morphology and apoptotic bodies. Upper image – DAPI-stained neuronal nuclei (blue) after 6 h of incubation with 2-μM thimerosal. Apoptotic doughnut-shaped nuclei with chromatin condensation on the nuclear membrane and apoptotic bodies are seen. Arrows indicate forming and free located apoptotic bodies (Bar = 50 μm). Lower panel – black/white image of DAPI-stained neuronal and fibro-blast cells after 6 h of incubation with 2- or 250-μM thimerosal. Arrows indicate condensation of chromatin on nuclear membrane or formation of apoptotic bodies. (Bar = 10 μm).

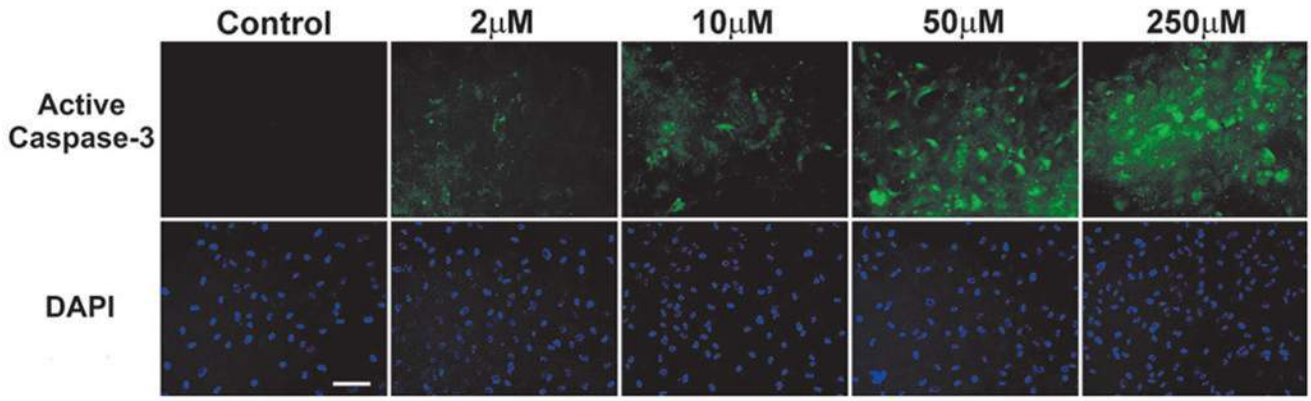

FIG 6.

Caspase-3 activation in cultured human cortical neurons after 6-h incubation with various concentrations of thimerosal. Detection of active caspase-3 was performed in live cell cultures using APO LOGIX™ carboxyfluorescein (FAM) caspase detection kit, which employs a FAM-labeled DEVD fluoromethyl ketone (FMK) caspase inhibitor (green fluorescence). The inhibitor irreversibly binds to active caspase-3. Note the primarily cytoplasmic localization of active caspase-3 at lower concentrations of thimerosal, whereas the higher concentrations demonstrate the predominantly nuclear localization of active caspase-3, indicating a later stage in progression towards cell death. Blue fluorescence – DAPI counterstaining performed on fixed cells to visualize all cellular nuclei. (Bar = 100 μm).

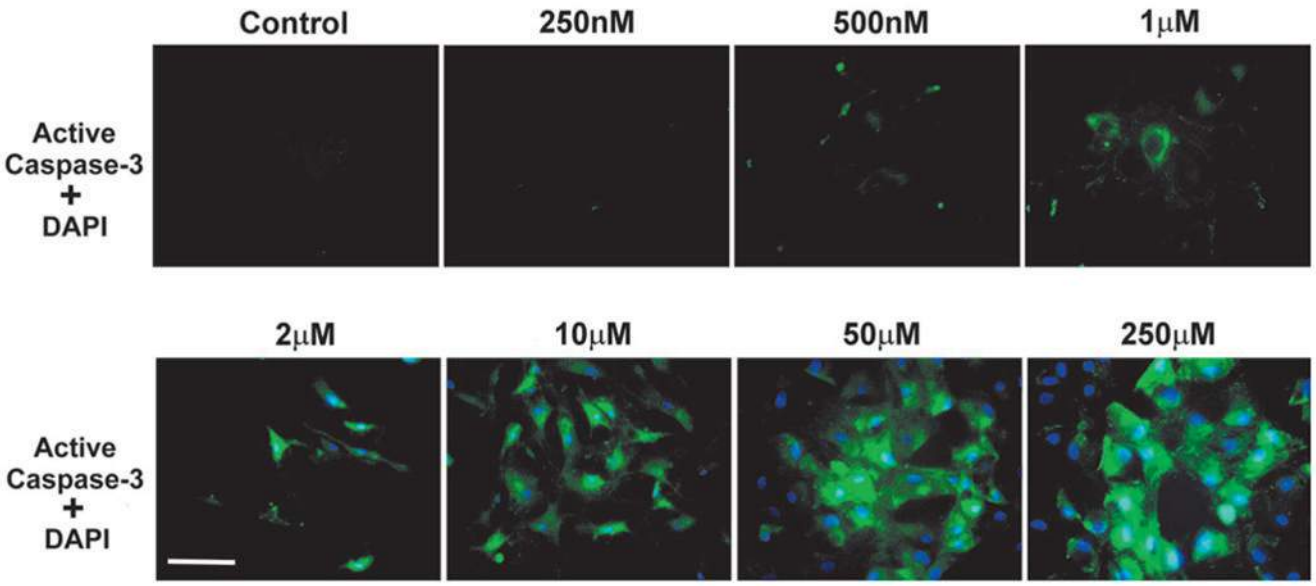

FIG 7.

Simultaneous detection of caspase-3 activation and nonviable cells in cultured human cortical neurons after 24-h incubation with various concentrations of thimerosal. Detection of active caspase-3 was performed in live cell cultures using a FAM-labeled DEVD fluoromethyl ketone caspase inhibitor (green fluorescence), which irreversibly binds to active caspase-3. Only nonviable cells are visualized by the simultaneously performed DAPI exclusion test (blue fluorescence), showing dead or dying cells with compromised membranes. Note that, in this case, DAPI is not used as a counterstain for fixed cells, like in the previous figure, but is employed as an exclusion dye (see Materials and Methods). 6 h of incubation with 2-μM concentration of thimerosal resulted in cytoplasmic localization of active caspase-3, while after 24 h active caspase-3 is now localized in the nuclei, indicating a later stage in cell death progression. Compare the cytoplasmic localization of active caspase-3 at 1-μM concentration of thimerosal to its nuclear localization at 2-μM concentration. The majority of caspase-3–positive cells have compromised cellular membranes (Bar = 100 μm). The composite images were created in *MetaMorph* 4.1 (Advanced Scientific, Inc.) by overlaying single color images. A Chroma Technology bandpass filter set was used to acquire single-color images: FITC excitation D490/40, emission 520/10; DAPI excitation D360/40, emission 460/20.

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Integrating experimental (in vitro and in vivo) neurotoxicity studies of low-dose thimerosal relevant to vaccines.

Dórea JG[1].

Author information

Abstract

There is a need to interpret neurotoxic studies to help deal with uncertainties surrounding pregnant mothers, newborns and young children who must receive repeated doses of Thimerosal-containing vaccines (TCVs). This review integrates information derived from emerging experimental studies (in vitro and in vivo) of low-dose Thimerosal (sodium ethyl mercury thiosalicylate). Major databases (PubMed and Web-of-science) were searched for in vitro and in vivo experimental studies that addressed the effects of low-dose Thimerosal (or ethylmercury) on neural tissues and animal behaviour. Information extracted from studies indicates that: (a) activity of low doses of Thimerosal against isolated human and animal brain cells was found in all studies and is consistent with Hg neurotoxicity; (b) the neurotoxic effect of ethylmercury has not been studied with co-occurring adjuvant-Al in TCVs; (c) animal studies have shown that exposure to Thimerosal-Hg can lead to accumulation of inorganic Hg in brain, and that (d) doses relevant to TCV exposure possess the potential to affect human neuro-development. Thimerosal at concentrations relevant for infants' exposure (in vaccines) is toxic to cultured human-brain cells and to laboratory animals. The persisting use of TCV (in developing countries) is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products; its continued use in TCV requires evaluation of a sufficiently nontoxic level of ethylmercury compatible with repeated exposure (co-occurring with adjuvant-Al) during early life.

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[Indexed for MEDLINE]

NeuroRx®: The Journal of the American Society for Experimental NeuroTherapeutics

The Blood-Brain Barrier: Bottleneck in Brain Drug Development

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Summary: The blood-brain barrier (BBB) is formed by the brain capillary endothelium and excludes from the brain ~100% of large-molecule neurotherapeutics and more than 98% of all small-molecule drugs. Despite the importance of the BBB to the neurotherapeutics mission, the BBB receives insufficient attention in either academic neuroscience or industry programs. The combination of so little effort in developing solutions to the BBB problem, and the minimal BBB transport of the majority of all potential CNS drugs, leads predictably to the present situation in neurotherapeutics, which is that there are few effective treatments for the majority of CNS disorders. This situation can be reversed by an accelerated effort to develop a knowledge base in the fundamental transport properties of the BBB, and the molecular and cellular biology of the brain capillary endothelium. This provides the platform for CNS drug delivery programs, which should be developed in parallel with traditional CNS drug discovery efforts in the molecular neurosciences. **Key Words:** Blood-brain barrier, endothelium, drug targeting, biological transport, neurotherapeutics.

INTRODUCTION

The blood-brain barrier (BBB) is the bottleneck in brain drug development and is the single most important factor limiting the future growth of neurotherapeutics.[1] The BBB problem is illustrated in Figure 1, which is a whole body autoradiogram of a mouse sacrificed 30 min after intravenous injection of radiolabeled histamine, a small molecule of only ~100 Da in molecular mass. Histamine readily crosses the porous capillaries perfusing all peripheral tissues but is excluded from entry into the brain or spinal cord by the BBB.

The histamine example in Figure 1 refutes a common misconception that most small molecules readily cross the BBB. As discussed below, the transport of small molecules across the BBB is the exception rather than the rule, and 98% of all small molecules do not cross the BBB (FIG. 1). Moreover, all large-molecule products of biotechnology, such as monoclonal antibodies (mAbs), recombinant proteins, antisense, or gene therapeutics, do not cross the BBB (FIG. 1). Despite the large number of patients with disorders of the CNS and despite the fact that so few large- or small-molecule therapeutics cross the BBB, there are few pharmaceutical companies in the world today that have built a BBB drug targeting program (FIG. 1). However, even if a pharmaceutical company decided to develop a BBB program, there would be few BBB-trained scientists to hire because less than 1% of U.S. academic neuroscience programs emphasize BBB transport biology.

Because most drugs do not cross the BBB, and because the industry is not providing solutions to the BBB problem, it is not surprising that most disorders of the CNS could benefit from improved drug therapy (FIG. 2). For a small-molecule drug to cross the BBB in pharmacologically significant amounts, the molecule must have the dual molecular characteristics of: 1) molecular mass under a 400- to 500-Da threshold, and 2) high lipid solubility.[1] There are only four categories of CNS disorders that consistently respond to such molecules, and these include affective disorders, chronic pain, and epilepsy (FIG. 2). Migraine headache may be a CNS disorder and could also be included in this category. In contrast, most CNS disorders such as those listed in Figure 2 have few treatment options. Parkinson's disease patients are given L-dihydroxyphenylalanine (L-DOPA) for dopamine replacement therapy.[2] As discussed below in the section on BBB carrier-mediated transport, L-DOPA is an example of a BBB drug targeting strategy. However, there is no neurotherapeutic that stops the neuro-

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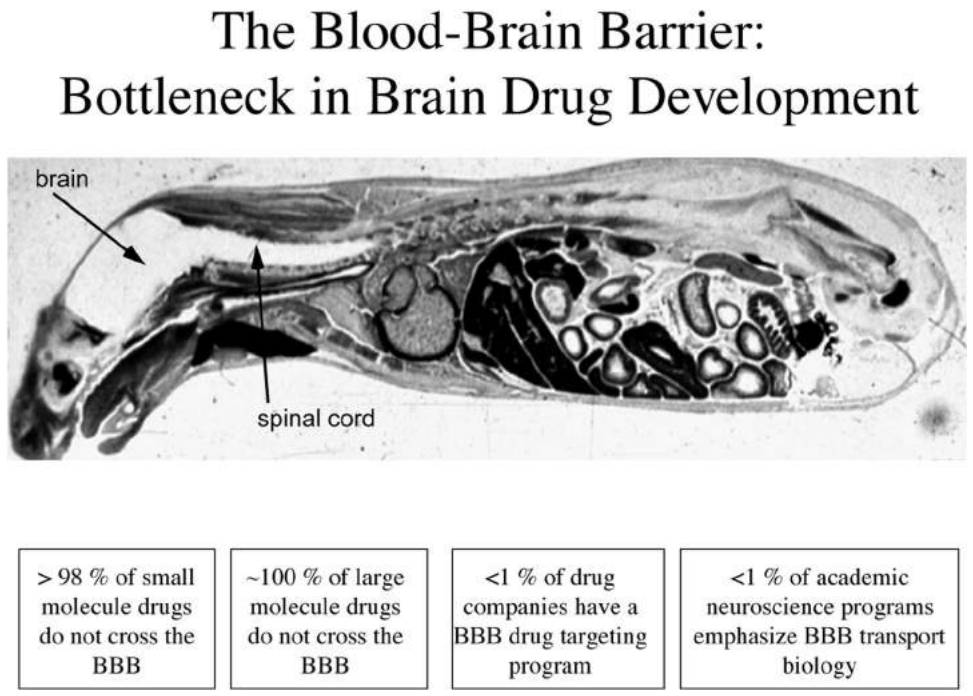

FIG. 1. Whole body autoradiogram of an adult mouse sacrificed 30 min after intravenous injection of radiolabeled histamine, a small molecule that readily enters all organs of the body, except for the brain and spinal cord.

degeneration of Parkinson's disease. Similarly, there is no therapy for other neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and amytrophic lateral sclerosis (ALS). Patients with multiple sclerosis (MS) are treated with cytokines that work on the peripheral immune system, but which do not permanently stop the progression of MS.[3] The human immunodeficiency virus (HIV) infects the brain early in the course of acquired immune deficiency syndrome (AIDS).[4] HIV in the periphery has been significantly reduced with highly active antiretroviral therapy (HAART) comprised of multiple small-molecule therapeutics. However, HAART drugs such as azidothymidine, 3TC, or protease inhibitors are substrates for BBB active efflux transporters, which are reviewed below, and HAART drugs have minimal penetration into brain parenchyma. Consequently, the brain remains a sanctuary for HIV in AIDS even with HAART.[4,5] Brain cancer, stroke, and brain or spinal cord trauma are all examples of serious CNS disorders for which there is no effective drug therapy. The childhood disorders including autism, lysosomal storage disorders, fragile X syndrome, the ataxis, and blindness, are serious disorders where there is little effective treatment. In many of these cases, the gene underlying the disease is known, but BBB delivery is the rate-limiting problem in gene therapy or enzyme replacement therapy, and no therapeutics have been developed. Many of the disorders listed in the right-hand column in Figure 2 could be treated with drugs, enzymes, or genes already discovered. However, these drugs do not cross the BBB and cannot enter into brain drug development because no BBB solutions have been developed by industry. Given the absence of effective BBB drug targeting technology, CNS drug developers are left with the traditional approaches to solving the brain drug delivery problem: small molecules, trans-cranial brain drug delivery, and BBB disruption. A review of these approaches

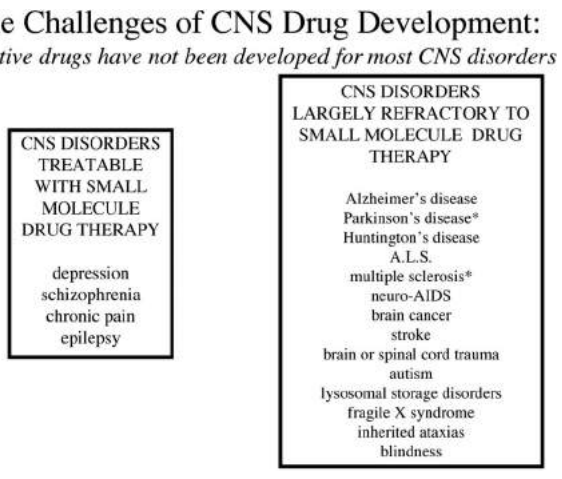

FIG. 2. A review of the Comprehensive Medicinal Chemistry database shows that, of more than 7000 small-molecule drugs, only 5% treat the CNS, and these drugs only treat four disorders: depression, schizophrenia, chronic pain, and epilepsy.[6,7] There are few effective small- or large-molecule drugs for the majority of CNS disorders, with the exception of Parkinson's disease, e.g., L-DOPA, and multiple sclerosis, e.g., cytokines.

shows that none provide solutions to the BBB problem that could be practically implemented in large numbers of patients.

SMALL MOLECULES

Most small-molecule drugs do not cross the BBB. Of over 7000 drugs in the comprehensive medicinal chemistry (CMC) database, only 5% of all drugs treat the CNS, and these CNS active drugs only treat depression, schizophrenia, and insomnia.[6] The average molecular mass of the CNS active drug is 357 Da. In another study, only 12% of drugs were active in the CNS, but only 1% of all drugs were active in the CNS for diseases other than affective disorders.[7]

BBB transport of small molecules is limited

Small molecules generally cross the BBB in pharmacologically significant amounts if 1) the molecular mass of the drug is less than 400-500 Da, and 2) the drug forms less than 8-10 hydrogen bonds with solvent water.[1]

The permeation of the drug across the BBB does not increase in proportion to lipid solubility when the molecular weight of the drug is increased. BBB permeation decreases 100-fold as the surface area of the drug is increased from 52 Angstroms^2 (e.g., a drug with molecular mass of 200 Da) to 105 Angstroms^2 (e.g., a drug of 450 Da).[8] Drug diffusion through a biological membrane is not analogous to drug diffusion through solvent water. In contrast to water, diffusion of a drug through a biological membrane is dependent on the volume of the drug. The classical Overton rules that relate membrane permeation to solute lipid solubility do not predict the molecular weight threshold effect. As noted by Leib and Stein nearly 20 years ago,[9] the molecular weight threshold effect is best predicted by the "hole-jumping" model of Trauble,[10] which posits that solutes undergo a form of molecular "hitch hiking" across a biological membrane by moving through small holes in the membrane formed by kinking of the mobile unsaturated fatty acyl side chains in the phospholipid bilayer.

Hydrogen bonding

BBB permeation decreases exponentially with the addition of each pair of hydrogen bonds added to the drug structure.[11] It does not matter whether the functional group is a hydrogen bond donor or a hydrogen bond acceptor because each hydrogen bond carries equal weight. Hydrogen bond donor groups such as hydroxyls form two hydrogen bonds because a hydroxyl group acts as both a hydrogen bond donor and hydrogen bond acceptor, whereas a carbonyl group only acts as a hydrogen bond acceptor. Once the total number of hydrogen bonds on the drug exceeds a threshold of 8-10, there is minimal transport of the drug across the BBB in pharmacologically active amounts. Both the hydrogen bonding and the molecular weight of drugs currently emanating from CNS drug discovery programs generally are higher than drugs discovered 20 years ago.[7] This is because CNS drug discovery programs now rely extensively on receptor-based high-throughput screening (HTS) programs. HTS-based drug screening invariably selects for drugs that have higher molecular weights and higher hydrogen bonding because these factors enable higher affinity drug binding to the target receptor.

HTS-based CNS drug discovery

Current CNS drug discovery programs are generally broken down into four major areas: 1) receptor target identification, 2) drug "hit" identification, 3) "lead" identification, and 4) drug lead optimization. After screening several hundred thousand small-molecule drugs with a given target, several hundred hits may be found, leading to a score of potential drug leads. The HTS drug lead compounds must then be optimized with respect to distribution, metabolism, and pharmacokinetics (DMPK).[12] However, the drugs generally require so much medicinal chemistry to block polar functional groups that the original high receptor affinity is lost in an attempt to produce a drug with acceptable DMPK properties. The difficulty in using medicinal chemistry to increase the lipid solubility of a drug is illustrated by considering that there is not a single drug currently in CNS clinical practice that is an example of a water soluble drug that was made lipid soluble with medicinal chemistry optimization such that the drug then became pharmacologically active in the brain *in vivo*.

The pharmacokinetic rule

When medicinal chemistry is used to increase the lipid solubility of the drug, this may increase penetration across the BBB, but it also increases penetration across all biological membranes *in vivo*. Therefore, the lipidized form of the drug is rapidly removed from the blood, and in pharmacokinetic terms, the plasma area under the concentration curve (AUC) is substantially decreased for the lipidized form of the drug. Drug action in brain is a function of drug uptake, expressed as percent of injected dose (ID) per gram brain, and the % ID/g is equally dependent on two factors, the BBB permeability-surface area (PS) product and the plasma AUC:

$$\%\ \mathrm{ID/g} = (\mathrm{BBB\ PS\ product}) \times (\mathrm{plasma\ AUC}) \quad \text{(Eq. 1)}$$

Although an increase in lipid solubility of the drug may increase the BBB PS product, there is a proportional decrease in the plasma AUC with lipidization. The increased BBB PS product and the decreased plasmid AUC have offsetting effects, which minimizes the increase in brain uptake caused by lipidization.[1]

Medicinal chemistry and brain drug lead optimization

The use of medicinal chemistry to increase the lipid solubility of drug to solve the BBB drug delivery problem is problematical for the reasons listed above. However, a new approach to the use of medicinal chemistry to solve the BBB drug delivery problem is discussed below. Medicinal chemistry can be used to alter the structure of a lead drug candidate to make that drug transportable on one of several carrier-mediated transport (CMT) systems within the BBB. However, redirection of the use of medicinal chemistry to increase the carrier-mediated transport of a drug, as oppose to the lipid-mediated transport of the drug, requires knowledge on the structural characteristics of a drug that enable CMT across the BBB. Therefore, a knowledge base in BBB CMT must be developed before the use of medicinal chemistry to increase drug penetration to the brain via endogenous BBB carriers.

TRANS-CRANIAL BRAIN DRUG DELIVERY

Trans-cranial brain drug delivery approaches attempt to bypass the BBB using one of three neurosurgical-based delivery approaches: intracerebral implantation, intracerebroventricular (ICV) infusion, and convection enhanced diffusion (CED). The factor limiting either the intracerebral or ICV infusion approach is that either method relies on diffusion for drug penetration into the brain from the depot site. Solute diffusion decreases with the square of the diffusion distance.[1] Therefore, the concentration of drug decreases logarithmically with each millimeter of brain tissue that is removed from the injection site, in the case of intracerebral implantation, or from the ependymal surface of the brain, in the case of ICV infusion. The concentration of a small molecule is decreased by 90% at a distance of only 0.5 mm from the intracerebral implantation site in rat brain.[13] The logarithmic decrease in drug concentration from the ependymal surface following an ICV infusion was shown in the 1970s in adult Rhesus monkeys; after ICV drug injection, the concentration of small molecules in brain parenchyma removed only 1-2 mm from the ependymal surface is only about 1-2% of the concentration in the CSF compartment.[14] The limited diffusion of drug from an intracerebral implant is shown in Figure 3, which is an autoradiogram of rat brain taken 2 days after the intracerebral implantation of a wafer embedded with radiolabeled NGF.[15] The size of the wafer is approximately equal to the magnification bar in the figure, which indicates that there has been minimal penetration of NGF into brain parenchyma from the implant site. The limited diffusion of BDNF into brain parenchyma following injection into a lateral ventricle (LV)[16] is shown in Figure 3. The BDNF is sequestered by the ependymal surface

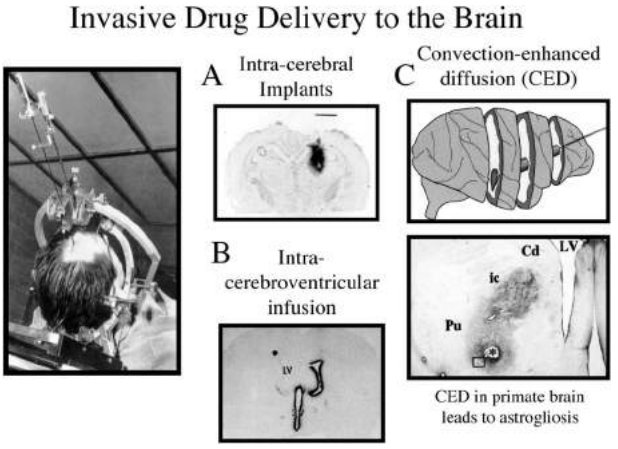

FIG. 3. Trans-cranial drug delivery to the brain. A: Autoradiogram of rat brain 48 h after an intracerebral implantation of a polymer carrying radiolabeled NGF.[15] The size of the polymer approximates the magnification bar, indicating the NGF has not significantly diffused from the implantation site. B: Autoradiogram of rat brain 24 h after an intracerebroventricular injection of BDNF into an LV.[16] The BDNF distributes to the ependymal surface of the ipsilateral LV and the third ventricle (3V), but not into brain parenchyma. C: Convection enhanced diffusion in the primate brain forces fluid through the brain tissue. The direction of fluid flow, principally via white matter tracts,[19] can be traced with immunocytochemistry using an antibody to GFAP, which shows an astrogliotic reaction in the path of fluid flow.[20] The hole in the brain left by the catheter is noted by the asterisk. The fluid moved from the catheter in the putamen (Pu) via the internal capsule (ic) white matter to the caudate (Cd).

but does not significantly diffuse into brain parenchyma. This limited diffusion of BDNF into brain parenchyma is not due to the fact that BDNF is a cationic protein, as a similar logarithmic decrease in brain penetration is found for any drug following ICV injection.[14] This slow rate of drug diffusion into brain parenchyma is to be contrasted with the rapid rate of bulk flow of CSF through the ventricular compartments. CSF is then rapidly absorped into the peripheral bloodstream at the superior sagittal sinus. The ICV injection of drug should be regarded as a slow intravenous infusion rather than a direct administration of drug into the brain.[17] The rapid rate of cytokine distribution into blood, but minimal penetration into brain, following an ICV injection has been demonstrated in adult rhesus monkeys.[18]

The effective penetration of drug into brain can be increased to a treatment radius of a few millimeters when bulk flow is used to deliver drug into brain parenchyma, and this is possible by forcing fluid through the brain with CED. However, the brain has no lymphatic system and is not designed for a significant intraparenchymal volume flow. CED in humans with glioblastoma multiform causes a preferential flow of the forced fluid along white matter tracts.[19] CED in the adult Rhesus monkey brain with glial-derived neurotrophic factor involved the infusion of relatively small volumes of ~0.1 ml/day over a 4-week period.[20] This led to diffuse white matter as-

TABLE 1. *BBB Disruption after Intracarotid Arterial Infusion of Noxious Agents*

Method	Comments (References)
Hyperosmolar	Leads to chronic neuropathologic changes and vasculopathy in the brain and seizures[21–25]
Vasoactive agents	Examples are bradykinin, histamine, and multiple other vasoactive compounds; opens BBB in brain tumor to greater extent than normal brain[72]
Solvents	BBB is solubilized with high dose ethanol, DMSO, SDS, Tween 80 (polysorbate-80)[27–30]
Alkylating agents	Examples are etoposide and melphalan; may alkylate key sulfhydryl residues similar to mercury[73,74]
Immune adjuvants	Freunds adjuvant opens BBB to IgG for weeks; enable IgG uptake into brain in rodent vaccine models, such as Alzheimer's disease[32]
Ultrasound	The combination of administration of high-dose air bubbles (2–4 μm) and high-dose ultrasound (10–1000 watt/cm^2) can induce BBB disruption[75]
Cytokines	Intracerebral interleukin-1β or CXC chemokines can attract white cells from blood and cause BBB disruption[76,77]
Miscellaneous	Intracarotid acid pH, cold temperatures, or high-dose free fatty acid all cause BBB disruption[78–80]

trogliosis, which was visualized by immunocytochemistry of the autopsy primate brain, and immunostaining with an antibody to GFAP as shown in Figure 3. In addition, there was a microglial response and demyelination around the catheter, with extension of the astrogliotic reaction from the catheter in the putamen (Pu) through the internal capsule (ic) to the caudate (cd) (FIG. 3). These findings of an intense astrogliotic reaction along white matter tracts after CED in the primate brain raise concerns about the long-term effects of this delivery approach for humans.

BLOOD-BRAIN BARRIER DISRUPTION

In parallel with trans-cranial brain drug delivery strategies, there has been a significant effort in delivering drugs to the brain with BBB disruption after the intracarotid arterial infusion of vasoactive agents such as those listed in Table 1. The intracarotid arterial infusion of 2 M concentrations of poorly diffusible solutes such as mannitol causes disruption of the BBB owing to osmotic shrinkage of the endothelial cells.[21] This is associated with severe vasculopathy[22] and chronic neuropathologic changes in rodent models[23] and is also associated with seizures in either animal models[24] or humans.[25] Plasma proteins such as albumin are toxic to brain cells,[26] and BBB disruption allows for the uptake of plasma into the brain.

Solvent/adjuvant-mediated BBB disruption

The BBB, like cell membranes in general, is subject to solvent-mediated disruption with chemicals such as ethanol, dimethylsulfoxide (DMSO), or detergents such as SDS, or Tween 80 also known as polysorbate-80.[27–30] There are numerous examples in the literature where the peripheral administration of a drug, which normally should not cross the BBB, is followed by pharmacological activity in the brain. Such an observation could arise because the drug is transported across the BBB via an endogenous transport system. However, an alternative explanation is that the drug is injected in a diluent that is membrane destabilizing, and causes BBB disruption. Often the drug is solubilized in solvents such as ethanol or DMSO, or surfactants such as SDS, a Tween detergent, or other surfactants, such as polyethyleneglycol hydroxy stearate. Doses of solvents such as ethanol or DMSO at a level of 1-4 g/kg may cause solvent-mediated disruption of the BBB.[27,28] This dose of DMSO or ethanol is given to animal models with surprising frequency, particularly small rodent models such as mice, which weigh only 20-30 g. The administration of just 50 μl of 50% DMSO to a 20-g mouse is equivalent to 1.25 g/kg DMSO, and there are examples in the literature of pharmacologic effects achieved in brain following systemic administration of drugs that normally do not cross the BBB. These drugs are administered in solvents such as ethanol or DMSO and the dose of solvent is such that BBB disruption may be caused by administration of the drug/solvent mixture. Tween 80, also known as polysorbate-80, is frequently administered in CNS drug formulations. A dose of polysorbate-80 of 3-30 mg/kg will cause BBB disruption in mice.[30] Analgesia with kyotorphin, a oligopeptide that normally does not cross the BBB, is possible following the peripheral administration of the peptide, providing Tween 80 is coadministered.[31] Low doses of another surfactant, SDS, are frequently included in CNS drug diluents. However, doses of SDS as low as 1.0 μg/kg can cause disruption of the BBB for short periods. Immune adjuvants such as Freund's complete or incomplete adjuvant cause disruption of the BBB to circulating IgG that can persist for weeks.[32] This is relevant to rodent vaccine models where active immunization is attempted as a new therapy for the treatment of brain diseases. The vaccine for Alzheimer's disease was based on the administration of the Aβ peptide mixed in

Freund's adjuvant to transgenic mice with brain amyloid.[33] The adjuvant has two effects. First, it recruits the immune system to the injection site so that antibodies are made to the target peptide, in this case the Aβ. Second, the immune adjuvant causes an inflammatory response that results in opening of the BBB. This latter property allows the circulating anti-Aβ antibodies to enter the brain. In the absence of BBB disruption, the circulating IgG cannot enter the brain. In either active or passive immunization approaches to brain disorders, the circulating IgG must be enabled to cross the BBB and enter brain to cause the intended pharmacological effect. IgG molecules do not cross the BBB, in the absence of specific transport mechanisms. It is unlikely that active or passive immunization will be effective in humans, if the BBB is not disrupted.

If a CNS drug is formulated in a vehicle other than a physiological buffer, then the amounts of any solvent, surfactant, or adjuvant, that are included in the formulation should be evaluated critically as to whether drug treatment is associated with solvent-mediated BBB disruption. In this setting, there is a high likelihood that chronic drug administration will have toxic side effects.

TRANS-NASAL DRUG DELIVERY TO THE BRAIN

The delivery of drugs after intranasal administration is based on the rationale that drugs can exit the submucous space of the nose and cross the arachnoid membrane, and enter into olfactory CSF. It is posited that drug may then enter the brain from the CSF flow tracts following intranasal administration of drug. There are two points to consider when evaluating the potential efficacy of transnasal drug delivery to the brain. First, any drug that enters into olfactory CSF will exit the CSF flow tracts and enter the peripheral bloodstream like any other ICV route of administration. The second consideration is that the arachnoid membrane, which separates olfactory CSF from the submucous spaces of the nose, has high resistance tight junctions, just like the capillary endothelium that forms the BBB.[34] Therefore, only lipid-soluble small molecules may cross the arachnoid membrane and enter into olfactory CSF in the absence of arachnoid membrane disruption. Conversely, if the arachnoid membrane and other membranes in the nose are physically or chemically disrupted, then drug may enter the CSF from the nose. The human nasal cavity can only receive about 100 μl per nostril without local injury.[35] The volume of drug administered into the nose is invariably $\gg$200 μl. Melanocyte-stimulating hormone, a seven-amino acid neuropeptide, entered CSF following intranasal instillation in humans after these subjects ingested 20 consecutive puffs of drug via an atomizer into each nares.[36] When drug is administered to the nose via volumes that are not injurious to the nose, then no distribution into CSF is found for a water-soluble drug such as vitamin B12 or a relatively lipid soluble drug such as melatonin.[35] In the absence of local injury, distribution of neuropeptides to olfactory CSF is nil, unless the protein has access to a specialized transport system that enables movement across the arachnoid membrane. This was demonstrated in the case of a conjugate of HRP and wheat germ agglutinin (WGA). The latter is a glycoprotein that crosses membranes via absorptive mediated endocytosis, based on binding to membrane lectin sites.[37] Whereas the HRP alone cannot penetrate the olfactory CSF, the HRP-WGA conjugate can cross plasma membranes via absorptive-mediated endocytosis.

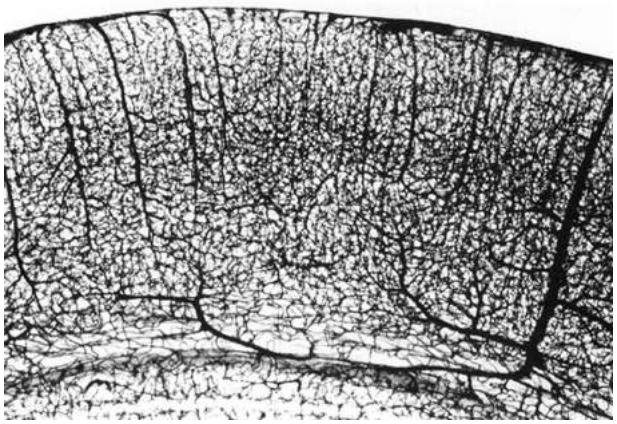

FIG. 4. India ink study shows vascular density in the cortex of adult rat brain. Reprinted with permission from Bar. The vascular system of the cerebral cortex. *Adv Anat Embryol Cell Biol* 59:I–VI, 1–62. Copyright © 1980, Springer-Verlag.[38] All rights reserved.

TRANSVASCULAR DRUG DELIVERY TO THE BRAIN VIA ENDOGENOUS BBB TRANSPORTERS

The complexity of the vascular tree in the cortex of rat brain is shown with the India ink[38] study in Figure 4. The vascular density in the human brain is even more complex. In the human brain, there are over 100 billion capillaries. The distance between capillaries is $\sim$50 μm. Therefore, the maximum diffusion distance in brain parenchyma following transvascular delivery is only 25 μm. Even a molecule as large as albumin, 68,000 Da molecular mass, will diffuse 25 μm in less than 1 s.[1] Because the intercapillary distance in brain is so small, every neuron is virtually perfused by its own blood vessel. The length of capillaries in human brain is $\sim$400 miles, and the surface area of the brain capillary endothelium in the human brain is $\sim$20 m^2. However, the volume of the intraendothelial space is only 1 μl for adult rat brain and is only 5 ml for the human brain. Therefore, the brain capillary endothelial surface, which forms the BBB *in vivo*, forms a very broad but thin

barrier system. The thickness of the endothelial cell is only ~200 nm, which is less than 5% of the thickness of most cells.

Transport across the BBB involves movement across two membranes in series: the luminal and abluminal membranes of the capillary endothelium, separated by the 200 nm of endothelial cytoplasm. The microvascular endothelium in brain is completely invested by a basement membrane, but the basement membrane constitutes no diffusion barrier. Approximately 90% of the brain side of the capillary is covered by astrocyte foot processes,[39] although these astrocyte foot processes similarly constitute no diffusion barrier. Therefore, solutes freely and instantaneously distribute throughout the entire brain extravascular volume after transport across the limiting membrane, which is the capillary endothelial membrane. The BBB has a very high resistance owing to the tight junctions, which cement adjacent endothelial cells together. Due to the presence of the tight junctions, there is no *para-cellular* pathway for solute distribution into brain interstitial fluid from blood. Circulating molecules can only gain access to brain interstitium via a *trans-cellular* route through the brain capillary endothelial membranes. If a molecule is lipid soluble and has a molecular mass less than 400 Da and is not avidly bound by plasma proteins or is a substrate for an active efflux transport system at the BBB, then the circulating molecule may gain access to brain by lipid-mediated free diffusion. In the absence of the lipid-mediated pathway, circulating molecules may gain access to brain only via transport on certain endogenous transport systems within the brain capillary endothelium. These endogenous transporters have an affinity for both small molecules and large molecules and can be broadly classified into three categories: 1) CMT; 2) active efflux transport, or AET; and 3) receptor-mediated transport, or RMT.

CMT

CMT systems for hexoses, monocarboxylic acids such as lactic acid, neutral amino acids such as phenylalanine, basic amino acids such as arginine, quaternary ammonium molecules such as choline, purine nucleosides such as adenosine, and purine bases such as adenine, are shown in Figure 5, which represents the luminal membrane of the brain capillary endothelium. The individual endogenous nutrients shown in Figure 5 are representative substrates because each carrier system transports a group of nutrients of common structure. The CMT systems shown in Figure 5 are all members of the Solute Carrier (SLC) gene family (Table 2). The BBB glucose carrier is GLUT1 (glucose transporter type 1), which is a member of the SLC2 family; the BBB monocarboxylic acid transporter is MCT1, which is a member of the SLC16 family; the BBB large neutral amino acid and cationic amino acid transporters are LAT1 and CAT1,

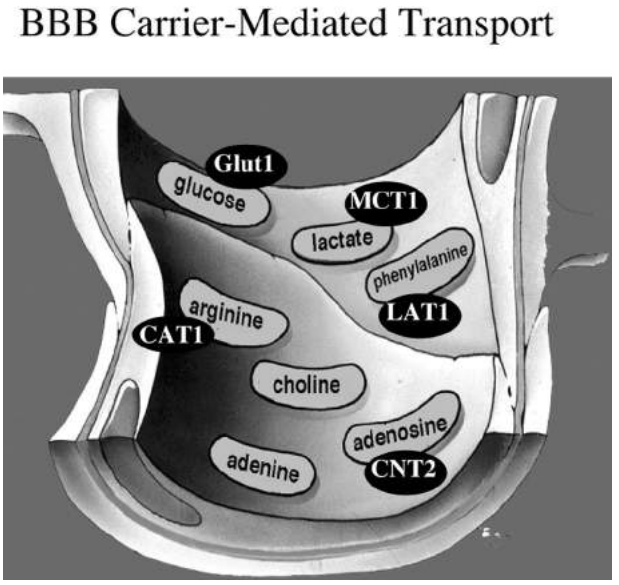

FIG. 5. BBB CMT systems are shown for seven different classes of nutrients, and the genes for five of these systems has been identified. GLUT1 = glucose transporter type 1; MCT1 = monocarboxylic acid transporter type 1; LAT1 = large neutral amino acid transporter type 1; CAT1 = cationic amino acid transporter type 1; CNT2 = concentrative nucleoside transporter type 2.

respectively, which are members of the SLC7 family; LAT1 and CAT1 are the light chains of heterodimeric proteins, and the heavy chain of the dimer is 4F2hc, which is a member of the SLC3 family; the BBB adenosine transporter is CNT2, which is a member of the SLC28 family (Table 2). Each of the SLC families shown in Table 2 represent many common genes of overlapping nucleotide identity and some of the SLC families are comprised of over 100 different genes.

BBB GLUT1 transports glucose, 2-deoxyglucose, 3-*O*-methyl-glucose, galactose, and mannose, but not L-glucose.[40] BBB MCT1 transports lactate, pyruvate, ketone bodies, and monocarboxylic acids.[41] BBB LAT1 transports the neutral amino acids with preferential affinity for the large neutral amino acids.[42] BBB CAT1 transports arginine, lysine, ornithine.[43] The BBB choline transporter transports choline, and perhaps other quaternary ammonium molecules.[44] To date, the BBB choline transporter has not been cloned. CHT1 is a sodium-dependent choline transporter member of the SLC5 family (Table 2), which corresponds to the sodium-dependent synaptosomal choline carrier. However, the BBB choline transporter is sodium independent[45] and is likely a member of a different SLC gene family. The BBB adenosine carrier transports adenosine, guanosine, and certain pyrimidine nucleosides such as uridine,[46] and is derived from the CNT2 gene,[47] where CNT = concentrative nucleoside transporter. Purine nucleosides are also transported by sodium independent or equilibrative nucleoside transporters (ENT), which are members of the SLC29 gene family (Table 2). However, BBB transport

TABLE 2. *Solute Carrier (SLC) Gene Families of Small-Molecule Transporters*

Family	Substrate Specificity	Abbreviations
SLC1	Acidic amino acid transporter	EEAT
	ASC small neutral amino acid transporter	ASCT
SLC2	Glucose transporter	GLUT
	H^+-myo-inositol transporter	HMIT
SLC3	Heavy chain of heterodimeric amino acid transporters	4F2hc
SLC4	Bicarbonate/carbonate exchangers and Na^+ coupled transporters	AE, NBC
SLC5	Sodium/substrate cotransporters (glucose, choline)	SGLT, CHT
SLC6	Neurotransmitter transporters (GABA, glycine, taurine, monoamines, creatine)	GAT, TAUT
SLC7	Cationic amino acid transporter	CAT
	Light chain of amino acid transporters	LAT
SLC8	Sodium/calcium exchanger	NCX
SLC9	Sodium/proton exchanger	NHE
SLC10	Sodium/bile salt cotransporter	NTCP, ASBT
SLC11	Natural resistance-associated macrophage protein	NRAMP
	Divalent metal-ion transporter	DMT
SLC12	Potassium/chloride cotransporter	KCC
SLC13	Sodium/sulphate cotransporter	NaS
	Sodium/dicarboxylate transporter	NaDC
SLC14	Urea transporter	UT
SLC15	Proton peptide transporter	PEPT
SLC16	Monocarboxylic acid transporter (lactate, pyruvate, ketone bodies)	MCT
SLC17	Vesicular glutamic acid transporter	VGLUT
SLC18	Vesicular amine transporter	VAT
SLC19	Vitamin transporters (folic acid, thiamine)	THTR
SLC20	Sodium-phosphate cotransporters	Pit
SLC21	Organic anion transporters	OATP
SLC22	Organic cation transporters	OCTN, OAT
SLC23	Sodium/ascorbic acid transporter	SVCT
SLC24	Sodium/calcium-potassium exchanger	NCKX
SLC25	Mitochondrial carriers	MC
SLC26	Anion exchangers	CFTR
SLC27	Fatty acid transport proteins	FATP
SLC28	Sodium dependent nucleoside transporters	CNT
SLC29	Equilibrative nucleoside transporters	ENT
SLC30	Zinc efflux transporters	ZNT
SLC31	Copper efflux transporters	CTR
SLC32	Vesicular neurotransmitter transporters	VIAAT, VGAT
SLC33	Acetyl-CoA transporters	AT
SLC34	Sodium/phosphate cotransporters	NaPi
SLC35	Nucleotide sugar transporters	UGT
SLC36	Lysosomal amino acid transporters	LYAAT
SLC37	Glucose-6-phosphate transporter	G6PT
SLC38	Sodium coupled neutral amino acid transporters	SNAT
SLC39	Metal ion transporters	ZIP
SLC40	Iron efflux transporter	MTP

in vivo on the blood side of the endothelium is sodium dependent,[48] which excludes the role of an ENT carrier in mediating uptake of circulating adenosine. Pyrimidine nucleosides are primarily transported by CNT1, and, to date, there is no evidence that the BBB expresses CNT1. Purine bases such as adenine and guanine are transported by a nucleobase transporter (NBT)[46] but, to date, no eukaryotic NBT transporter gene has been cloned.

In addition to the CMT systems shown in Figure 5, there are many other CMT genes expressed at the BBB, which enable the BBB transport of water-soluble vitamins, thyroid hormones, and other compounds. All of these CMT systems at the BBB, which may number in the dozens, are potential portals of entry of drugs to the brain. The CMT systems comprise highly stereospecific pore-based transporters, and there are significant structural requirements for transporter affinity. Therefore, it is unlikely that a drug, which is normally not transported across the BBB, would be made transportable by simply coupling to the drug to another molecule that undergoes CMT across the BBB. Rather, the structure of the pharmaceutical should be altered with medicinal chemistry so that it takes on the structure of a pseudo-nutrient and thus is able to undergo transport across the BBB via one of the

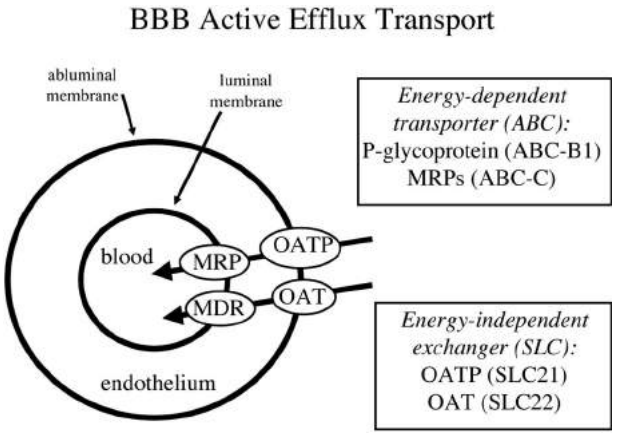

FIG. 6. BBB AET systems are comprised of an energy-dependent system at one side of the brain capillary endothelium and an energy-independent system at the opposite endothelial membrane. As a hypothetical example, members of the ABC gene family are shown at the luminal endothelial membrane, and members of the SLC gene family are shown at the abluminal endothelial membrane.

CMT systems. For example, the α-carboxylation of dopamine results in the formation of L-DOPA, and DOPA, a large neutral amino acid, is a substrate for the BBB LAT1. Once across the BBB, the L-DOPA is decarboxylated back to dopamine via aromatic amino acid decarboxylase. L-DOPA is the primary example of a pro-drug that traverses biological membranes, not via lipid mediation, but via carrier mediation.

AET

P-glycoprotein is the prototypic AET system at the BBB, and accounts for the active efflux of molecules in the brain to blood direction. P-glycoprotein, which is a product of the ABC-B1 gene (FIG. 6), is just one of many members of the ATP binding cassette (ABC) gene family of transporters. There are several multidrug resistance protein (MRP) transporters, which also belong to the ABC gene family. The excessive focus on p-glycoprotein, also called the multidrug resistance (MDR) gene product, overlooks the fact that P-glycoprotein is just one member of a large gene family, and many members of the ABC gene family may participate in BBB AET. A second consideration is that active efflux in the brain to blood direction requires the concerted actions of two different types of transporters: an energy requiring transporter at one membrane of the endothelium, and an energy-independent transporter, or exchanger, at the opposite membrane of the capillary endothelium. Examples of energy-independent exchangers are members of the solute carrier (SLC) transporter gene family and include the organic anion transporter (OAT) gene family or the organic anion transporter polypeptide (OATP) gene family (FIG. 6). OATP and OAT are members of the SLC21 and SLC22 gene families, respectively (Table 2).

Certain drugs are excluded from penetration into brain because these drugs are substrates for BBB AET systems. One strategy for increasing brain penetration of such drugs is the development of "co-drugs" that inhibit BBB AET systems and thereby allow increased brain penetration of the therapeutic drug. The development of pro-drugs to increase brain penetration of therapeutics might focus on MRP, OATP, or OAT transporters at the BBB in addition to p-glycoprotein.

RMT

Certain large-molecule peptides or proteins undergo transport from brain to blood via RMT across the BBB. There are at least three different types of BBB receptor systems as depicted in Figure 7. The transferrin receptor (TfR) is an example of a bidirectional RMT system that causes both the receptor-mediated transcytosis of holotransferrin in the blood to brain direction, and the reverse transcytosis of apo-transferrin in the brain to blood direction.[49,50] The neonatal Fc receptor (FcRn) is an example of a reverse RMT system that functions only to mediate the reverse transcytosis of IgG in the brain to blood direction, but not in the blood to brain direction.[51,52] The type 1 scavenger receptor (SR-VI) is an example of a receptor-mediated endocytosis system that mediates the uptake of modified low-density lipoprotein (LDL) from the blood compartment into the intraendothelial compartment, and this endocytosis is not followed by exocytosis into brain interstitial fluid.[53]

Molecular Trojan horses and BBB RMT

Certain endogenous ligands or peptidomimetic mAbs that bind exofacial epitopes on BBB RMT systems and that are endocytosing antibodies can act as molecular Trojan horses to ferry drugs, proteins, and nonviral gene medicines across the BBB using the endogenous RMT

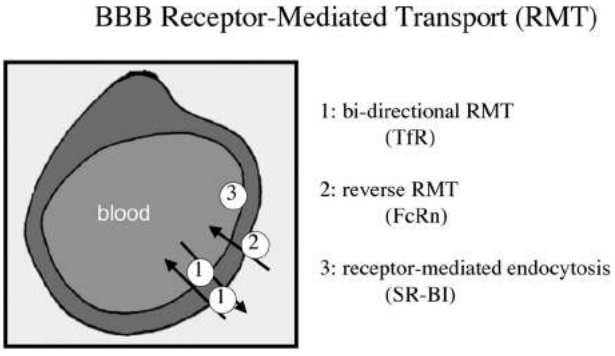

FIG. 7. BBB RMT systems are shown for three classes of systems. An example of a bidirectional RMT system is the endothelial transferrin receptor (TfR), which mediates the transport of holo-transferrin (Tf) in the blood to brain direction, and the transport of apo-Tf in the brain to blood direction. A reverse RMT system such as the neonatal Fc receptor (FcRn) transports IgG in the brain to blood direction only. An endocytosis system is illustrated by the type I scavenger receptor (SR-BI), which mediates the endocytosis of acetylated low-density lipoprotein into the endothelial compartment without transcytosis across the BBB.

systems. This BBB molecular Trojan horse technology has been reduced to practice *in vivo* in the following systems:

- Vasoactive intestinal peptide (VIP) causes a 60% increase in cerebral blood flow after intravenous injection in conscious rats.[54]
- BDNF causes 100% normalization of the pyramidal cell density in the CA1 sector of the hippocampus in adult rats subjected to transient forebrain ischemia after delayed intravenous administration.[55]
- BDNF reduces stroke volume 65-70% in adult rats with either permanent or reversible middle cerebral artery occlusion (MCAO) after delayed intravenous administration.[56,57]
- FGF-2 causes an 80% reduction in stroke volume in a permanent MCAO model in adult rats after delayed intravenous administration.[58]
- Epidermal growth factor (EGF) can be used as a peptide radiopharmaceutical to enable early detection of brain cancer that overexpresses the EGF receptor.[59]
- $A\beta^{1\text{-}40}$ can be used as a peptide radiopharmaceutical for the early detection of brain amyloid in Alzheimer's disease.[60]
- Sequence-specific peptide nucleic acids (PNA) can be used as antisense radiopharmaceuticals for the *in vivo* imaging of gene expression in brain, in either transgenic mouse models or adult rats with experimental brain cancer.[61,62]

In all of these studies, the peptide or antisense agent was ineffective in the brain *in vivo* after intravenous administration owing to the lack of transport of the molecule across the BBB. However, the intended CNS pharmacologic effect *in vivo* was achieved after intravenous administration, owing to conjugation of the peptide or antisense therapeutic to a BBB molecular Trojan horse. Molecular Trojan horses can also target liposomes[63] and nanoparticles[64] across the BBB. Nonviral plasmid DNA is encapsulated in pegylated liposomes, which are then targeted across the BBB and the brain cell membrane with peptidomimetic monoclonal antibodies that function as molecular Trojan horses.[65] The pegylated immunoliposome (PIL) nonviral gene transfer technology has enabled 100% normalization of striatal tyrosine hydroxylase activity in experimental Parkinson's,[66] and a 100% increase in survival time of adult mice with experimental brain cancer.[67] After intravenous administration of PILs carrying an exogenous reporter gene, the exogenous gene was globally expressed in all regions of the brain of the adult Rhesus monkey after intravenous injection of a nonviral formulation.[68] Plasmid DNA that produces short hairpin RNA for the purposes of silencing genes

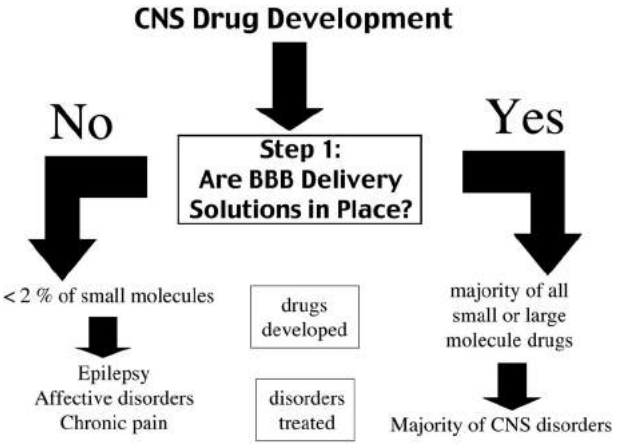

FIG. 8. Step 1 in CNS drug development is the availability of effective BBB drug or gene targeting technology. In the absence of a BBB technology, then the CNS drug developer is limited to lipid-soluble low molecular weight drugs, and only a few CNS diseases consistently respond to this class of molecule.

through a mechanism of RNA interference (RNAi) can be delivered across the BBB with the PIL gene targeting technology.[69] This resulted in an 88% increase in survival time in adult mice with experimental human brain cancer that were treated with DNA-based RNAi therapeutics directed against the human EGF receptor.[70]

CONCLUSIONS

The development of new drugs for brain disorders is a formidable challenge, and there is no effective treatment for the majority of brain diseases (FIG. 2). The inability to treat most brain diseases is incongruous with the tremendous progress made in the molecular neurosciences. The brain drug discovery sciences have, in fact, been highly successful, and many new therapeutics have been discovered, which could potentially be used to treat the brain, if the BBB problem was solved. However, if the drugs cannot be delivered across the BBB, then there is no translation from the lab to the clinic. Step number 1 in CNS drug development is providing solutions to the BBB problem (FIG. 8). If no BBB delivery solutions are in place, which is the standard in the pharmaceutical industry, then the number of drugs that can be developed as new neurotherapeutics is less than 2% of small molecules and is ~0% of large molecules. The few small molecules that do cross the BBB are those drugs that have high lipid solubility and molecular mass less than 400 Da, and these drugs generally only treat certain CNS disorders, such as epilepsy, affective disorders, and chronic pain (FIG. 8). In the absence of an effective BBB technology, the pharmaceutical industry cannot provide therapeutics for the majority of patients with brain disorders. It is estimated that the global CNS pharmaceutical market would have to grow by more than 500% just to equal the cardiovascular market,[71] and there are more

patients with CNS disorders than there are with cardiovascular disease. If BBB delivery solutions were in place for either small or large molecules, then almost any pharmaceutical could enter clinical drug development programs and therapies could be developed for most CNS disorders (FIG. 8).

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Specific role of polysorbate 80 coating on the targeting of nanoparticles to the brain.

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Author information

Abstract

It was reported that nanoparticles with polysorbate 80 (Tween 80, T-80) coating represented tools used for delivering drugs to brain. Nevertheless, disputations were once aroused for some complications. Aimed to have a better understanding of the specific role of T-80 coating on nanoparticles and simplify the problem, the direct observation of brain targeting combined with in vivo experiments was carried out in this work using the model nanoparticles (MNPs). The presence of a complex composed by the model loading, T-80 and nanoparticles was found in the preparation of MNPs. The result was further supported by some surface properties of MNPs. Being bound to nanoparticles that were overcoated by T-80 later, was necessary for the loading to be delivered to brain. Partial coverage was enough for T-80 coating to play a specific role in brain targeting. It seemed that brain targeting of nanoparticles was concerned with the interaction between T-80 coating and brain micro-vessel endothelial cells. Therefore, the specific role of T-80 coating on nanoparticles in brain targeting was confirmed.

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The use of fetal bovine serum: ethical or scientific problem?

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Author information

Abstract

Fetal bovine serum (FBS) is a common component of animal cell culture media. It is harvested from bovine fetuses taken from pregnant cows during slaughter. FBS is commonly harvested by means of a cardiac puncture without any form of anaesthesia. Fetuses are probably exposed to pain and/or discomfort, so the current practice of fetal blood harvesting is inhumane. Apart from moral concerns, several scientific and technical problems exist with regard to the use of FBS in cell culture. Efforts should be made to reduce the use of FBS or, preferably, to replace it with synthetic alternatives.

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EXPERIENCE AND REASON

Hyperosmolality in Small Infants Due to Propylene Glycol

ALLEN M. GLASGOW, ROGER L. BOECKX, MARILEA K. MILLER, MHAIRI G. MACDONALD, GILBERT P. AUGUST, STEPHEN I. GOODMAN

Abstract

Propylene glycol (1,2-propanediol) is used in many drug preparations. Although propylene glycol is regarded as having low toxicity in adults, in humans and animals there have been reports of CNS, renal, hematologic, and cardiac toxicity.[1-5] The absorption of propylene glycol through large burn wounds has recently been documented as a cause of serum hyperosmolality.[6,7]

Investigation of the cause of unexplained hyperosmolality in a premature infant led to the finding that several infants in our nursery were hyperosmolar due to administration of propylene glycol in a multivitamin preparation used in parenteral nutrition. This finding raises concern about the relatively large dose of propylene glycol that may be received by very small infants, especially those receiving multiple medications.

Note: Parenteral = Intravenous, intramuscular, subcutaneous, or intradermal administration.

Previous Next

Glyphosate pathways to modern diseases VI: Prions, amyloidoses and autoimmune neurological diseases

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Usage of the herbicide glyphosate on core crops in the USA has increased exponentially over the past two decades, in step with the exponential increase in autoimmune diseases including autism, multiple sclerosis, inflammatory bowel disease, type 1 diabetes, coeliac disease, neuromyelitis optica and many others. In this paper we explain how glyphosate, acting as a non-coding amino acid analogue of glycine, could erroneously be integrated with or incorporated into protein synthesis in place of glycine, producing a defective product that resists proteolysis. Whether produced by a microbe or present in a food source, such a peptide could lead to autoimmune disease through molecular mimicry. We discuss similarities in other naturally produced disease-causing amino acid analogues, such as the herbicide glufosinate and the insecticide L-canavanine, and provide multiple examples of glycine-containing short peptides linked to autoimmune disease, particularly with respect to multiple sclerosis. Most disturbing is the presence of glyphosate in many popular vaccines including the measles, mumps and rubella (MMR) vaccine, which we have verified here for the first time. Contamination may come through bovine protein, bovine calf serum, bovine casein, egg protein and/or gelatin. Gelatin sourced from the skin and bones of pigs and cattle given glyphosate-contaminated feed contains the herbicide. Collagen, the principal component of gelatin, contains very high levels of glycine, as do the digestive enzymes: pepsin, trypsin and lipase. The live measles virus could produce glyphosate-containing haemagglutinin, which might induce an autoimmune attack on myelin basic protein, commonly observed in autism. Regulatory agencies urgently need to reconsider the risks associated with the indiscriminate use of glyphosate to control weeds.

Keywords: autism, autoimmune disease, collagen, glycine, glyphosate, multiple sclerosis, protein misfolding, vaccines

1. INTRODUCTION

At first glance, multiple sclerosis (MS) and autism appear to have little in common, aside from the fact that both are neurological diseases. Autism is a condition with prenatal or early childhood onset, characterized by repetitive behaviours, impaired social interaction and cognitive impairment. The male:female ratio for autism is 4:1, while multiple sclerosis is twice as common in women as in men; its first symptoms usually begin in early adulthood to involve impaired lower limb mobility, although in later stages it affects both mental and physical capabilities. Both conditions are, however, associated with inflammatory autoimmune features [1, 2], and both diseases are viewed as having an environmental and a genetic component [3–6].

A study comparing a population of 658 MS patients with the general population found an association between MS and increased rates of asthma, inflammatory bowel disease (IBD), type 1 diabetes mellitus, pernicious anaemia and autoimmune thyroid disease [7], all of which have also been linked to autism [8–11]. These conditions are all considered to be *autoimmune diseases*, which can be triggered through molecular mimicry, where an antibody responding to a foreign protein that resembles a native protein becomes sensitized to the native protein as well [12]. A paper by Shoenfeld and Aron-Maor in 2000 developed the argument that both autism and MS may be examples of an autoimmune reaction via mimicry following exposure to an antigenic stimulus, possibly from an infection or through vaccination [13]. They further propose specifically that myelin basic protein (MBP) and other proteins constituting the myelin sheath are attacked by the immune system in both autism and MS. This has been recognized by many others in autism [14, 15] and MS [16–20]. In 1982, Weizman et al. reported a cell-mediated autoimmune response to human MBP in 76% of the autistic children studied [16]. Immune sensitization to the myelin sheath proteins could arise either through mimicry as a consequence of exposure of the immune system to a foreign antigen with a similar peptide sequence that is

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resistant to clearance, or because the proteins themselves have been altered in some way that renders them defective, exposed and/or resistant to proteolysis.

Unlike DNA synthesis, protein synthesis is highly prone to error [21, 22]. It appears that biological systems have adopted a strategy of allowing coding errors to survive during active synthesis, but use protein misfolding as a criterion to mark a defective peptide for degradation and recycling through ubiquitination. It is estimated that 15% of average-length proteins will have at least one misincorporated amino acid. Typically, 10–15% of random substitutions disrupt protein function, mostly because of misfolding [22]. Such destabilization causes protein–protein aggregation, and can lead to multiple neurological diseases and amyloidoses. Drummond et al. propose that early-forming toxic oligomers of amyloidogenic proteins are enriched with missense errors [22].

Glyphosate is the active ingredient in the pervasive herbicide Roundup and in many other formulations of herbicides used to control weeds on agricultural, residential and public land worldwide. A recent study based in Germany involving 399 urine samples from adults not involved in agricultural work revealed glyphosate residues above the detection limit in the urine of 32% of the subjects, and residues of AMPA, a metabolite, in 40% [23]. In a paper published in 2014, Swanson et al. showed a remarkable correlation between the rising rate of glyphosate usage on corn (maize) and soy crops in the USA and an alarming rise in a number of different chronic diseases [24]. Additional strong correlations for other conditions and diseases are provided in two follow-on papers [25, 26]. While correlation does not necessarily mean causation, causation becomes much more likely if a plausible mechanism can be found. Swanson et al. found a remarkable 0.98 correlation coefficient between the rise in autism rates in the USA and the use of glyphosate on crops (P-value $\leq 9.6 \times 10^{-6}$). The correlation for multiple sclerosis was not as high, but still highly significant at 0.83 (P-value $\leq 1.1 \times 10^{-5}$). IBD had a correlation coefficient of 0.94 (P-value $\leq 7.1 \times 10^{-8}$) (see Table 1 for other diseases).

Table 1. Correlations between time trends in several diseases and conditions recorded by the US Centers for Disease Control (CDC) with glyphosate usage on corn (maize) and soy crops reported by the USDA. Data reproduced from [23] and [25].

Disease	Correlation coefficient (R)	P-value
Autism (prevalence)	0.98	9.6×10^{-6}
MS (deaths)	0.83	1.1×10^{-5}
IBD	0.94	7.1×10^{-8}
Anaemia	0.90	1.8×10^{-4}
Diabetes (prevalence)	0.97	9.2×10^{-9}
Thyroid cancer (incidence)	0.99	7.6×10^{-9}

IBD, especially among children, is an emerging global epidemic [27] that is linked to autism [28, 29]. Impairment of intestinal barrier function is a core feature of IBD [30]. Increased intestinal permeability promotes infiltration of unmetabolized peptides into the lymph system and general circulation. This provides an opportunity for an immune antigenic response, which by molecular mimicry can lead to an attack on crucial proteins in the brain and spinal column. Disturbances of collagen texture are a major factor leading to the onset of diverticular disease and IBD along with the disturbed wound-healing mechanisms seen in the pathogenesis of anastomatic leakage following large bowel surgery [31].

In a recent paper [32], we suggested that glyphosate, a non-coding amino acid analogue of glycine, could substitute for glycine in error during protein synthesis. Such misincorporation and disruption of proteostasis could explain the strong correlations observed between glyphosate usage and multiple modern diseases. *In this paper, we show that this could be one of the most important mechanisms by which glyphosate could induce multiple autoimmune diseases.*

A prime site for initiation of the disease process is the colon, where misfolded collagen, resistant to degradation, could lead to an autoimmune disease and, subsequently, a leaky gut. Autoantibodies against type VII collagen have been detected in up to 68% of IBD patients [33]. Glycine is the most common amino acid in collagen, making up one fourth of the residues in the protein. Proline is also a very common component of collagen and, as we discuss later in this paper, proline resists hydrolysis. Incomplete collagen degradation by matrix metalloproteinases in the gut could lead to the accumulation of short pro–gly–pro peptides that are resistant to proteolysis. These could then induce the infiltration of neutrophils or the activation of resident immune cells to induce an inflammatory response [34].

An unpublished study conducted by Monsanto and submitted to the US Environmental Protection Agency (EPA) traced the accumulation of radiolabeled glyphosate in various tissues of rats following low-dose oral administration (10 mg/kg body weight) [35]. By far the highest accumulation was found in the bones (Table 11 in [36]). Radioactive levels in the colon were 4–6 times as high as those in the stomach and small intestine.

The production of novel non-coding amino acids by plants and microbes wards off predators. The toxicity of these products may be due to the fact that they replace coding analogues during protein synthesis. Examples include: azetidine-2-carboxylic acid (Aze), a proline analogue [37, 38]; glufosinate, a glutamate analogue that is also a popular herbicide [39]; β-N-methylamino-L-alanine

(BMAA), an analogue of serine [40]; and L-canavanine, a natural analogue of L-arginine that is exploited as an insecticide [41, 42].

A remarkable true-life story involving a 119-day Alaskan wilderness experiment conducted by Christopher McCandless was recounted in the book *Into the Wild* by Jon Krakauer (later made into a popular movie) [43]. McCandless was thought to have died in the wilderness from starvation; however, Krakauer always suspected a toxin in the seeds of the wild potato, *Hedysarum alpinum*, which formed a staple of his diet in his last month of life. Krakauer had originally suspected a poisonous alkaloid but, through later research, was able to identify a significant level of L-canavanine in the wild potato seeds and published a paper on this analysis with several other authors in 2016 [42].

A key factor in L-canavanine's toxicity is its ability to insinuate itself into peptides in place of L-arginine. L-canavanine can be assimilated into essentially any protein to create aberrant canavanyl proteins that can disrupt many fundamentally important biochemical reactions across a broad spectrum of organisms [41, 44]. L-canavanine is exploited in agriculture as a potent insecticide against the tobacco hornworm [45], although the tobacco budworm has developed tolerance with a unique enzyme, canavanine hydrolase, which can quickly metabolize it [46]. Larvae exposed to L-canavanine incorporate it into the protein lysozyme, resulting in a 48% loss in catalytic activity [41]. Furthermore, diptericins B and C of *Protoformia terranovae*, but not diptericin A, are negatively impacted by L-canavanine. The distinction is that diptericin A has histidine at position 38 instead of the L-arginine found in the other two diptericins. Presciently, with respect to glyphosate, Rosenthal wrote: "These insect studies support the view that the biological effects of canavanine result from its incorporation into a protein, resulting in an alteration in protein conformation that leads ultimately to impairment of protein function" [41].

2. SHIKIMATE PATHWAY INHIBITION REVISITED

The shikimate pathway enzyme, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) is believed to be the main target of glyphosate's toxicity to plants [47]. A 1991 paper by Padgette et al. describes studies to gain insight into the mechanism by which glyphosate disrupts EPSPS [47]. Surprisingly, it is not understood exactly how glyphosate binds to the active site.

The microbes *Klebsiella pneumoniae, Escherichia coli* [47, 48] and *Agrobacterium sp.* strain CP4 [48, 49] have all evolved to produce versions of EPSPS that are glyphosate-resistant. The CP4 variant has been widely exploited by importing it into genetically modified glyphosate-resistant crops [48]. Insight can be gained by investigating the alterations to the peptide sequence that afforded resistance. All three mutations involved replacing a glycine residue at the active site with alanine [47, 48]. In the case of *E. coli*, the mutated enzyme is about 72 times *less* efficient than the wild-type enzyme, but 69 times *more* efficient in the presence of glyphosate. Changing the DNA code from glycine to alanine completely disables glyphosate's inhibiting effects on the enzyme [48].

Substitution of gly-96 at the active site in *E. coli* by serine leads to a version of the enzyme that is unable to bind PEP, most likely due to steric hindrance. The authors speculated that the hydroxymethyl group of serine displaces the phosphate of PEP and functions as a nucleophile. In fact, this mutated enzyme achieves a kind of reverse reaction, breaking EPSP down into shikimate-3-phosphate and pyruvate via hydrolysis.

We propose that substitution of gly-96 (gly-100 in the CP4 variant) by glyphosate during protein synthesis could explain its disruption of the enzyme's function. One can expect that the highly reactive and bulky glyphosate molecule, if substituted for gly-96, would behave more like serine than alanine. An additional disruptive factor is glyphosate's chelation of manganese, which would disrupt the catalytic action of EPSPS. A cell containing both wild-type and glyphosate-substituted forms of the enzyme would arguably circuitously convert PEP to pyruvate via EPSP without producing ATP from ADP; i.e., would waste the energy in the phosphate bond, as shown in Fig. 1, and end up with excess pyruvate and a deficiency in EPSP.

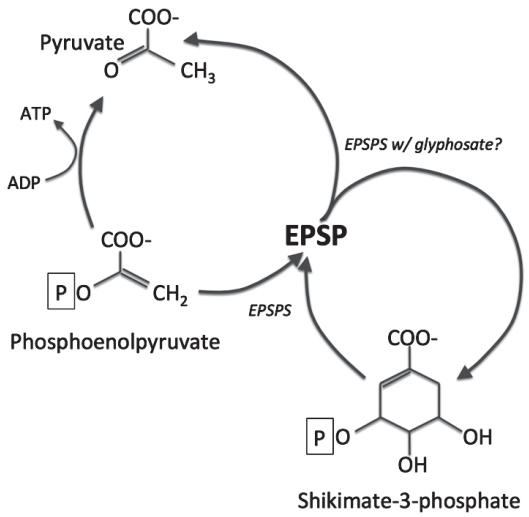

Figure 1. Diagram of the hypothetical pathway by which glyphosate substitution for glycine in EPSPS could result in the synthesis of pyruvate from PEP without generating ATP; i.e., wasting the energy in the phosphate group, as discussed in the text.

3. GLYPHOSATE AS A GLYCINE ANALOGUE

While glyphosate's main mechanism of toxicity to plants is considered to be disruption of the shikimate pathway, it is also likely that it disrupts other biological pathways where glycine is either a substrate or a ligand, due to the fact that it is a glycine analogue. It has been proposed that, through glycine mimicry, glyphosate's rôle as a ligand to NMDA receptors in the brain could explain its known ability to activate NMDA receptors and cause neuronal damage [49, 50]. In [51], acute exposure of rat hippocampal slices to Roundup (0.00005–0.1%) for 30 minutes caused oxidative stress and neuronal cell death, which was attributed to NMDA receptor activation. Glyphosate also interferes with the synthesis of porphyrin, a precursor to haem, by disrupting the first step in the pathway where glycine is substrate [52].

N-substituted glycine "peptoids" are an attractive class of synthetic molecules that can be constructed by linking component N-substituted glycines at sequential nitrogen–carbon bonds; they are directly analogous to the linking of amino acids into peptides [53]. Glyphosate is of course an N-substituted glycine, where the nitrogen side chain is a methyl phosphonyl group. Part of the attraction of peptoids is that they are highly resistant to proteolysis, just as is the amino acid proline, in which the carbon side chain circles back and binds to the peptide nitrogen. Impaired ability to break down proline-rich gliadin has been proposed as a contributing factor in coeliac disease and gluten intolerance [54]. This can explain why common cereals with high proline contents are especially problematic to gluten-sensitive individuals [55, 56].

Glyphosate is probably particularly problematic when it substitutes for N-terminal glycines in proteins where these glycines are highly conserved and play a significant rôle. Several proteins rely on an N-terminal glycine for anchoring to the plasma membrane (e.g., endothelial nitric oxide synthase (eNOS) [57]) or to the cytoskeleton (e.g., Kelch-like ECH-associated protein 1 (KEAP1) [58]). Protein N-myristoylation and prenylation depend on an amide bond to the N-terminal glycine residue [59]. For example, myristoylated G proteins involved in many signaling mechanisms depend on an N-terminal glycine residue [59]. This would be disrupted if the nitrogen atom has a side chain through glyphosate substitution for the terminal glycine.

N-nitrosoamino acids form a reasonable model for N-nitrosoglyphosate, a carcinogenic derivative of glyphosate that was of concern to the EPA during Monsanto's early studies. N-nitrosoproline is particularly relevant because proline, like glyphosate, has an extra carbon atom bound to the nitrogen atom. With respect to non-coding amino acids, and especially the incorporation of N-nitrosoamino acids into peptides and proteins, R.C. Massey remarked: "In addition to their presence as free N-nitrosoamino acids, species such as N-nitrosoproline (NPRO) and N-nitroso-4-hydroxyproline (HONPRO) may exist in a peptide- or protein-bound form as a result of N-nitrosation of an N-terminal imino acid residue" [62]. Tricker et al. [63] and Kubacki et al. [64] devised high performance liquid chromatography–thermal energy analyser (HPLC–TEA) techniques for analysis of multiple dipeptides with a nitrosylated N-terminal, including N-nitrosoprolylalanine (NPROALA), N-nitrosoprolyl-4-hydroxyproline (NPROHOPRO) and N-nitrosoprolylglycine (NPROGLY) [63, 64]. Tricker notes that the average recoveries for NPROALA, NPROHOPRO and NPROGLY, 200 μg of which was added to cured meat, were between 69 and 88%. Tricker also used the method to analyse the nitroso-tripeptide N-nitrosoprolylglycylglycine [65].

Nitrosamines of glyphosate (N-phosphonomethylglycine), its salts and esters include: N-nitrosoglyphosate (NNG) (Monsanto CP 76976), N-nitrosoiminodiacetic acid (NNIDA), N-nitrosoglyphosate sodium salt (NNGNa), N-nitrosoglyphosate isopropylamine ester (NNGIPA), N-nitrosoglyphosate potassium salt (NNGK), the metabolite N-nitrosoAMPA (NNAMPA), the metabolites N-nitrosodimethyl amine (NDMA) and N-nitrosarcosine (NSAR), which occur in glyphosate products or may be generated *in vivo* or in soils and waterways. N-nitroso compounds derived from secondary amines are considered carcinogenic.

Monsanto glyphosate documents reveal analysis and quantification of five nitrosamines of concern [61]. Out of six lots of Roundup analysed for NNG, four lots contained NNG residues of 0.61 to 0.78 ppm and two lots had residues from 0.22 to 0.40 ppm NNG. Analysis of six lots of Monsanto Rodeo revealed NNG residues in the range 0.13–0.49 ppm.

Recently, a powerful metatranscriptome study on bacterial gene expression following glyphosate treatment was conducted on microbes growing within the rhizosphere of glyphosate-tolerant corn [66]. RNA transcript abundance was compared between control and glyphosate-treated samples in order to characterize which protein genes were upregulated or downregulated. While they found many changes in gene expression, most striking to us was the upregulation of genes involved in both protein synthesis and protein hydrolysis. The ribosomal proteins L16p (L10e) and Firmicutes ribosomal L7Ae family proteins involved in the synthesis of the ribosomal large subunit increased 1.4- and two-fold, respectively, and the small subunit ribosomal protein S11p (S14e) increased 1.5-fold. Upregulation of genes involved in protein degradation was even more dramatic. For

example, transcripts for a proteasome β 2 subunit (EC 3.4.25.1) increased 4.3-fold and aminopeptidase YpdF increased threefold. An explanation could be an increase in the number of proteins that fail to fold properly due to glyphosate substitution for glycine in the protein. These authors also suggested a potential shift towards an increase in glyphosate-tolerant bacteria, a point that will become important later in this paper.

These results are corroborated by a study on pea plants grown in hydroponic culture, which revealed that glyphosate induced a significant increase in two major systems for proteolytic degradation: the ubiquitin-26 S proteasome system and papain-like cysteine proteases [67]. It also increased the total free amino acid content and decreased the soluble protein in the root system.

4. GLYPHOSATE-CONTAMINATED COLLAGEN AND PROTEOLYSIS RESISTANCE

We mentioned in the Introduction the gly–pro–gly peptide sequence that is common in collagen and linked to autoimmune disease. There are several enzymes in multiple organisms that are devoted to the proteolysis of peptide sequences containing proline, particularly the gly–pro sequence. These include enzymes that detach a terminal proline, enzymes that detach a dipeptide sequence where the second residue is a proline molecule and the first one is often glycine, and enzymes that break apart the X–pro dipeptide to release two free amino acids, one of which is proline. Certain pathogens have special modified versions of these enzymes, and there are genetic diseases related to pathologies in these enzymes. Substitution of glyphosate for glycine in this sequence is likely to cause extra stress to the enzymes that break down these sequences, potentially leading to autoimmune disease.

Prolyl aminopeptidase is an enzyme that detaches a terminal proline residue from a peptide. The enzyme is expressed predominantly by pathogenic bacteria in the gut, in particular *Serratia marcescens*, a common pathogen in the gut as well as in the urinary tract; it is often multiply antibiotic-resistant and is a serious threat in hospital-acquired infection [34]. This enzyme is especially important to the pathogens for degrading collagen, providing amino acids as fuel. It is conceivable that the pathogens are able to degrade glyphosate-contaminated peptides terminating in proline whereas the human form of the enzyme is not. It is intriguing that the *S. marcescens* version of prolyl aminopeptidase is unusual in having extra space at the active site [34], which could potentially accommodate the larger glyphosate molecule adjacent to the terminal proline residue. This might also contribute to glyphosate's observed effect on the gut microbiome: excessive growth of pathogens.

Multiple strains of the toxic mould *Aspergillus* secrete an X–prolyl dipeptidyl aminopeptidase (X-PDAP) that is important for digesting collagen because it can separate out an X–pro pair to bypass the difficult step of breaking the X–pro bond. Research has shown that this enzyme is essential for hydrolysing proline-containing peptides [69, 70]. It is likely that it becomes even more essential when X is glyphosate, as the peptoid sequence glyphosate–proline is likely almost impossible to break. Since gly–pro is a very common sequence in collagen, glyphosate–pro is likely to impede the breakdown of collagen fragments, which may then encourage *Aspergillus* infection in both plants and animals. Glyphosate has been shown to increase the growth rate of *Aspergillus* [71].

The most disturbing question is, what happens in the absence of pathogens that can effectively clear collagen peptides contaminated with glyphosate? As we will see later in this paper, antibodies to collagen are linked to antibodies to vaccines. A genetic defect in the enzyme prolidase, which can break apart the very common gly–pro dipeptide to release the individual amino acids, leads to a severe disease with mental deficiencies and multiple skin lesions [72]. Intriguingly, a common plant pathogen, *Xanthomonas campestris*, which causes blight on multiple plant species has a unique variant of prolidase with two mutations, a substitution of tyrosine for gly-385 and valine for tyr-387, two highly conserved residues in the peptide sequence [73]. Is it possible that swapping out glycine affords protection from glyphosate substitution for this residue? We hypothesize that peptides derived from multiple proline and glyphosate-contaminated proteins, which are highly resistant to proteolysis, are causing an autoimmmune epidemic that is an important contributor to autism and other autoimmune disorders.

5. BMAA AND ALS IN GUAM

β-N-methylamino-L-alanine (BMAA) is another noncoding amino acid and an analogue of serine [40]. BMAA is synthesized by cyanobacteria, the microbes responsible for the toxic algal blooms that occur in lakes experiencing an accumulation of nitrogen and phosphate nutrients following hot, rainy weather [74]. An *in vitro* study by Dunlop et al. in 2013 demonstrated that BMAA can be misincorporated into human proteins, causing protein misfolding that could lead to neurological diseases [40].

BMAA has, in fact, been linked to several neurodegenerative diseases, including Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) [75]. A 2013 study linked an ALS cluster in Chesapeake Bay to consumption of BMAA-contaminated crabs [76]. A study in France investigated an ALS cluster near a lagoon that supplied oysters and mussels to the local

population. The authors demonstrated that the shellfish were contaminated with BMAA, but also remarked that there was intensive chemical-based agriculture in the region [77]. Interestingly, cyanobacteria have been found to be remarkably resistant to glyphosate [78, 79], and this could contribute to the recent record-setting algal blooms in the Great Lakes region, where glyphosate is extensively used on genetically modified (GM) Roundup-Ready crops [80].

One likely molecule that could be adversely affected by BMAA is the glutamate transporter, whose defective expression has been linked to ALS [81]. Glutamate excitotoxicity in motor neurons is associated with ALS, and this could be caused by an impaired glutamate transport system. Ordinarily, astrocytes quickly clear glutamate from the synapse, following its release by neurons, and the transporter is essential for this clearance. A conserved serine-rich motif in the glutamate transporter forms a reëntrant loop, similar to a structure found in many ion channels [82]. This loop is crucial for the enzyme's proper function, and would be disrupted by substitution of BMAA for serine.

An interesting detective story has evolved around an epidemic of a complex neurological condition termed amyotrophic lateral sclerosis–Parkinsonism dementia complex (ALS–PDC), which reached epidemic proportions during a short interval after World War II among the native Chamorro people on the small island of Guam in the South Pacific. At the peak of the epidemic, the natives had a hundredfold increased risk to ALS and Parkinson's disease compared to the risk in the general human population.

A plausible explanation for this epidemic relates to a popular native food source: seeds from the cycad trees [83–85]. Cycad seeds contain BMAA, likely derived from associated cyanobacteria. However, what is especially interesting is that the BMAA becomes concentrated in the skin of fruit bats that feed on the cycad seeds. Fruit bats were a popular delicacy among the natives, who ate every part of them, including the skin. Increased access to firearms from the USA during the war may have made it easier to kill the bats, on which the natives then feasted, ultimately leading to the natives' near-extinction through the accumulation of BMAA in their brains [86]. Meanwhile the near-extermination of the bats through the hunting removed the presumed source of the epidemic [83].

However, the warfare also led to the accumulation of many toxic chemicals in the soil, which could have encouraged the proliferation of cyanobacteria, which are especially resilient in the face of stressors. The bats' demise was undoubtedly hastened by the accumulation of excess BMAA in their tissues. A measurement of the amount of BMAA in three dried specimens of fruit bats from Guam taken from a museum in Berkeley found concentrations between 1200 and 7500 μg/g, which indicates up to hundredfold bioamplification over the level in the seeds of the cycad tree [87].

There have been inconsistent results in measuring the levels of BMAA in different tissue samples, but this has been explained recently by the realization that any BMAA incorporated into proteins may be missed in analysis without sufficient proteolysis. Ince et al. wrote: "When the insoluble, protein-containing fraction following TCA (trichloroacetic acid) extraction is further hydrolysed to release BMAA from protein, there is a further pool of protein-bound BMAA that is present in a ratio of between 60:1 and 120:1 compared with the pool of free BMAA" [84, p. 348]. We believe that this point has great significance when it comes to glyphosate: we highly suspect that different methodologies used to measure glyphosate contamination in any situation where there is a significant protein-bound component may yield different results depending on the degree to which protein hydrolysis is carried out.

6. GLYPHOSATE CONTAMINATION IN COLLAGEN, ENZYMES, GELATIN AND VACCINES

Gelatin is commonly used as an excipient stabilizer in vaccines, particularly the live virus vaccines. Gelatin is derived from animal skin and bone, especially of pigs and cattle; they may be fed glyphosate-contaminated forages, including GM Roundup-Ready corn and soy feed, which are sometimes supplemented with GM Roundup-Ready beet pulp. Gelatin is mainly derived by partial hydrolysis from the collagen in skin and bone. 26% of the amino acids in collagen are glycine; proline and hydroxyproline together make up 18% [88]; and glutamate constitutes 6%. All three of these components are problematic. The proline could be substituted by Aze from the sugar beet, the glycine could be substituted by residual glyphosate in the feed, and glutamate is a neurotransmitter but known to be neurotoxic at high concentrations; it works together with glycine to excite NMDA receptors in the brain. The vaccine virus may incorporate some of the noncoding amino acids into its own proteins to produce versions of them that resist proteolysis and induce autoimmunity through molecular mimicry.

One of us (Samsel) analysed a number of animal protein products for glyphosate. These included the bones of pigs, cows, horses' hooves, bees and bee products, collagen and gelatin products, vitamins, protein powders, enzymes and vaccines. Results are shown in Tables 2 and 3. Both high performance liquid

chromatography with tandem mass spectrometry (HPLC–MSMS) and enzyme-linked immunosorbent assay (ELISA) methods were utilized. It has been shown that both HPLC and ELISA are comparable in terms of accuracy and precision for detection and quantification of glyphosate in water-based analysis and including Nanopure, tap and river waters. Water-based solvents for glyphosate demonstrate a detection limit of 0.6 ng/mL and a linear functional range of 1–25 ng/mL [200]. However, HPLC was not able to achieve detection below 5 ppb;[1] hence, in cases including water-based vaccines, analysis using numerous sample runs was made including using two independent labs to test the same samples.

Table 2. Residues of glyphosate found in animal-based products that were reported to the US Food and Drug Administration (FDA) by Samsel Environmental & Public Health Services. The limit of detection for glyphosate using hot water extraction is 0.075 parts per billion (ppb).[1]

Protein substrate	Type	Test date	Glyphosate residue (ppb)[1]
GELATIN	JELL-O ORANGE #07 JAN 2018 DB02 02:36	29 July 2016	9.00
GELATIN	POWER-MAX PROTEIN POWDER ADVANCED NUTRITION	29 July 2016	14.94
GELATIN	DISNEY GUMMIES VITAMINS	9 August 2016	8.27
GELATIN	FLINTSTONES GUMMIES VITAMINS	9 August 2016	5.32
ORAGEL	CHILDREN'S ORAGEL 7.5% BENZOCAINE FORMULA	26 September 2016	2.81

HPLC–MSMS was also later used, where the method detection limit (MDL) permitted, for additional confirmation and quantification of glyphosate in digestive enzymes and collagens. Spiked sample recoveries were done for all samples tested. Freshly prepared glyphosate standard solutions were run as controls and results were calculated based on a standard curve.

In 1989, Monsanto researchers conducted an experiment on exposure of bluegill sunfish to ^{14}C-radiolabeled glyphosate [89]. One of us (Samsel) obtained the (unpublished) report from the EPA through the Freedom of Information Act. The researchers had found that, with EDTA extraction, the amount of radiolabel in tissue samples was much higher than the amount of detected glyphosate. They decided to apply a digestive enzyme, proteinase K, and discovered that this "caused a substantial improvement in extractability". It brought the yield from 17–20% in the case of EDTA to 57–70% following digestion with proteinase K. They summed up as follows: "Proteinase K hydrolyses proteins to amino acids and small oligopeptides, suggesting that a significant portion of the ^{14}C activity residing in the bluegill sunfish tissue was tightly associated with *or incorporated into* protein" (present authors' emphasis). In this context it is important to recall that a 60- to 120-fold higher detection level of BMAA was obtained following protein *hydrolysis* of contaminated proteins [84].

Since Monsanto found bioaccumulation of glyphosate in all animal tissues, with the highest levels in the bones and marrow [35, 36], one would expect that all tissues derived from animals fed a diet containing glyphosate residues and used for food by people around the globe would be contaminated. Knowing that the bioaccumulation of glyphosate would be evident in the vast majority of animals raised for market and fed a contaminated diet, as well as their products; and suspecting the possibility of contamination of even the digestive enzymes derived from these animals, one of us (Samsel) decided to analyse random samples.

Results from various gelatin-based products, along with the results for several different vaccines (discussed later) were reported to the FDA by Samsel Environmental & Public Health Services in August 2016. Table 2 shows results for glyphosate residues found in these gelatin-based products. The highest level found in a gelatin sample was almost 15 ppb.[1]

Having found glyphosate in animal gelatins, analysing the collagen at the source was a logical next step. Tissues from pork and cattle obtained from a local supermarket, commercially available collagen sourced from industrially-raised swine and oxen, as well as the purified digestive enzymes pepsin, lipase and trypsin, derived from pigs, were selected for evaluation. Three methods of laboratory analysis were used to determine if

[1] Parts per (US) billion. To put this into perspective, 1 ppb = 1 μg/kg, and 1 μg of glyphosate (N-phosphonomethylglycine) contains 3.561×10^{12} molecules of the substance, each one of which could integrate with a protein.

glyphosate was present in porcine pepsin and in the glycine-rich collagen from the tissues of pigs and cattle, protein sources that are regularly consumed by Americans. The results are given in Table 3.

Glyphosate integration with enzymes is a serious consideration, as glyphosate may serve as an enzyme inhibitor like other phosphonates [90–92]. Inhibition and immobilization of enzymes may occur via three basic categories: covalent linkage; adsorption on a carrier; or entrapment within macromolecules [93].

Inhibition of enzymes may be reversible or irreversible. Types of reversible enzyme inhibition include competitive, noncompetitive and uncompetitive. *Irreversible* inhibitors covalently bond to the functional groups of the active site, thus permanently inactivating catalytic activity. Irreversible inhibition includes two types: group-specific inhibition and "suicide" inhibition.

The importance of fully functional digestive enzymes cannot be understated. They are essential for metabolic function, as they convert food into nutrients and other molecules that are then available to cells for tissue and organ growth, maintenance and repair. The precursor trypsinogen, produced in the pancreas, is enzymatically transformed into the serine protease trypsin. Trypsin catalyses the hydrolysis of proteins into peptides and provides substrates for further enzymatic hydrolysis for protein absorption.

Pepsin, a primary protease of digestion, is also responsible for the metabolism of dietary protein. Pepsin's cleavage of peptide bonds is responsible for the availability of the aromatic amino acids phenylalanine, tyrosine and tryptophan. It is also responsible for the cleavage and release of several other amino acids, including valine, glycine, histamine, glutamine, alanine and leucine.

Lipase participates in cell signaling, inflammation and metabolism. Pancreatic lipase is the catalyst for the hydrolysis of dietary lipids, which include fats, oils, cholesterol esters and triglycerides [94]. Triglyceride triester is metabolized for utilization as glucose and three fatty acids. Glyphosate integration into and inhibition of lipase could induce excessive bioaccumulation of fatty material in the blood vessels, gut, liver, spleen and other organs, as well as mimic lysosomal acid lipase deficiency. It would also allow for an increase in triglycerides in the blood, leading to numerous disease cascades, including malabsorption, fatty liver disease, jaundice, failure to thrive in infants, calcification of the adrenal gland, anaemia, hypercholesterolaemia, biliary dysfunction, decreased HDL, increased LDL, blood clots, fat-enlarged hepatocytes and liver fibrosis and failure. Samsel found that radiolabeled glyphosate was not detectable by HPLC–MSMS in samples of lipase deliberately spiked for analysis, suggesting that glyphosate may irreversibly inhibit lipase. On the other hand, pepsin and trypsin had good spike recoveries, demonstrating reversibility as glyphosate was released from the protein.

Table 3. Integration of glyphosate residues in various proteins, assessed using three testing methods.[a]

Protein substrate (Method)	Type	Glyphosate residue (ppb)
Bone (ELISA)	Bovine leg	11.56
Bone marrow (ELISA)	Bovine leg marrow	4.22
Bone (ELISA)	Porcine foot	9.81
Skin (ELISA)	Porcine	0.325
Gelatin (ELISA)	Bovine, Sigma Aldrich, gel strength 225 Type B	2.04
Collagen (ELISA)	Bovine I & III	120.18
Collagen (GC-MS)	Bovine I & III	130 µg/kg
Collagen (HPLC-MSMS)	Bovine I & III	95 µg/kg
Pepsin (ELISA)	Purified porcine enzyme	< 40.00
Pepsin (GC-MS)	Purified porcine enzyme	430 µg/kg
Pepsin (HPLC-MSMS)	Purified porcine enzyme	290 µg/kg
Trypsin (ELISA)	Purified porcine enzyme	61.99
Lipase (ELISA)	Purified porcine enzyme	24.43
Bee bread (HPLC-MSMS)	Bee bread	2300 µg/kg
Bees (HPLC-MSMS)	*Apis mellifera*	< 10 µg/kg trace
Honey & comb (HPLC-MSMS)	Honey	< 10 µg/kg trace

[a] The trace amount found in the bee substrates appeared as a small peak, which directly corresponded to glyphosate, complete with retention time and molecular features confirming contamination using HPLC–MSMS.

Table 3 shows results for various bovine and porcine products, including enzymes, bone, bone marrow, skin, collagen and gelatin. Acid hydrolysis was used on the bovine and porcine skin, bones and marrow, which were shaken and digested with 0.15 M hydrochloric acid for 24 h. The analysis methods were ELISA, gas chromatography–mass spectrometry (GC–MS) and HPLC–MSMS. All of the tested products were contaminated, with the highest level detected being 430 µg/kg in porcine pepsin (via GC–MS).

Additional evidence of glyphosate accumulation was found by Samsel in 2015 in the bodies of dead bees, bee bread and honey from bee hives suspected of colony collapse disorder (CCD), and these are also shown in the table. Colony collapse disorder (CCD) is an ever-increasing problem threatening pollination of crops globally. It may share a similar aetiology to that of Alzheimer's disease with regard to learning and memory within the bee's brain. Integration of glyphosate with the structural proteins and enzymes of the bee may affect protein folding and function. Additionally, glyphosate may also affect the digestive enzymes and bacterial homeostasis within the digestive system, which in turn may affect the quality of the honey produced. Glyphosate in bees may become part of their chitin, which has a structural function, in their bodies, analogous to glyphosate becoming part of the collagens of humans and other animals.

The results in Table 3 show ubiquitous contamination of the bee and bee products. Honey is derived from nectar and is the source of carbohydrates in the bee diet, whereas pollen turned into bee bread supplies the fats and proteins. Royal jelly, made from the secretions of the glands found in the hypopharynx of the worker bees, is fed to the queen and developing larvae [96].

Results for nineteen different vaccines, from five manufacturers, are shown in Table 4. Some vaccines do not contain live viruses and do not involve gelatin in their preparation, but many involve the use of eggs, bovine calf serum, fetal bovine serum or bovine proteins [95]. Engerix Hepatitis B vaccine is manufactured through a novel procedure, which involves culturing genetically engineered *Saccharomyces cerevisiae* yeast cells that carry the surface antigen gene of the hepatitis B virus. The procedures result in a product that can contain up to 5% yeast proteins, which could be a source of glyphosate if the yeast is grown on broths or media that utilize glyphosate-contaminated nutrient sources such as animal or plant proteins.

Vaccines that tested negative for glyphosate included Merck's Hep-B vaccine, most of the pneumococcal vaccines and the sterile diluent included as a control. Gelatin is not listed as an ingredient in any of these vaccines, nor is bovine serum. In contrast, all of the vaccines that listed gelatin as an excipient tested positive for glyphosate, and nearly all of them also included bovine serum (including Varicella, MMR-II, MMRV and Zoster).

It is significant that MMR-II consistently contained the highest levels of glyphosate, significantly more than any of the other vaccines. This vaccine uses up to 12% hydrolysed gelatin as an excipient–stabilizer; as well as foetal bovine serum albumin, human serum albumin and residual chick embryo; all of which are contaminated by glyphosate during animal production.

7. EVIDENCE FOR A ROLE FOR COLLAGEN IN VACCINE ADVERSE REACTIONS

Post-vaccination allergic reactions to MMR and varicella vaccines have been linked to the gelatin excipient, and confirmed through observation of induced gelatin-specific IgE antibodies [97–100]. 24 out of 26 children with allergic reactions to vaccines (e.g., anaphylactic shock) had anti-gelatin IgE ranging from 1.2 to 250 µg/mL. Seven were allergic to gelatin-containing foods. A pool of 26 control children all tested negative for anti-gelatin IgE [99]. A study from 2009 that looked at gelatin sensitivity in children who were sensitive to cows' milk, beef and/or pork as determined by IgE antibody levels [101] found that 16% of beef-sensitized children and 38% of pork-sensitized children had IgE antibodies to beef- or pork-derived gelatins that were cross-reactive with each other.

In a published case study, a 2-month-old baby developed Kawasaki disease one day after receiving its first dose of Infanrix (DTaP-IPV-Hib) and Prevenar, a pneumococcal conjugate vaccine [102]. Kawasaki disease is an acute, multisystemic vasculitis whose occurrence very early in life is extremely rare. Extensive tests for the presence of infection with multiple bacteria and viruses were all negative. We suggest that glyphosate contamination in one or both of the vaccines may have contributed to the vasculitis through glyphosate uptake into common proteins such as collagen in the vasculature to induce the autoimmune reaction.

Kelso (1993) reported the case of a 17-year-old girl who experienced anaphylaxis within minutes of receiving an MMR vaccine [98]. The girl described the event as "kind of like what happens when I eat Jell-O[2]". Further testing found gelatin to be the component of the vaccine

[2] Jell-O is a proprietary brand of gelatin-based desserts, popular in the USA, and manufactured by Kraft Foods, part of the Kraft Heinz Company, headquartered in Chicago.

Table 4. Glyphosate levels in vaccines determined by ELISA reported to the US CDC, NIH, FDA and UN WHO of the Americas in September 2016 by Samsel Environmental & Public Health Services.[a]

Vaccine undiluted	Manufacturer	Lot number Exp date	Test date Lab #	Glyphosate residue (ppb)	% Recovery in spiked sample
DTaP ADACEL	SANOFI PASTEUR NDC	58160-820-43 3-30-2018	7-15-2016 LAB #1	0.109	82%
DTaP	SANOFI PASTEUR	C50418A 9-2-2018	5-11-2016 LAB #1	< 0.075	81%
DTaP ADACEL	SANOFI PASTEUR	NDC 58160-820-43 3-30-2018	7-12-2016 LAB #2	ND	-
HEPATITIS-B	MERCK	LO16427 4-13-2017	5-11-2016 LAB #1	< 0.075	97%
HEPATITIS ENGERIX-B	GLAXOSMITH- KLINE	NDC 58160-820-43 6-1-2018	7-15-2016 LAB #1	0.337	73%
INFLUENZA FLUZONE QUAD	SANOFI PASTEUR	6762 6-30-2016	7-15-2016 LAB #1	0.170	95%
INFLUENZA	NOVARTIS	1573 3P 05/2016	5-11-2016 LAB #1	0.227	106%
Pneumococcal PNEUMOVAX 23	MERCK	700281601 5-18-2017	9-19-2016 LAB #1	0.112	118%
MMR II	MERCK	7002151400 9-9-2017	7-15-2016 LAB #1	3.740	-
MMR II	MERCK	009545 3-19-2017	5-11-2016 LAB #1	2.963	-
MMR II	MERCK	7002151400 9-9-2017	9-19-2016 LAB #1	3.154	-
MMR II	MERCK	7002151400 9-9-2017	7-12-2016 LAB #2	2.90	-
MMRV PROQUAD	MERCK	7002305700 9-12-2017	9-19-2016 LAB #1	0.659	103%
MMRV PROQUAD	MERCK	7002305700 9-12-2017	7-15–2016 LAB #1	0.512	86%
MRV PROQUAD	MERCK	7002305700 9-12-2017	7-12-2016 LAB #2	0.43	-
Pneumococcal PNEUMOVAX 23	MERCK	700281601 5-18-2017	7-15-2016 LAB #1	< 0.075	77%
Pneumococcal PREVNAR 13	WYETH	73332 07/2017	5-11-2016 LAB #1	< 0.075	82%
Pneumococcal PNEUMOVAX 23	MERCK	7002681601 5-18-2017	7-12-2016 LAB #2	ND	-
STERILE DILUENT	MERCK, SHARP & DOHME	LO 40058 5-11-2018	7-15-2016 LAB #1	< 0.075	97%
VARICELLA VARIVAX	MERCK	7002025000 2-8-2018	7-15–2016 LAB #1	0.556	84%
MVARICELLA VARIVAX	MERCK	7002025000 2-8-2018	7-12-2016 LAB #2	0.41	-
ZOSTER ZOSTAVAX	MERCK	7002502401 6-1-2017	9-19-2016 LAB #1	0.620	95%
ZOSTER ZOSTAVAX	MERCK	7002602401 6-1-2017	7-15-2016 LAB #1	0.558	98%
ZOSTER ZOSTAVAX	MERCK	7002602401 6-1-2017	7-12-2016 LAB #2	0.42	-

[a] Limits of detection for glyphosate in vaccines in parts per billion (ppb):[1] 0.075 (LAB #1); 0.15 (LAB #2).

to which the girl was allergic. The connexion may be to misfolded proteins, which include the collagens and associated partially hydrolysed gelatins. Indeed, both Jell-O and vaccines have been contaminated by glyphosate, as we reported in the previous section.

Puppies immunized with the rabies vaccine and a multivalent canine vaccine were compared to unvaccinated control puppies [103]. The vaccinated puppies, but not the unvaccinated ones, developed autoantibodies to their own collagen. A follow-up study where either just the rabies vaccine or just the multivalent vaccine was administered produced a similar result. The authors suggested that this could explain issues of joint pain that are currently common among dogs, particularly as they age.

8. MULTIPLE SCLEROSIS (MS)

8.1 Sugar beet and MS

The world obtains 30% of its sugar supply from beet sugar. While sugar cane is grown in tropical regions, sugar beet requires a temperate climate. The highest incidences of MS worldwide are in the USA, Canada and western Europe [5], where most of the beet sugar is produced. MS rates are higher in the northern states of the USA compared to the south, corresponding to the distribution of sugar beet cultivation. MS rates in Canada are highest in the Alberta prairie region, at the centre of the Canadian sugar beet industry [104]. Studies on migrants have shown that those who move from a low-risk to a high-risk area tend to adopt high-risk only if they migrated during childhood [105]. This implicates local environmental factors acting before adolescence. Tokachi province in Japan hosts only 0.3% of the population, but produces 45% of the sugar beet consumed in Japan [37]; this province has the highest rate of MS among all Asian populations [106].

A fascinating proposition how sugar beet could cause MS implicates a unique noncoding amino acid that is produced by sugar beet, namely Aze. Both proline and Aze have a unique structure for an amino acid: the side chain loops back round to connect up to the nitrogen atom. In the case of Aze, there are only 3 carbons in the ring instead of the 4 carbons in proline (Fig. 2). It has been shown experimentally that Aze can be inserted by mistake into proteins in place of proline [38].

Myelin basic protein (MBP) is an essential protein for maintaining the myelin sheath, and it interacts with actin, tubulin, calmodulin and SH3 domains [107]. It assembles actin filaments and microtubules, binds actin filaments and SH3 domains to membrane surfaces, and participates in signal transduction in oligodendrocytes and myelin. A central proline-rich region in MBP is functionally significant [108–110] and, in particular, is a binding site for Fyn-SH3, a key regulatory protein [111]. Proline substitutions of the SH3 ligand decrease its affinity for the Fyn-SH3 domain [108]. Fyn is localized to the cytoplasmic leaflet of the oligodendrocyte plasma membrane, where it participates in numerous signaling pathways during development of the central nervous system [112, 113]. Phosphorylation at a polyproline structure in the Fyn-binding region of MBP affects its structure.

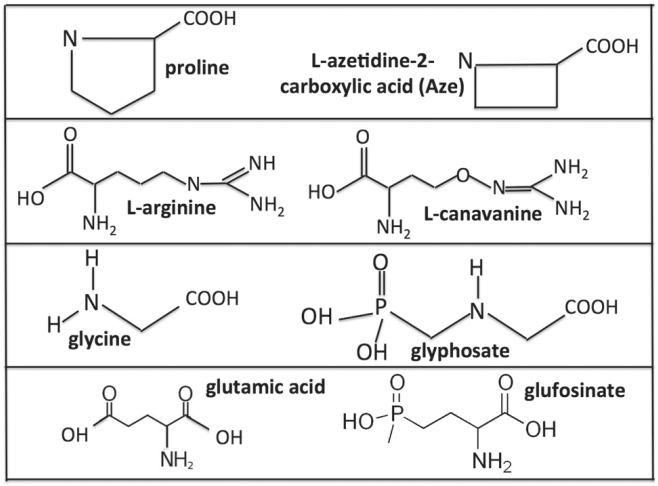

Figure 2. Molecular structures of the coding amino acids proline, L-arginine, glycine and glutamic acid; and their respective noncoding analogues Aze, L-canavanine, glyphosate and glufosinate.

A study using recombinant murine MBP inserted into *E. coli* strains demonstrated conclusively that Aze makes its way into MBP, substituting for up to three of the eleven possible proline sites. Molecular modeling of a proline-rich region of the recombinant MBP illustrated that misincorporation of Aze at any site would cause a severe bend in the polypeptide chain, and that multiple Aze substitutions would completely disrupt the structure of MBP [114, 115].

A possible concern regarding Aze is that over 90% of the sugar beet grown in the USA and Canada is genetically engineered to resist glyphosate. Therefore, the crops are exposed to significant amounts of glyphosate. The electronic *Code of Federal Regulations e-CFR 180.364 Glyphosate; Tolerances for Residues*, allows up to 25 ppm residue of glyphosate in dried sugar beet pulp. In 1999, Monsanto realized that its GM sugar beet crop well exceeded the upper limit established by the EPA for glyphosate residues. They requested, and were granted, a 125-fold increase in the upper residue limit for dried beet pulp (from 0.2 to 25 ppm). At the same time, the upper limit for fresh beet was increased fiftyfold to 10 ppm.

Glyphosate has been shown to increase the risk of root rot in sugar beet, caused by fungi [116]. Aze has been demonstrated to have antifungal activity [117]. Plants tend to increase synthesis of toxins under stress conditions, and it is plausible that an increased potential for root rot would result in increased synthesis of Aze. This is especially likely given that plants increase proline synthesis under a variety of different stress conditions [118]. However, to our knowledge, whether glyphosate causes an increase in either proline or Aze synthesis in sugar beet has not been investigated.

Consumption of milk worldwide is strongly correlated with MS risk (Spearman's correlation test = 0.836; $P < 0.001$) [119]. For the past several decades, cows' feed has been supplemented with either beet

molasses or sugar beet pulp, left as a residue after the sugar has been extracted [120]. Aze has been experimentally found in three sugar beet by-products that are fed to farm animals: sugar beet molasses, and both shredded and pelleted sugar beet pulp [38]. Casein is relatively enriched in proline [121]. If cows are exposed to Aze from the sugar beet, it will likely get inserted by mistake into casein, causing it to resist proteolysis. MBP's critical proline-rich sequence is vulnerable to misincorporation of Aze. The characteristic plaques of MS show loss of MBP within lesions in axon sheaths [107]. It is unclear whether this autoimmune reaction would arise through molecular mimicry from antibodies to unmetabolized peptides from casein or as a direct result of improperly folded MBP due to Aze insertion.

Glyphosate, an analogue of glycine, can be expected to be found in all tissues, including the milk of all mammals consuming glyphosate residues in the diet. Radiolabeled glyphosate studies conducted with lactating goats found ^{13}C and ^{14}C residues of glyphosate (N-phosphonomethylglycine), N-acetylglyphosate and other radiolabeled metabolites in milk. Monsanto found daily average ^{14}C residue levels from 19 to 86 ppb, with levels falling after five days of depuration to 6 ppb prior to sacrifice for organ examination. Results disseminated by Monsanto indicate that lactating animals (goats) fed a diet containing glyphosate and AMPA can be expected to have measured residue levels in edible tissues and milk [122]. In 2007 Dupont, in a similar study, examined the metabolism of N-acetylglyphosate in lactating goats. Detectable residues of N-acetylglyphosate, glyphosate and AMPA were detected in milk and other tissues. Milk, liver and kidney each contained 0.03% of the administered dose. Individual daily radiolabeled residues in the milk ranged from 0.030 to 0.036 μg/g [123].

Lactobacillus plays an important rôle in metabolizing casein in the human gut. A detailed study of the prolyl aminopeptidase from *Lactobacillus* revealed that it is a member of the class of α/β hydrolases. Multiple sequence alignment has revealed three distinct highly conserved regions in this family and all three contain at least two highly conserved glycines [124] that would be vulnerable to displacement by glyphosate. The motif gly-x-ser-x-gly-gly characterizes the domain surrounding the catalytic serine residue of prolyl oligopeptidases in general. The glycine residues in this motif contribute to the correct positioning of the catalytic serine with respect to its substrate. A second glycine-rich domain appears essential to activity, as it likely corresponds to the oxyanion hole. The function of the third highly conserved glycine-rich domain, with the motif asp-x-x-gly-x-gly-x-ser, remains unknown. *Lactobacillus spp*. are also highly dependent on manganese to protect them from oxidative damage, hence glyphosate's preferential chelation of manganese likely harms *Lactobacillus* [125].

An examination of collagen in the jugular veins of MS patients undergoing surgical reconstruction revealed an abnormal collagen structure, characterized by thin, loosely packed type III fibres [126]. Collagen is rich in proline. If too many of the prolines in procollagen are displaced by Aze, the polypeptide does not fold into a stable triple-helical conformation, which is a prerequisite for normal secretion of procollagen [127]. This reduces the release of procollagen and the misfolded molecules are subjected to proteolysis for recycling. resulting in the useless expenditure of energy for building and degrading procollagen molecules. Those that are released can be expected to produce defective collagen matrices. Collagen is even more highly enriched in glycine than in proline, as its core structure consists of a triple peptide repeat, where glycine is always the third residue of the triplet, and proline and hydroxproline often occupy the other two positions [128]. Glyphosate substitution for glycine in structural proteins; i.e., collagen, elastin, fibronectin and laminin; would contribute to disrupted folding as well as defective strength and elasticity.

Conserved prolines also play a crucial rôle in ion channel gating, the regulation of hypoxia-inducible factor (HIF) and embroygenesis; in fact, substituting Aze for proline is a technique used to test whether a particular proline residue is critical to the protein's proper functioning [37].

8.2 Rôle of *Acinetobacter* and *Pseudomonas aeruginosa* in MS

A series of papers by Ebringer et al. have suggested an important rôle for the Gram-negative bacteria *Acinetobacter* and *Pseudomonas aeruginosa* in MS [129–131] as well as a proposed link to prion diseases. Their most recent paper in *Medical Hypotheses* presents the evidence to support this idea from multiple dimensions [130]. First, MS patients were shown to have elevated levels of antibodies to these two microbes but not to the common gut microbe *E. coli* [132, 116]. They have autoantibodies to MBP and myelin oligodendrocyte glycoprotein (MOG) [131]. MS patients are also prone to sinusitis and *Acinetobacter* is one of the most common microbes found in nasal sinuses. Ebringer et al. also proposed that the increased prevalence of sinusitis in colder climates may explain the geographical distribution of MS in more northerly latitudes [130]. *P. aeruginosa* causes upper respiratory infections and it is among the microbes that have developed multiple antibiotic

resistance in recent years, presenting a huge problem in hospital infection [133]. *Acinetobacter* has also become resistant to multiple antibiotics [134].

The number of microbial species that can metabolize glyphosate is quite small. A 1996 study showed that *Acinetobacter* is able to fully metabolize both glyphosate and AMPA and utilize these molecules as a source of phosphorus [135]. A study of agricultural soil heavily polluted with glyphosate identified only three species capable of degrading glyphosate when exposed at a level of 1000 ppm: *Pseudomonas putida*, *P. aeruginosa* and *Acetobacter faecalis* [136]. Another study on marine species identified *Pseudomonas* as being among the rare microbial species that can utilize the phosphonate in glyphosate as a source of phosphorus [137]. It can be predicted that *Pseudomonas* and *Acinetobacter* species in the nasal or digestive tracts would have a substantial advantage over other microbes if they can degrade glyphosate. On the other hand, they would also be heavily exposed if they actively take it up, and it would not be unreasonable to assume that some of the glyphosate might end up in their synthesized proteins by mistake in place of glycine. Both *Pseudomonas aeruginosa* and *Acinetobacter* strains have recently become a serious problem in hospitals, and a public health issue, due to their multiple-antibiotic resistance [138]. Glyphosate has been shown to induce generic antibiotic resistance in other microbial species, including *E. coli* and *Salmonella*, through the induction of a generic capability to export toxic chemicals through efflux pumps [139].

A PEP transferase enzyme synthesized by *Acinetobacter calcaceticus* has sequence homology with a bovine prion sequence, and antibodies against synthetic peptides containing the structurally related sequences were found to be significantly elevated in cattle with bovine spongiform encephalopathy (BSE) compared to negative controls [140]. Ebringer et al. (2005) [129] link MS to BSE, also known as "mad cow disease", and to the related human disease, Creutzfeldt–Jakob disease (CJD). Cows suffering from BSE manifest hindquarters paralysis early after onset, similar to the mobility issues afflicting MS patients at onset. Ebringer et al. found elevated levels of antibodies to both *Acinetobacter* and *Pseudomonas*, along with autoantibodies to both white and grey matter components, in BSE-affected animals, as is also the case for MS [129].

Of particular note are the molecular similarities they identified between certain peptides found in these two microbes and peptides in MOG and MBP that are known to be allergenic. Strikingly, all three of the microbial sequences they identified and all three of their human protein analogues contain conserved glycines (Table 5).

Table 5. Amino acid sequences of three peptides from *Acinetobacter* and *Pseudomonas* and the corresponding human peptides from MBP that they mimic.[a]

Microbe	Acinetobacter	Acinetobacter	Pseudomonas
Protein	3-OACT-A	4-CMLD	Gamma-CMLD
Peptide	Leu-Tyr-Arg-Ala-Gly-Lys	Ser-Arg-Phe-Ala-Tyr-Gly	Thr-Arg-His-Ala-Tyr-Gly
MBP	Leu-Tyr-Arg-Asp-Gly-Lys	Ser-Arg-Phe-Ser-Tyr-Gly	Ser-Arg-Phe-Ser-Tyr-Gly

[a] Note that all six peptides have a glycine residue.

MOG is strongly implicated in the disease pathology of MS; autoantibodies recognizing MOG have been found in the CNS of MS patients [141]. One of the major encephalitogenic peptides in MOG is the sequence from residue 92 to residue 106, which contains a highly conserved glycine near its centre [142].

Both diabetes and MS are associated with abnormal T-cell immunity to proteins found in cow's milk [143]. In a study conducted in dairy cows by Monsanto in 1973, ^{14}C-radiolabeled glyphosate was studied in the distribution of residues in milk, urine, faeces and other tissues of the lactating cow. Glyphosate contamination of milk ranged from 9 to 15 ppb with the highest accumulation in the kidney and rumen fluid (201 ppb and 109 ppb, respectively) [201]. An epitope of bovine serine albumin found in milk that is linked to MS but not to diabetes is BSA193. It shows structural homology with exon 2 of MBP through the peptide sequence GLCHMYK. Note that the first peptide in this sequence is glycine. Exon 2 is a target peptide in both MS autoimmunity and in experimental autoimmune encephalitis (EAE), an animal model of MS [144–146]. Exon 2 of MBP is implicated in remyelination [144]. Its expression is largely restricted to the developing brain and to areas of myelin reconstruction, notably MS lesions [147].

The gly-ser-gly-lys tetrapeptide is highly conserved among MBPs from multiple species [148]. The serine in this sequence is the site of attachment of polyphosphoinositide. The highly conserved nature of this sequence suggests that the phospholipidation of MBP is important biologically. Substitution of glyphosate for either of the glycines would likely disrupt this modification.

9. MMR VACCINE AND AUTISM

In this section, we make a case for a direct link between the measles, mumps, and rubella (MMR) vaccine and autism, via autoantibody induction through molecular mimicry. In a paper provocatively titled, "Peptide cross-reactivity: the original sin of vaccines", Kanduc makes the point that massive cross-reactivity between antigens in vaccines and similar sequences in human proteins makes it almost inevitable that vaccines lead to autoimmune disease through molecular mimicry [149]. Reported post-vaccination autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, multiple sclerosis, Guillain–Barré syndrome and vasculitis [150].

It is becoming increasingly acknowledged that autism may be an autoimmune disease. Family members of autistic children have a significant increased risk to other known autoimmune diseases such as hypothyroidism, rheumatic fever and multiple sclerosis [151]. Several studies on both humans and monkeys have revealed a potential link between maternal antibodies directed against specific foetal brain proteins and a future autism diagnosis in the foetus [152–155]. Furthermore, it has already been demonstrated that vaccines are capable of inducing autoimmune antibodies against proteins in the brain. The narcolepsy epidemic in Europe following an aggressive immunization campaign against the H1N1 'flu virus was eventually conclusively resolved as being attributed to autoimmune reactions to the hypocretin receptor through molecular mimicry from a peptide in the surface-exposed region of the influenza nucleoprotein A that was present in the H1N1 vaccine [156] (hypocretin is an important regulator of sleep).

Much controversy surrounds the concept that the MMR vaccine may be contributing to the autism epidemic in the USA and elsewhere. In an immune-compromised child, the live measles virus from the vaccine is capable of infecting the brain and sustaining a chronic measles infection, resulting in loss of neurons, eosinophilic intranuclear inclusions and gliosis, a condition termed "subacute measles encephalitis". This can result in a seizure disorder and developmental delay in language and motor skills (as was clearly observed in a case study involving an HIV-positive 2-year-old boy [157]).

Singh et al. have published a series of papers over the past two decades [14, 158–160] proposing that there is a subpopulation among the autism community who can be characterized as suffering from "autoimmune autistic disorder" [14]. The 1998 study by Singh et al. found that 90% of measles-IgG-positive autistic sera were also positive for anti-MBP antibodies, supporting the hypothesis that a virus-induced autoimmune response may be causal in autism [158]. A follow-on serologic study of antibodies to viruses associated with autism published in 2003 revealed a statistically significantly elevated level of measles antibody in children with autism compared to their siblings ($P = 0.0001$) or to unrelated children ($P = 0.003$), but not with antibodies to mumps or rubella [159]. In a later study, 60% of 125 autistic children had significantly elevated levels of antibodies to measles haemagglutinin unique to the MMR strain of the virus, compared to the 92 control children [160]. Over 90% of the children who had elevated antibody levels also tested positive for MBP autoantibodies. It was suggested that this could be linked to virus-induced autoimmunity through mimicry.

In fact, there is a sequence homology of 78% between a peptide sequence from MBP (EISFKLGQEGRDSRSGTP) and one found in a measles virus protein, MP3 (EISDNLGQEGRASTSGTP) [161, Table 2, p. 7]. Three of the matches between these two sequences are glycines. Measles virus-neutralizing antibodies are mainly directed to haemagglutinin, implying that it is essential for acquired immunity from the vaccine [162]; yet over-production, particularly if the virus penetrates the blood–brain barrier, runs the risk of inducing an autoimmune response to the myelin sheath. In fact, high measles antibody titres have been previously linked to MS [163].

Gonzalez-Granow et al. found high titres of autoantibodies in both the IgG and IgA classes specific to MBP in the serum of patients with autism [15]. The IgA antibodies in particular were shown to act as serine proteinases to degrade MBP *in vitro*. They also induced a decrease in long-term potentiation in perfused rat hippocampi. Reduced long-term potentiation in the hippocampus is a feature of autism, as has been clearly demonstrated in studies using mouse models of autism [164].

Dr Andrew Wakefield was the first to reveal a possible connexion between MMR and autism. His controversial *Lancet* paper, published in 1998 and then later retracted, proposed that this vaccine caused an acute reaction in children with gut dysbiosis (abdominal pain, diarrhoea, food intolerances, bloating etc.) [9]. The paper reported on a group of 12 children who had experienced developmental delay following an MMR vaccine and who were diagnosed with autism. These children suffered from rash, fever, delirium and seizures following the vaccination with MMR. He and several colleagues later published additional papers elaborating the hypothesis that dysbiosis in the gut, combined with impaired protein hydrolysis, leads to autoimmune lesions in the duodenum that are associated with extensive colonic lymphoid hyperplasia. The release of undigested peptides

into the vasculature across a leaky gut barrier and, ultimately, from the vasculature across a leaky blood–brain barrier, could induce encephalopathy [165–167].

In an epidemiological study from 1998, encephalopathy was clearly demonstrated as an acute reaction to measles vaccine, where 48 cases were found following vaccination, with no cases identified after administration of either monovalent mumps or rubella [168]. Among these 48 children, eight died, and the remainder experienced mental regression, chronic seizures, movement disorders and sensory deficits in the subsequent months.

The FDA's vaccine adverse event reporting system (VAERS) database is a valuable tool for uncovering trends in vaccine adverse reactions. Our earlier studies on VAERS comparing MMR with an age-matched, equal-sized distribution of all other vaccines showed a significant association of MMR with autism ($P < 0.007$) [169]. This was puzzling, because MMR has never contained either aluminium or mercury, the two prime candidates for the kind of neurological damage that might lead to autism [170–174]. Strong associations also appeared with fever and rash. In that paper, we proposed that the adverse reaction might be caused by the acetaminophen administered to the child to try to curb the seizures.

Since glyphosate usage on crops has gone up dramatically since the GM Roundup Ready crops were first introduced in 1996, we decided it would be worthwhile to compare the early data on MMR in VAERS with the later data. We defined a cutoff date on 1 January 2003, such that the events where MMR was included as an administered vaccine could be separated into "early" and "late", based on whether they were before or after that date. Each dataset represented a 13-year interval. We found 10 639 events in the early set and 19 447 events in the late set; thus, the raw number of events nearly doubled in the later years.

We also tabulated the frequency of different adverse reactions in the two sets, and used a standard statistical analysis to compute the significance of any differences observed: we randomly down-sampled both sets as needed such that there was an identical total count and an identical distribution over age in the two datasets. Results were surprising: many symptoms associated with atopy or with an allergic reaction were significantly higher in the later set, and "hospitalization" was highly significantly overrepresented in the later set [Table 6]. Other overrepresented symptoms included seizures, dyspnea, hyperventilation, asthma, eczema, autism, hives, anaphylatic [shock], and irregular heart rate. Interestingly, the early set had more frequent occurrences of joint pain and arthritis, suggesting that the toxic elements in the vaccine impacted the joints rather than the brain.

Table 6. Frequency of various adverse reactions to MMR before and after January 2003 [US FDA, VAERS]. The *P*-values were computed according to a χ^2 goodness-of-fit test.

More common before 2003			
Reaction	Count < 2003	Count ≥ 2003	*P*-value
Arthritis	52	18	0.045
Joint pain	175	75	0.012

More common after 2002			
Reaction	Count < 2003	Count ≥ 2003	*P*-value
Hospital	132	423	0.00041
Seizures	314	534	0.0055
Dyspnea	139	279	0.0086
Hives	444	654	0.011
Anaphylactic	28	91	0.017
Eczema	10	47	0.028
Autism	105	184	0.031
Hyperventilation	18	57	0.035
General infection	77	136	0.044
Asthma	22	58	0.046
Immunoglobulin G	0	17	0.048
Ear infection	32	72	0.048
Heart rate irregular	11	39	0.049

To our knowledge, there have been no significant changes to the formulation of MMR since its introduction. The explanation for the significant changes in adverse reactions must, therefore, lie in external factors, one of which is likely to be glyphosate. We suggest that both chronic exposure to glyphosate from food, water and air and direct exposure to glyphosate residues in the vaccine are relevant factors. A child with a disrupted gut microbiome due to chronic glyphosate exposure will also suffer from a leaky blood–brain barrier, and this will lead to a much greater possibility of measles antigenic proteins entering the brain and causing anaphylaxis and seizures.

The measles virus is a member of the family of paramyxoviruses, which have two highly-conserved glycine residues at positions 3 and 7 in the hydrophobic fusion peptide (FP) region of the viral fusion-mediating glycoproteins [175]. This FP region is the most highly conserved region of the glycoproteins, and it plays a critical rôle in destabilizing the membrane of the host cell to gain entry. Substitutions of other amino acids for either the G3A or G7A glycines caused increases in both cell–cell fusion and the reactivity of the protein to antibodies, leading to both a higher infection rate and increased chances for an autoimmune reaction. Glyphosate substitution is likely to do the same, as well as leading to a form of the protein that would resist proteolysis.

The FPs of both the influenza virus and human immunodeficiency virus (HIV) gp41 contain numerous glycine residues at regular intervals, with glycine overall making up 29 and 26%, respectively, of the total peptide sequence [175]. Optic neuritis, an immune-mediated demyelinating injury of the optic nerve, has been recognized as a side effect of the influenza vaccine that can lead to blindness [176].

10. OTHER AUTOIMMUNE DISEASES

10.1 Neuromyelitis optica and aquiporin

Neuromyelitis optica is a rare severe inflammatory demyelinating disorder of the central nervous system, which is related to multiple sclerosis but distinctly different and manifested mainly by paralysis and optic nerve damage [177, 178]. It has been conclusively demonstrated that this condition is caused by an autoimmune reaction to aquaporin-4, which is highly expressed in the astrocyte membrane [177, 178].

Aquaporins are important membrane proteins, which can transport water molecules through pores into the cell while excluding protons [179]. They are highly expressed by astrocytes, one of whose rôles is to mediate water flow among the vasculature, the cerebrospinal fluid and the lymph system [178]. Thus, aquaporins are implicated in brain oedema [180]. Plants produce aquaporins as well, and mimicry between plant and human aquaporins has been proposed as a mechanism for the development of an autoimmune sensitivity to this protein [181]. Plants considered to show aquaporin mimicry notably include corn and soy as well as tomato, tobacco and spinach [182].

Autoimmune sensitivity to aquaporin has also been found in association with MS [182]. Vojdani et al. found significant elevations in antibodies against both human and plant aquaporin 4, in addition to antibodies against MB, MOG and S100 calcium-binding protein B (S100B) in patients suffering from MS.

Among the aquaporins, aquaporin-6 is unique in that it operates as an anion channel instead of as a water channel. Analysis of the peptide sequence in comparison to other aquaporins reveals that aquaporin-6 has an asparagine substituted in place of a glycine at residue 60. This one small difference completely changes the way the molecule behaves in the membrane. A glycine at this position is conserved among all the other aquaporins. Furthermore, aquaporins are constructed of α-helices, and there are three sites where the helices cross. Highly conserved glycine residues are found at all three sites [57, 183].

Aquaporin is also found in bacteria, although homology with human aquaporin is only about 20%. The bacterial aquaporin is a 27 kDa trypsin-resistant protein called aquaporin-Z, which was originally described in *E. coli* [184]. Sequence analysis conducted by Ren et al. [185] revealed four regions where homology was considerably stronger (90%, 60%, 50% and 45% respectively). They convincingly showed cross immunoreactivity between the human and bacterial versions of the protein. Antibodies to aquaporin Z bind to astrocytes, activate complement, and cause death.

Ren et al. [185] identified all the residues where the bacterial and human peptides were identical (Fig. 1 in [185]). A tally of counts reveals that glycine was by far the most common among these matched residues, representing 14 of the total 66 matches. The second most common amino acid was lysine with 8 matches. Alanine, isoleucine and valine had 7, 5 and 4 matches respectively, and all other amino acids had less than four.

Thus, it appears that glyphosate-substituted trypsin-resistant aquaporin from both gut microbes and from GM glyphosate-resistant corn and soy foods are plausible sources of antigens that could induce neuromyelitis optica and contribute to the disease process in MS through misincorporation.

10.2 Type 1 diabetes

Type 1 diabetes is considered a genetic disease, but its incidence has been increasing by 3–4% worldwide every year in the recent past [186, 168]. Although an environmental component is highly suspected, environmental factors have not yet been identified. An increased incidence of type 1 diabetes is associated with both MS [187] and autism [188]. The disease is characterized by an autoimmune reaction to various proteins expressed in the pancreatic islet cells. Specifically, antibodies against glutamic acid decarboxylase (GAD65) are often found [189]. Cross-reactivity with proteins from foods and microbes in the gut are both possibilities.

One microbe that may be inducing antibody production through mimicry is *Mycobacterium avium paratuberculosis* (MAP). Blast analysis revealed 75% homology between a previously identified antigenic region of GAD65 [190] and a MAP heat-shock protein (HSP65) [189]. The specific 16-residue matched sequence in HSP65 centrally contains a pair of glycines which could be substituted by glyphosate to cause resistance to proteolysis. This microbe has been linked to numerous other human diseases including ulcerative colitis, irritable bowel syndrome, sarcoidosis, Hashimoto's thyroiditis, MS and autism [188]. With respect to MS and autism, cross-reactivity between HSP65 and MBP through mimicry may provide the link.

Patients with type-1 diabetes commonly have an antibody reaction to bovine serum albumin, a component of cows' milk [191]. The hypothesized explanation is an autoimmune reaction to a beta-cell specific surface protein through mimicry.

Insulin-derived amyloidosis is a condition that can develop following long-term insulin therapy, whereby an "insulin ball" develops at the site of injection. This hard mass has been analysed and found to contain accumulations of insulin fibrils reminiscent of amyloid β-plaque in the Alzheimer's brain. Insulin amyloidosis is more common for animal (cows and pigs)-derived than human-derived insulin products. Nowadays, cows and pigs are chronically exposed to glyphosate in their feed. The rôle of glycine residues in proteins may indeed be to protect from aggregation into amyloid fibrils [192]. Substitution of glyphosate for any of these conserved glycines would therefore tend to promote amyloidosis.

Glutamic acid and glycine are by far the largest component amino acids of bovine proinsulin and make up 25% of the amino acid residues in the molecule [193]. The same is true for human insulin, which differs very little from the animal versions. The herbicide glufosinate is a natural noncoding amino acid analogue of glutamic acid (Fig. 2). Substitution of either glufosinate for glutamic acid or glyphosate for glycine in insulin is likely to impair its function, and may also lead to amyloidosis.

The widespread appearance of glyphosate-resistant weeds among the glyphosate-resistant crops has forced some farmers to turn to glufosinate as the herbicide of choice [194]. Glufosinate-tolerant corn and soybean have been available on the US market since their approval by the USDA in 1995 and 1996, respectively. A tri-resistant form of soybean tolerant of glyphosate, glufosinate, and 2,4-D was approved by the FDA in September 2014. Dual resistance to glufosinate and glyphosate in corn was approved in November 2015.

10.3 Coeliac disease

Coeliac disease and, more generally, gluten intolerance, have reached epidemic proportions in the USA in the past decade [195]. Wheat grown there is being routinely sprayed with glyphosate for staging and desiccation just before harvest. This practice clears the field of weeds prior to harvest and planting of the next crop, but increases the amount of residual glyphosate in the grain. The practice has been increasing in popularity in step with the increase in gluten intolerance. Glyphosate is systemic in the plant and enters the seed as the plant dies, hence eventually ending up in wheat-based foods.

Proline residues make up 20% of the first 100 amino acids of both α- and γ-gliadins [54]. Related proteins from rye and barley are also unusually proline-rich [56]. As we implied earlier, proline is inaccessible to most digestive proteases because the bond between the peptide nitrogen atom and the side group complicates hydrolytic attack. As a consequence, specialized prolyl aminopeptidases detach the amino-terminal proline from a peptide. These enzymes depend on manganese as a catalyst, and manganese is one of the metals most dramatically affected by glyphosate chelation [125]. Unhydrolysed gliadin peptides bind to HLA-DQ molecules (receptors on antigen-presenting cells) and trigger pathogenic T-cell responses [196]. Genetic variants of HLA-DQ are linked to both coeliac disease and type 1 diabetes [197, 198].

Analysis of the X-ray crystal structure of a human cytosolic prolyl aminopeptidase worked out in 2008 revealed that it is a dimer with a dependency on two manganese ions as the catalytic centres [199]. The full sequence of the catalytic domains of six prolyl peptidases from both human and microbial species is shown in Fig. 6 in ref. 199. Six of the twenty sites of fully conserved residues across all species were glycine residues, three were histidine, two were tyrosine and two were proline. The remaining seven were seven different amino acids.

11. CONCLUSION

In this paper, we have shown that widespread misincorporation of glyphosate for glycine during protein synthesis could explain the aetiology of multiple autoimmune diseases that are currently increasing in incidence in the USA. Misincorporation is plausible by analogy with multiple known toxins produced by organisms in defence against pathogens, including Aze, BMAA, L-canavanine and glufosinate, which work in a similar manner. We have shown that proteins from foods such as milk, wheat and sugar beet, as well as peptides derived from microbes resident in the gut or nasal tract or introduced iatrogenically through vaccination, are all potential causes of autoimmune disease induced through molecular mimicry. It is highly significant that two microbes linked to MS through molecular mimicry are among the very few microbes that can fully metabolize glyphosate. Using the VAERS database, we have shown that severe adverse reactions to the MMR vaccine have increased significantly over the past decade in step with the increased use of glyphosate. Glyphosate in MMR may originate from growth of the live virus on culture materials derived from glyphosate-exposed animals and/or from gelatin used as an excipient stabilizer. We have confirmed the presence of glyphosate contamination in MMR and in many other vaccines where the live virus is cultured in eggs, bovine protein or gelatin, or where animal products are used as an excipient component. Notably, some vaccines prepared without live culture on gelatin were free of glyphosate contamination. Substitution of glyphosate for glycine during protein synthesis could yield a peptide that resists proteolysis, making it more likely to induce an immune response. Furthermore, enzymes involved in proteolysis are likely to be disrupted due to their confirmed contamination with glyphosate. A non-exhaustive list of possible diseases that can be attributed to this mechanism include autism, multiple sclerosis, type 1 diabetes, coeliac disease, inflammatory bowel disease and neuromyelitis optica.

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FDA Study Helps Provide an Understanding of Rising Rates of Whooping Cough and Response to Vaccination

November 27, 2013

A new study is helping to provide a better understanding of vaccines for whooping cough, the common name for the disease pertussis. Based on an animal model, the study conducted by the U.S. Food and Drug Administration (FDA) and published November 25, 2013, in *The Proceedings of the National Academy of Sciences*, shows that acellular pertussis vaccines licensed by the FDA are effective in preventing the disease among those vaccinated, but suggests that they may not prevent infection from the bacteria that causes whooping cough in those vaccinated or its spread to other people, including those who may not be vaccinated.

Whooping cough rates in the United States have been increasing since the 1980s and reached a 50-year high in 2012. Whooping cough is a contagious respiratory disease caused by *Bordetella pertussis* bacteria. Initial symptoms include runny nose, sneezing, and a mild cough, which may seem like a typical cold. Usually, the cough slowly becomes more severe, and eventually the patient may experience bouts of rapid, violent coughing followed by the "whooping" sound that gives the disease its common name, when trying to take a breath. Whooping cough can cause serious and sometimes life-threatening complications, permanent disability, and even death, especially in infants and young children.

There are two types of pertussis vaccines, whole-cell and acellular. Whole-cell pertussis vaccines contain a whole-cell preparation, which means they contain killed, but complete, *B. pertussis* bacteria. The acellular pertussis vaccine is more purified and uses only selected portions of the pertussis bacteria to stimulate an immune response in an individual. In response to concerns about the side effects of the whole cell pertussis vaccine, acellular vaccines were developed and replaced the use of whole-cell pertussis vaccines in the U.S. and other countries in the 1990s; however, whole-cell pertussis vaccines are still used in many other countries.

"This study is critically important to understanding some of the reasons for the rising rates of pertussis and informing potential strategies to address this public health concern," said Karen Midthun, M.D., director of the FDA's Center for Biologics Evaluation and Research, where the study was conducted. "This research is a valuable contribution and brings us one step closer to understanding the problem. We are optimistic that more research on pertussis will lead to the identification of new and improved methods for preventing the disease."

"There were 48,000 cases reported last year despite high rates of vaccination," said Anthony S. Fauci, M.D., director of the NIH's National Institute of Allergy and Infectious Diseases. "This resurgence suggests a need for research into the causes behind the increase in infections and improved ways to prevent the disease from spreading."

The FDA conducted the study in baboons, an animal model that closely reproduces the way whooping cough affects people. The scientists vaccinated two groups of baboons-one group with a whole-cell pertussis vaccine and the other group with an acellular pertussis vaccine currently used in the U.S. The animals were vaccinated at ages two, four, and six months, simulating the infant

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NIAID At a Glance

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animals were vaccinated at ages two, four, and six months, simulating the infant immunization schedule. The results of the FDA study found that both types of vaccines generated robust antibody responses in the animals, and none of the vaccinated animals developed outward signs of pertussis disease after being exposed to *B. pertussis*. However, there were differences in other aspects of the immune response. Animals that received an acellular pertussis vaccine had the bacteria in their airways for up to six weeks and were able to spread the infection to unvaccinated animals. In contrast, animals that received whole-cell vaccine cleared the bacteria within three weeks.

This research suggests that although individuals immunized with an acellular pertussis vaccine may be protected from disease, they may still become infected with the bacteria without always getting sick and are able to spread infection to others, including young infants who are susceptible to pertussis disease.

For more information, see FDA: Vaccines.

Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

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Pertussis is a highly contagious respiratory illness caused by the bacterial pathogen *Bordetella pertussis*. Pertussis rates in the United States have been rising and reached a 50-y high of 42,000 cases in 2012. Although pertussis resurgence is not completely understood, we hypothesize that current acellular pertussis (aP) vaccines fail to prevent colonization and transmission. To test our hypothesis, infant baboons were vaccinated at 2, 4, and 6 mo of age with aP or whole-cell pertussis (wP) vaccines and challenged with *B. pertussis* at 7 mo. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring leukocytosis and symptoms. Baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonization, did not clear the infection faster than naïve animals, and readily transmitted *B. pertussis* to unvaccinated contacts. Vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals. By comparison, previously infected animals were not colonized upon secondary infection. Although all vaccinated and previously infected animals had robust serum antibody responses, we found key differences in T-cell immunity. Previously infected animals and wP-vaccinated animals possess strong *B. pertussis*-specific T helper 17 (Th17) memory and Th1 memory, whereas aP vaccination induced a Th1/Th2 response instead. The observation that aP, which induces an immune response mismatched to that induced by natural infection, fails to prevent colonization or transmission provides a plausible explanation for the resurgence of pertussis and suggests that optimal control of pertussis will require the development of improved vaccines.

whooping cough | T-cell memory | animal models | adaptive immunity | IL-17

Pertussis is a highly contagious, acute respiratory illness caused by the bacterial pathogen *Bordetella pertussis* (1, 2). Infection results in a wide spectrum of clinical manifestations ranging from mild respiratory symptoms to a severe cough illness accompanied by marked leukocytosis and the hallmark inspiratory whoop and posttussive emesis (3). Because acellular pertussis vaccines replaced whole-cell vaccines in the 1990s, pertussis has reemerged at a startling rate in the United States despite nationwide vaccine coverage in excess of 95% (4). With a 50-y high of 42,000 reported cases in the United States in 2012, pertussis is the most common of the vaccine-preventable diseases (5). This resurgence is mirrored throughout the industrial world despite similar high rates of vaccination (6–9). Two common hypotheses for the resurgence have been proposed: *i*) current acellular pertussis vaccines (aP) vaccines are less effective than the whole-cell pertussis (wP) vaccines they replaced and *ii*) aP-induced immunity wanes more quickly than anticipated (10–13). However, pertussis resurgence is not completely understood (14, 15).

Hampering our ability to counteract this resurgence is the fact that pertussis pathogenesis and immunity to natural infection have not been well studied in humans because typical pertussis is sporadic given high rates of vaccination in developed countries. Human challenge studies have been proposed but never conducted due to a variety of logistical and ethical problems including the potential for severe disease, the lack of an effective therapeutic for established disease, and the highly contagious nature of pertussis. Although a variety of small-animal models have been used to study pertussis, none of them adequately reproduce the human disease (16). To address this gap, we recently developed a nonhuman primate model of pertussis using baboons (*Papio anubis*) and found the disease is very similar to severe clinical pertussis. Upon challenge, baboons experience 2 wk of heavy respiratory colonization and leukocytosis peaking between 30,000–80,000 cells/mL, similar to the range in pertussis-infected infants (1, 17). In addition, baboons experience a paroxysmal cough illness characterized by repeated fits of 5–10 coughs. The coughing fits last on average >2 wk in the baboon, although this is less than some severely infected children, where the cough can last up to 12 wk (1, 17). We also characterized airborne transmission of *B. pertussis* from infected to naïve animals, which is the route of transmission postulated to occur between humans (18). Because this is the only model of pertussis to reproduce the cough illness and transmission of the human disease, we believe it provides the unique opportunity to test our hypothesis that aP vaccines fail to prevent *B. pertussis* colonization, thus enabling transmission among vaccinated individuals.

Using this model we have confirmed that, as in humans, aP vaccines provide excellent protection against severe disease in baboons. However, aP vaccines do not prevent colonization following direct challenge or infection by transmission. In addition, aP-vaccinated animals are capable of transmitting disease to naïve contacts. By comparison, wP-vaccinated animals cleared infection significantly more quickly than aP-vaccinated or naïve

Significance

Pertussis has reemerged as an important public health concern since current acellular pertussis vaccines (aP) replaced older whole-cell vaccines (wP). In this study, we show nonhuman primates vaccinated with aP were protected from severe symptoms but not infection and readily transmitted *Bordetella pertussis* to contacts. Vaccination with wP and previous infection induced a more rapid clearance compared with naïve and aP-vaccinated animals. While all groups possessed robust antibody responses, key differences in T-cell memory suggest that aP vaccination induces a suboptimal immune response that is unable to prevent infection. These data provide a plausible explanation for pertussis resurgence and suggest that attaining herd immunity will require the development of improved vaccination strategies that prevent *B. pertussis* colonization and transmission.

Author contributions: J.M.W. and T.J.M. designed research; J.M.W., L.I.Z., and T.J.M. performed research; J.M.W. and T.J.M. analyzed data; and J.M.W. and T.J.M. wrote the paper.

The authors declare no conflict of interest.

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See Commentary on page 575.

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animals. We also found that aP vaccination induces T helper 2 (Th2) and T helper 1 (Th1) immune memory responses, whereas infection and—to a lesser extent—wP vaccination induce Th17 and Th1 memory. Our results suggest that in addition to the potential contribution of reduced efficacy and waning immunity of aP, the inability of aP to prevent colonization and transmission provides a plausible explanation for pertussis resurgence.

Results

Acellular Pertussis Vaccines Protect Against Disease but Fail to Prevent Infection. Several observational studies recently concluded that children primed with aP vaccine are at greater risk for pertussis diagnosis compared with wP-primed children (19–22). Although these data suggest aP vaccine is less effective than wP vaccine at preventing colonization, the rate of undiagnosed *B. pertussis* carriage in vaccinated individuals is unknown. To assess the ability of each vaccine to prevent colonization and clinical pertussis symptoms, baboons were vaccinated according to the US schedule at 2, 4, and 6 mo of age with human doses of combination diphtheria, tetanus, and pertussis vaccines containing aP or inactivated wP (Table 1 provides a list of the components of each vaccine). At 7 mo of age, vaccinated, naïve, and previously infected (convalescent) animals were challenged with D420, a *B. pertussis* clinical isolate that causes severe infection in humans and baboons (17). Naïve animals were heavily colonized with peak levels between 10^7–10^8 cfu/mL in nasopharyngeal washes (Fig. 1*A*). After 2 wk, colonization gradually decreased, and the infection cleared after 30 d. Consistent with our previous finding, none of the convalescent animals were colonized (17). Compared with naïve animals, aP-vaccinated animals had slightly reduced colonization for the first 10 d but remained consistently colonized before clearing after 35 d. In wP-vaccinated animals the initial colonization was similar to aP-vaccinated animals but the infection cleared after 18 d, significantly faster than naïve and aP-vaccinated animals (Fig. 1*B*).

To assess the efficacy of the vaccines in preventing the symptoms of severe pertussis, peripheral blood was drawn serially, and complete blood counts were performed to monitor leukocytosis, a significant marker of morbidity in pertussis-infected infants (23). Compared with preinfection levels, naïve animals had a significant increase in circulating white blood cells at each time point, peaking at over 40,000 cells per μL, an eightfold increase over preinfection levels (Fig. 1*C*). In contrast to the colonization data, aP vaccination, wP vaccination, and convalescence all prevented leukocytosis (Fig. 1*C*). In addition, wP-vaccinated, aP-vaccinated, and convalescent animals did not cough and showed no reduction of activity, loss of appetite, or other outward signs of disease.

Acellular Vaccines Fail to Prevent Infection Following Natural Transmission. To assess the ability of vaccination to prevent pertussis infection by transmission, two aP-vaccinated animals and one unvaccinated animal were cohoused with a directly challenged, unvaccinated animal. Similar to our previous findings (18), all animals became colonized 7–10 d after cohousing with the infected animal (Fig. 2). The peak levels and kinetics of colonization were indistinguishable between the naïve and aP-vaccinated animals.

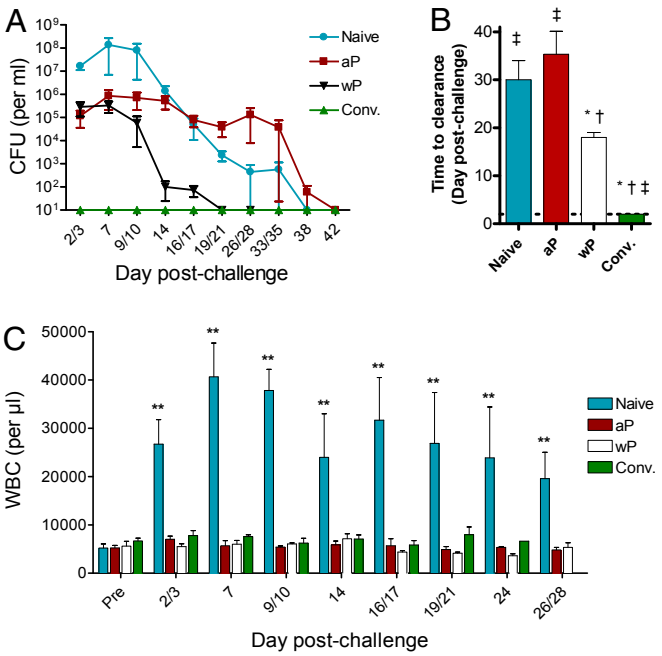

Fig. 1. The effect of vaccination or convalescence on colonization and leukocytosis. Naïve animals, aP-vaccinated animals, wP-vaccinated animals, and previously infected [convalescent conv.)] animals were directly challenged with *B. pertussis* ($n = 3$–4 per group). (*A*) Colonization was monitored by quantifying *B. pertussis* cfu per mL in biweekly nasopharyngeal washes with a limit of detection of 10 cfu per mL. For each animal the time to clearance is defined as the first day that no *B. pertussis* cfu were recovered from nasopharyngeal washes. (*B*) The mean time to clearance is shown for each group ($n = 3$ per group). Because no *B. pertussis* organisms were recovered from the conv. animals, the mean time to clearance was defined as the first day of sampling (day 2, indicated by the dashed line). *$P < 0.05$ vs. Naïve, †$P < 0.05$ vs. aP, ‡$P < 0.05$ vs. wP. (*C*) The mean circulating white blood cell counts before and after challenge are shown for each group of animals ($n = 3$–4 per group). **$P < 0.01$ vs. preinfection from same group.

Acellular-Vaccinated Animals Are Capable of Transmitting *B. pertussis* to Naïve Contacts. Because aP fails to prevent colonization we hypothesized that aP-vaccinated animals can transmit *B. pertussis* infection to contacts. To test this hypothesis, two aP-vaccinated animals were challenged with *B. pertussis* and placed in separate cages. After 24 h, a naïve animal was added to each cage, and all animals were followed for colonization. Both of the naïve animals were infected by transmission from their aP-vaccinated cage mates (Fig. 3).

Vaccination and Previous Infection Induce Robust Antibody Responses. Sera collected before vaccination or primary infection and again at 1 wk before challenge were analyzed for IgG antibodies against heat-killed *B. pertussis* and the vaccine antigens

Table 1. Components of aP and wP vaccines used in this study

Vaccine component	Daptacel	Infanrix	Triple antigen
Diphtheria toxoid	15 Lf	25 Lf	20–30 Lf
Tetanus toxoid	5 Lf	10 Lf	5–25 Lf
Whole-cell *Bordetella pertussis*	—	—	≥4 IU
Inactivated pertussis toxin	10 μg	25 μg	—
Filamentous hemagglutinin	5 μg	25 μg	—
Pertactin	3 μg	8 μg	—
Fimbriae types 2 and 3	5 μg	—	—
Aluminum (from aluminum phosphate)	0.33 mg	≤0.625 mg	≤1.25 mg

IU, international units; Lf, limit of flocculation units.

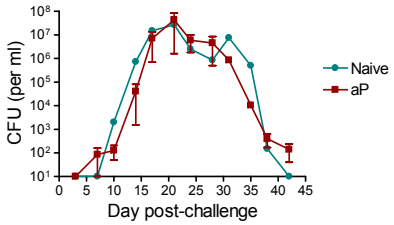

Fig. 2. aP does not protect against colonization following natural transmission. A naïve animal was directly challenged. After 24 h, a naïve animal and two aP-vaccinated animals were placed in the same cage as the directly challenged animal and followed for colonization as in Fig. 1.

pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM). We show that wP, aP, and natural infection induce high-antibody titers to all antigens, and the aP group generally possessed equivalent or greater pre-challenge titers, suggesting that the differences in colonization between the groups do not correlate with levels of circulating antipertussis antibodies (Fig. 4). Following challenge, the titers for vaccinated animals were essentially unchanged, whereas boosting was observed for some antigens in convalescent animals (Fig. S1).

T-Cell Memory Response Elicited by Acellular Pertussis Vaccination Is Mismatched Compared with Natural Infection. Although a large number of clinical studies have characterized the antibody response to pertussis infection and vaccination, key deficiencies remain in our understanding of pertussis-induced helper T-cell immune responses in humans and primates. Importantly, no clinical studies have investigated whether the primary series of pertussis vaccines induce Th17 memory, a recently identified T cell that specializes in controlling extracellular bacterial infections at mucosal surfaces through stimulating neutrophil recruitment (24). To assess *B. pertussis*-specific T-cell memory responses in naïve, aP-vaccinated, wP-vaccinated, and convalescent animals, peripheral blood mononucleated cells (PBMCs) were collected 1 wk before infection. Total PBMC were incubated either with medium alone or with heat-killed *B. pertussis* as an ex vivo simulation of the memory responses recalled during the ensuing challenge. Following an overnight incubation, nonadherent PBMC, including T cells, were collected and separated using magnetic beads into the following fractions: CD4−, CD4+, CD95–CD4+, or left unseparated (total nonadherent cells). Memory helper T cells in primates are characterized by surface expression of CD4 and CD95 (25, 26). After further culture of all fractions, the supernatants were analyzed for secretion of IL-17, IFN-γ, and IL-5; cytokines that are characteristic of Th17, Th1, and Th2 cells, respectively. Very low background cytokine secretion was observed from nonstimulated cells isolated from naïve, vaccinated, or convalescent animals or from stimulated cells from naïve animals (Figs. S2 and S3). When stimulated with heat-killed *B. pertussis*, both total nonadherent cells and CD4+ cells from convalescent animals secreted high levels of IL-17, some IFN-γ, and no IL-5. When the CD95+ memory cells were depleted, the CD95–CD4+ cells did not secrete IL-17 or IFN-γ, consistent with induction of *B. pertussis*-specific Th17 and Th1 memory cells (Fig. 5). Stimulated total nonadherent cells and CD4+ cells from aP-vaccinated animals secreted significant IFN-γ, but the response was weaker than convalescent cells ($P = 0.01$), and there was no significant increase in IL-17 secretion. However, there was a significant IL-5 response, consistent with skewing toward Th2 and Th1 memory (Fig. 5). Total nonadherent cells and CD4+ cells from wP-vaccinated animals secreted similar IFN-γ compared with aP cells, but no IL-5. IL-17 secretion was between levels for naïve and convalescent cells, suggesting that T-cell memory induced by wP vaccination is similar to natural infection, but the Th17 and Th1 memory responses were weaker.

Discussion

The introduction of whole-cell vaccines consisting of inactivated *Bordetella pertussis* organisms in the United States in the 1940s caused a precipitous decrease in pertussis incidence (27). However, over the past 30 y, pertussis has resurged in the United States. The resurgence began during the wP vaccine era, but the pace has quickened since aP vaccines were recommended for all primary and booster doses (11). This correlation has led many to hypothesize that aP vaccines are less effective on a population scale than the wP vaccines they replaced (10, 12, 13). Consistent with this notion, several recent observational studies concluded that children primed with aP vaccine had a twofold to fivefold greater risk of pertussis diagnosis compared with wP-primed children (19–22). Our results in nonhuman primates add to these findings by showing that animals vaccinated with wP cleared infection by a direct challenge twice as fast as animals vaccinated with aP. However, neither vaccine was able to prevent colonization as well as immunity from a previous infection.

Another hypothesis as to why pertussis is reemerging is that the duration of immunity in aP-vaccinated children is shorter than anticipated. Although some first-generation acellular vaccines had poor immunity and efficacy, double-blinded clinical trials and field-efficacy studies for the US-licensed acellular vaccines estimated the short-term efficacy to be excellent: ∼85% after three doses and 98% after five doses (28–30). However, recent cohort and case-control studies concluded that 5 y following the fifth aP dose, children are fourfold to 15-fold more likely to acquire pertussis compared with within the first year, consistent with waning aP immunity (30–33).

We hypothesized an additional explanation for pertussis resurgence is that aP-vaccinated individuals can act as asymptomatic or mildly symptomatic carriers and contribute significantly to transmission in the population. Observational studies suggest that asymptomatic pertussis can occur in vaccinated children and adults based on PCR or serological data (34, 35). However, during the aP vaccine trials, participants were not screened for *B. pertussis* infection unless they presented with pertussis-like symptoms and at least 7–21 d cough (12). Therefore, no experimental data exist on whether vaccination prevents *B. pertussis* colonization or transmission in humans. In the present study we show that aP-vaccinated primates were heavily infected following direct challenge, and the time to clearance was not different compared with naïve animals. Similarly, there was no difference in the kinetics or peak level of colonization between aP-vaccinated and naïve animals that were infected by natural transmission. Importantly, we also show in two experiments that aP-vaccinated animals transmitted *B. pertussis* to naïve cage mates. Together these data form the key finding of this study: aP vaccines do not prevent infection or

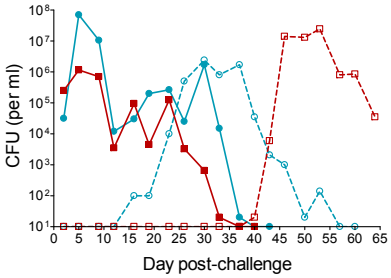

Fig. 3. Infected aP vaccinees can transmit pertussis to naïve contacts. Two animals vaccinated with aP were housed in separate cages, and each was directly challenged. Twenty four hours after challenge, an unchallenged naïve animal was placed in each cage. All animals were followed for colonization as in Fig. 1. One cage pairing is shown with turquoise lines with circles, and the other is shown with maroon lines with squares. Solid lines with closed symbols indicate the aP-vaccinated, directly challenged animals, and open symbols with dashed lines are used for the unchallenged, naïve contacts.

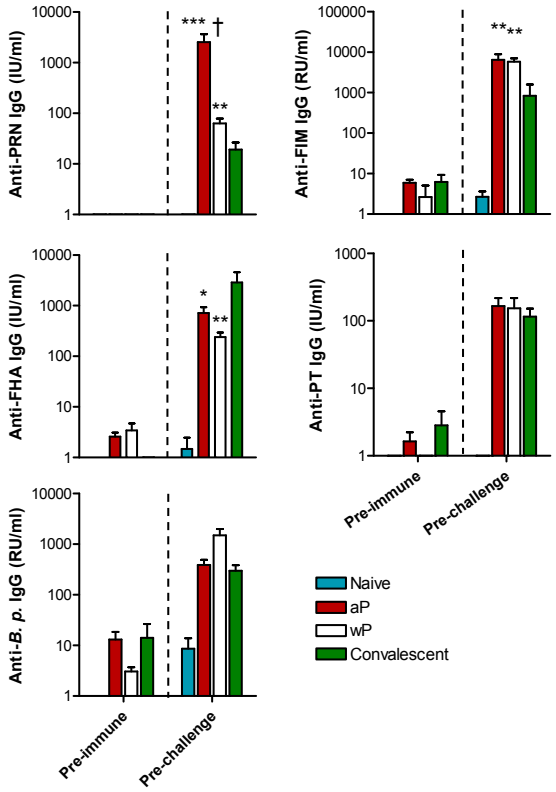

Fig. 4. Vaccination and previous infection induce robust serum antibody responses. Antibody responses to the four vaccine antigens—PRN, FIM, FHA, and PT—and to heat-killed *B. pertussis* (*B. p.*) were measured by ELISA. Preimmune sera were collected from vaccinated animals before immunization and from conv. animals before initial infection (n = 3–4 per group). Because Infanrix does not contain FIM, four Daptacel-vaccinated animals were included in the anti-FIM ELISA. Prechallenge sera were collected from all animals 1 wk before challenge. International Units (IU) or relative units (RU) in each sample were determined by comparing the responses to the WHO international standard pertussis antiserum on each plate. ***P < 0.001, **P < 0.01, *P < 0.05 vs. Convalescent. †P < 0.001 vs. wP.

transmission of *Bordetella pertussis* even 1 mo after completing the primary vaccination series.

We show that wP, aP, and natural infection all induce high-antibody titers. The prechallenge titers in aP-vaccinated animals were generally equivalent or higher than those observed in convalescent and wP-vaccinated animals, suggesting that aP is immunogenic in baboons and that the inability to prevent infection was not due to low-antibody titers. Compared with the large number of clinical studies that have characterized the antibody response to pertussis infection and vaccination, very few have investigated pertussis-induced helper T-cell immune responses in humans. Taken as a whole, these limited data suggest that aP vaccination induces Th2 or mixed Th2/Th1 responses, whereas wP vaccination and natural infection induce a Th1 response (13). However, none of these studies tested for Th17 memory, a recently identified T cell that specializes in controlling extracellular bacterial infections at mucosal surfaces (24). Our data show that natural infection induced robust Th17 and Th1 immunity. Animals vaccinated with wP, which cleared infection faster than naïve and aP-vaccinated animals, showed similar but weaker T-cell responses. wP vaccination is generally believed to induce strong Th1 responses, but what we observed here was relatively weak. This observation might be explained by heterogeneity in the manufacturing of different wP vaccines. Future studies will compare the immune response induced by wP vaccines produced by three different manufacturers. In comparison with natural infection and wP, aP-induced immunity was mismatched, showing a Th2 response with a weaker Th1 response and no significant Th17 response.

Together, the cytokine and T-cell immunological data observed in baboons are generally consistent with those observed in mice (13). We previously showed that pertussis infection in baboons induces a mucosal immune response characterized by production of IL-17 and a variety of chemokines and cytokines associated with IL-17 signaling, including IL-6 and IL-8. This primary immune response correlated with long-lived Th17 and Th1 memory responses that lasted >2 y (36). Mice infected with *B. pertussis* also express mucosal IL-17, IL-6, and IL-8 homologs and induce Th17 and Th1 memory (37–40). Mice vaccinated with wP also develop Th17 and Th1 memory that results in partial protective immunity, similar to what we observed in the baboon model (41, 42). A recent report by Ross et al. (42) concluded that an aP containing PT, FHA, and PRN induces Th1, Th2, and Th17 immune responses in C57BL/6 mice (42). However, a previous study from the same group found Th1 and Th2 but no

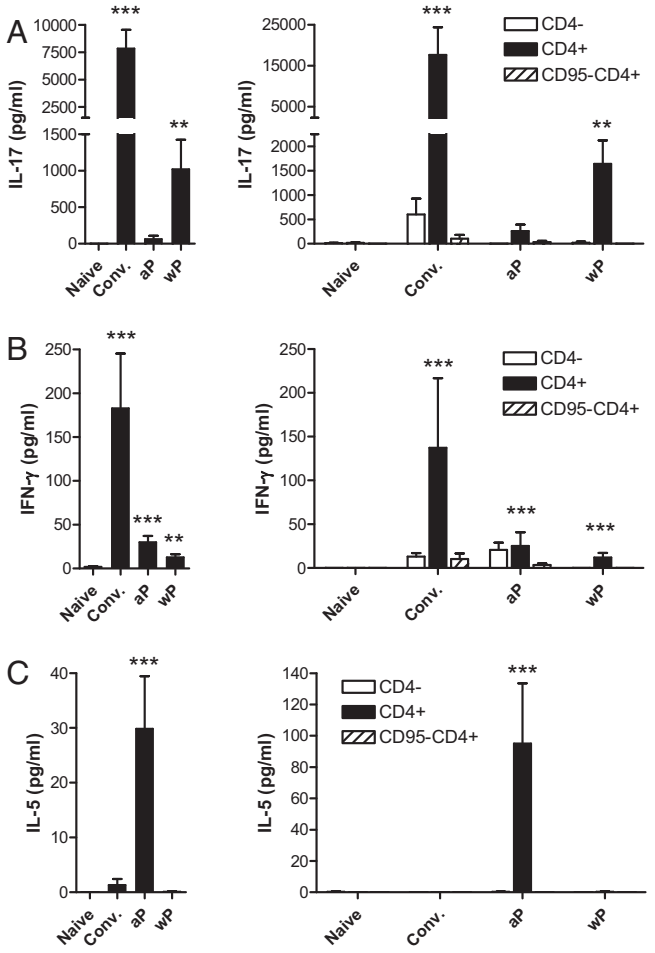

Fig. 5. Helper T-cell responses induced by vaccination and infection. PBMC collected from naïve, aP-vaccinated, wP-vaccinated, and conv. animals 1 wk before infection were incubated overnight with either medium alone or medium containing heat-killed *B. pertussis* (n = 3–4 per group). For each growth condition, nonadherent cells were collected and either left unseparated (total nonadherent cells) or separated using anti-CD4 and anti-CD95 magnetic particles. Total nonadherent, CD4–, CD4+, and CD95–CD4+ cells were then cultured under the same conditions as before (with medium alone or stimulated with heat-killed *B. pertussis*). After 36 h, supernatants were collected and analyzed for IL-17 (*A*), IFN-γ (*B*), and IL-5 (*C*). Cytokine secretion in response to *B. pertussis* stimulation is presented for total nonadherent cells (*Left*) and separated cells (*Right*). ***P < 0.001, **P < 0.01, *P < 0.05 vs. same fraction from naïve animals.

significant Th17 responses in C3H/HeJ and C3H/HeN mouse strains vaccinated with an aP containing PT and FHA (41). Nevertheless, data from two clinical studies recently showed negligible Th17 recall responses (~10 pg/mL) in PBMC isolated from aP-vaccinated 4-y-old children before and after booster, suggesting aP does not induce Th17 memory in humans (43, 44).

Taken as a whole, the data presented in this study suggest that antibodies induced by aP vaccination are sufficient for preventing severe pertussis symptoms but do not mitigate colonization. Inhibition of leukocytosis likely occurs through antibody-mediated neutralization of PT, a toxin which interferes with leukocyte extravasation by blocking chemokine receptor signaling (1). The mechanism by which aP prevents coughing despite heavy bacterial colonization is not known but deserves further attention. On the other hand, induction of Th17/Th1 memory responses correlated with the ability to clear infection: convalescent and wP-vaccinated animals possessed strong Th17 responses and Th1 responses and cleared infection more quickly than aP-vaccinated animals which lacked Th17 responses but possessed Th1/ Th2 memory. Although we have not definitively shown that Th17 cells are required for *B. pertussis* clearance, this correlation is consistent with the role these cells play in fighting extracellular bacterial infections at mucosal surfaces by inducing neutrophil chemotaxis. The current studies were not designed to look at immune cell recruitment to the respiratory tract, but additional experiments are underway to determine the role of neutrophils in the immune response to pertussis infection and vaccination in baboons. We are also investigating other possible mechanisms that could prevent mucosal colonization; for example, a possible role for IgA and IgD which are secreted in primate lower and upper respiratory tracts, respectively (45, 46).

The baboon model offers many advantages, chiefly the ability to investigate pertussis pathogenesis, transmission, and host immune responses to infection and vaccination in a primate species that is >96% genetically similar to humans (47). However, there are also several limitations associated with this model. There are far fewer animals available for research compared with smaller-animal models. In addition, there is a paucity of immunological reagents that are validated for baboons compared with mice and humans. Although antibodies against cell surface markers are generally cross-reactive, anti-cytokine antibodies tend to be much more species-specific. For this reason we have so far been unable to assess T-cell responses using intracellular cytokine staining and flow cytometry. This led us to develop the cell separation assay as an alternative method for phenotyping the memory T-cell responses induced by pertussis infection and vaccination (36). One limitation of our assay is that during the CD4+ cell purification, antigen-presenting cells such as macrophages and dendritic cells are removed after an overnight incubation. This likely explains the low IFN-γ secretion observed in all groups because antigen-presenting cells increase IFN-γ secretion by antigen-specific CD4+ T cells through a positive feedback loop (48). In line with this hypothesis, our previous data showed that restimulated whole PBMC from convalescent animals secreted much higher levels of IFN-γ. In addition, restimulation assays using human PBMC or murine splenocytes after infection or vaccination also show higher levels of secreted IFN-γ (42, 49). Together these observations suggest that although our assay is valuable for phenotyping T-cell memory, it likely underrepresents the magnitude of Th1 memory responses. We used heat-killed *B. pertussis* as an antigen for our restimulation assays because we believe this is the most relevant method for ex vivo simulation of T-cell memory recalled during infection. However, it is possible that this assay underdetects immune responses that would be observed had we used purified vaccine antigens. Another disadvantage of primate models is that it is not feasible to directly link an immune response to protection. Although protection from pertussis has been shown to be mediated by IFN-γ and, to a lesser extent, IL-17 signaling using knockout mouse strains lacking specific gene products (13), the relative protection afforded by Th17 or Th1 responses in vaccinated or convalescent baboons or humans is not known.

Currently, a major focus of public health agencies is the prevention of pertussis infection in young infants who have not completed their primary aP series and have considerable morbidity and mortality to pertussis infection (1). One recommendation to reduce transmission of pertussis to infants is by "cocooning," or vaccinating people who have contact with infants (11). Our data show that aP-vaccinated animals are infected and transmit pertussis to naïve contacts. Consistent with these findings, seroepidemiological studies have concluded that *B. pertussis* circulation is still high in countries with excellent aP uptake (27, 50), and a cross-sectional study showed that postpartum aP vaccination of mothers did not reduce pertussis illness in young infants (51). These data suggest that cocooning is unlikely to be an effective strategy to reduce the burden of pertussis in infants. However, it is important to note that our data in combination with human data show that vaccination with aP provides excellent protection from severe pertussis (52). Therefore, any short-term plan for addressing the resurgence of pertussis should include continued efforts to enhance aP immunization. However, to protect the most vulnerable members of the population and achieve optimal herd immunity, it will be necessary to develop a vaccination strategy that effectively blocks pertussis infection and transmission.

Materials and Methods

Ethics Statement. All animal procedures were performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International in accordance with protocols approved by the Center for Biologics Evaluation and Research Animal Care and Use Committee and the principles outlined in the *Guide for the Care and Use of Laboratory Animals* by the Institute for Laboratory Animal Resources, National Research Council (53).

Bacterial Strains and Media. *B. pertussis* strain D420 was grown on Bordet–Gengou and Regan–Lowe plates prepared as described previously (17). Heat-killed *B. pertussis* was prepared by resuspending to an OD_{600} of 0.90 (5×10^9 cfu/mL) in PBS and heating at 65 °C for 30 min.

Vaccination, Infection, and Evaluation of Baboons. Baboons obtained from the Oklahoma Baboon Research Resource at the University of Oklahoma Health Sciences Center were inoculated with human doses of aP or wP administered intramuscularly at 2, 4, and 6 mo of age. For studies using aP, equal numbers of animals were vaccinated with Daptacel (Sanofi Pasteur Ltd.) and Infanrix (GlaxoSmithKline). For wP, animals were vaccinated with Triple Antigen (Serum Institute of India Ltd.), which meets the World Health Organization (WHO) recommendations for potency. Naïve animals were age-matched but not vaccinated. Previously infected animals were clear of *B. pertussis* infection for 1 to 2 mo before reinfection. Direct challenge and transmission studies were performed as described previously (17, 18). The inoculum for each direct challenge was between 10^9–10^{10} cfu as determined by measurement of optical density and confirmed by serial dilution and plating to determine the number of cfu per mL of inoculum. Baboons were evaluated twice weekly as described previously for enumeration of circulating white blood cells and serum separation (17). Nasopharyngeal washes were diluted and plated on Regan–Lowe plates to quantify bacterial cell counts.

Isolation of PBMC and Cell Separation. Baboons were anesthetized, and PBMC were isolated from peripheral blood as described previously (36) and cryopreserved in RPMI-1640 medium supplemented with 10% (vol/vol) DMSO and 12.5% (wt/vol) BSA using Mr. Frosty containers (Nalgene). After thawing, cells were washed twice and nonadherent cells were collected as described previously. For each growth condition, cells were incubated overnight with either medium alone or medium containing heat-killed *B. pertussis* (50 bacteria:1 PBMC). Nonadherent cells were collected, and 2×10^6 cells were left unseparated (total nonadherent cells). Using the method previously described, 4×10^6 cells were separated using anti-CD4 magnetic particles, and another 4×10^6 cells were depleted of CD95+ cells and then separated with anti-CD4 magnetic particles (36). The following fractions were collected: Total nonadherent, CD4–, CD4+, and CD95–CD4+. After incubation with or without heat-killed *B. pertussis*, cells were pelleted and supernatants were collected for IL-17A quantitation by ELISA (Aniara) and quantitation of IFN-γ and IL-5 using the Milliplex MAP nonhuman primate kit according to the manufacturer's instructions (Millipore). Data are presented as

the cytokine concentration secreted by *B. pertussis*-stimulated cells minus the basal concentration secreted by cells incubated with medium alone.

Detection of Serum Antibodies to Pertussis Antigens. Nunc Maxisorp 96-well plates were coated overnight with 0.2 μg/mL PT, 0.5 μg/mL FHA, 2 μg/mL PRN, or 0.2 μg/mL FIM (List Biologicals) as described previously (17, 54). For whole-bacteria ELISA, plates were coated overnight at 37 °C with heat-killed *B. pertussis* prepared as described above. Serum IgG for each antigen was measured as described previously (17). Each plate contained a standard curve from the WHO international standard pertussis antiserum (National Institute for Biological Standards and Control) used to assign international units for PT, FHA, and PRN and relative units for FIM and heat-killed *B. pertussis* by comparison with the linear portion of the standard curve. Because Infanrix does not contain FIM, only Daptacel-vaccinated animals were included in the anti-FIM ELISA.

Statistics. All data are reported as mean ± SEM. Statistical analyses were performed by ANOVA with post hoc *t* test using JMP (version 9) software (SAS Institute, Inc.). Antibody and cytokine data were normalized by log transformation before analysis.

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Proc Biol Sci. 2010 Jul 7;277(1690):2017-25. doi: 10.1098/rspb.2010.0010. Epub 2010 Mar 3.

Acellular pertussis vaccination facilitates Bordetella parapertussis infection in a rodent model of bordetellosis.

Long GH[1], Karanikas AT, Harvill ET, Read AF, Hudson PJ.

Author information

Abstract

Despite over 50 years of population-wide vaccination, whooping cough incidence is on the rise. Although Bordetella pertussis is considered the main causative agent of whooping cough in humans, Bordetella parapertussis infections are not uncommon. The widely used acellular whooping cough vaccines (aP) are comprised solely of B. pertussis antigens that hold little or no efficacy against B. parapertussis. Here, we ask how aP vaccination affects competitive interactions between Bordetella species within co-infected rodent hosts and thus the aP-driven strength and direction of in-host selection. We show that aP vaccination helped clear B. pertussis but resulted in an approximately 40-fold increase in B. parapertussis lung colony-forming units (CFUs). Such vaccine-mediated facilitation of B. parapertussis did not arise as a result of competitive release; B. parapertussis CFUs were higher in aP-relative to sham-vaccinated hosts regardless of whether infections were single or mixed. Further, we show that aP vaccination impedes host immunity against B. parapertussis-measured as reduced lung inflammatory and neutrophil responses. Thus, we conclude that aP vaccination interferes with the optimal clearance of B. parapertussis and enhances the performance of this pathogen. Our data raise the possibility that widespread aP vaccination can create hosts more susceptible to B. parapertussis infection.

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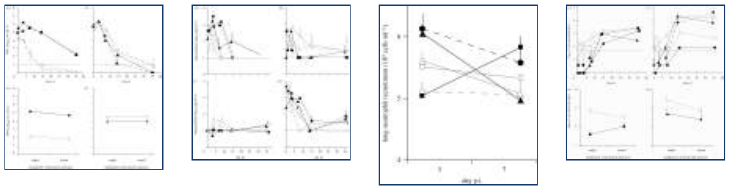

Publication types, MeSH terms, Substances, Grant support

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Vaccine. 2015 Oct 13;33(42):5654-5661. doi: 10.1016/j.vaccine.2015.08.066. Epub 2015 Aug 29.

The impact of parental postpartum pertussis vaccination on infection in infants: A population-based study of cocooning in Western Australia.

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Author information

Abstract

During a pertussis epidemic in 2011-2012 the Western Australian (WA) Department of Health implemented a 'cocooning' programme, offering free pertussis-containing vaccine (dTpa) to new parents. We assessed the impact of vaccinating parents with dTpa on the incidence of pertussis infection in newborns. Births in WA during 2011-2012 were linked to a register of parental pertussis vaccinations and to notified reports of laboratory-proven pertussis in children <6 months of age. Parents who received dTpa during the four weeks after their child's birth were defined as 'vaccinated postpartum.' Cox proportional-hazards methods were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of pertussis infection among infants born to parents vaccinated postpartum vs. unvaccinated parents, adjusted for maternal age, geographic region, timing of birth, and number of siblings. Of 64,364 live-births, 43,480 (68%) infants had at least one vaccinated parent (60% of mothers and 36% of fathers). After excluding records where parent(s) were either vaccinated prior to the birth, vaccinated >28 days after the birth, the vaccination date was uncertain, or the child died at birth (n=42), the final cohort contained 53,149 children, 118 of whom developed pertussis. There was no difference in the incidence of pertussis among infants whose parents were both vaccinated postpartum compared to those with unvaccinated parents (1.9 vs 2.2 infections per 1000 infants; adjusted HR 0.91; 95%CI 0.55-1.53). Similarly, when assessed independently, maternal postpartum vaccination was not protective (adjusted HR 1.19; 95%CI 0.82-1.72). Supplemental sensitivity analyses which varied the time period for parental vaccination and accounted for under-reporting of vaccination status did not significantly alter these findings. In our setting, vaccinating parents with dTpa during the four weeks following delivery did not reduce pertussis diagnoses in infants. WA now provides dTpa vaccine to pregnant women during the third trimester.

KEYWORDS: Bordetella pertussis; Cocooning; Immunisation; Pertussis vaccine; Public health; Whooping cough

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MeSH terms, Substance

LinkOut - more resources

Finding the 'who' in whooping cough: vaccinated siblings are important pertussis sources in infants 6 months of age and under

Christina Bertilone, Tania Wallace, Linda A Selvey

Abstract

Objectives: To describe the epidemiology of pertussis, and to identify changes in the source of pertussis in infants 6 months of age and under, during the 2008–2012 epidemic in south metropolitan Perth.

Design and setting: Analysis of all pertussis cases notified to the South Metropolitan Population Health Unit and recorded on the Western Australian Notifiable Infectious Disease Database over the study period. Information on the source of pertussis was obtained from enhanced surveillance data.

Results: Notification rates were highest in the 5–9 years age group, followed by the 0–4 years and 10–14 years age groups. There was a significant increase in the proportion of known sources who were siblings from the early epidemic period of 2008–2010, compared with the peak epidemic period of 2011–2012 (14.3% versus 51.4%, p = 0.002). The majority of sibling sources were fully vaccinated children aged 2 and 3 years.

Conclusions: The incidence of pertussis was highest in children aged 12 years and under in this epidemic. At its peak, siblings were the most important sources of pertussis in infants 6 months and younger, particularly fully vaccinated children aged 2 and 3 years. Waning immunity before the booster at 4 years may leave this age group susceptible to infection. Even if cocooning programs could achieve full vaccination coverage of parents and ensure all siblings were fully vaccinated according to national schedules, waning immunity in siblings could provide a means for ongoing transmission to infants. Recent evidence suggests that maternal antenatal vaccination would significantly reduce the risk of pertussis in infants 3 months of age and under. *Commun Dis Intell* 2014;38(3):E195–E200.

Keywords: pertussis, whooping cough, infants, source, vaccination, immunisation

Introduction

The incidence of pertussis (whooping cough) has risen both in Australia and internationally over recent years, and large epidemics have occurred.[1,2] Increased clinician awareness and laboratory testing are likely to be partially responsible for the apparent increase in disease incidence.[3] However, the epidemiology of pertussis in Australia and the United States of America has also changed in recent times, with an increasing proportion of disease occurring in children.[4–7] Possible reasons for this include the increasing use of less effective acellular vaccines[8–10] and increasing circulation of *Bordetella pertussis* strains deficient of vaccine antigen.[11,12] Within vaccinated populations, the fewer whole cell vaccines received, the greater the risk of pertussis.[8,10] Additionally, immunity from acellular pertussis vaccination wanes more rapidly than that from whole cell vaccination.[13–15] Pertussis morbidity and mortality are greatest in infants under the age of 6 months, who are too young to have completed a primary vaccination course. The implications of these changes for the source of infant pertussis remain unclear.

Household contacts are the most likely sources of infant pertussis, but there is variation in the proportion of sources reported to be parents as opposed to siblings. A recently published Australian review on infant pertussis sources reported the source as a parent in 55% (range 39%–57%) and a sibling in 16%–43%.[16] The proportion of sources that were siblings varied widely between studies, in comparison to the proportion that were parents, which were more consistent. The conclusion was that siblings may be more important sources of infant pertussis than previously realised.[16]

A prolonged outbreak of pertussis occurred in Australia, including south metropolitan Perth, between 2008 and 2012. A cocooning strategy involving the vaccination of caregivers of newborns was implemented in Western Australia and ran for 2011 and 2012 in attempts to protect newborns during the outbreak. This strategy can only be effective if caregivers are the main source of pertussis in infants.

Over the study period, the South Metropolitan Population Health Unit (SMPHU) collected enhanced surveillance data for pertussis cases in

children under 5 years of age. These data are not collected or reported at the national level so provide valuable additional information, particularly regarding source of infection, to that routinely collected for the National Notifiable Diseases Surveillance System. This study aimed to describe the epidemiology of the epidemic in south metropolitan Perth in relation to the source of infant pertussis, as well as any changes in the epidemiology and the source that occurred over the 5-year period.

Methods

The SMPHU is responsible for the follow up of notifiable diseases for the area covered by the South Metropolitan Health Service, which spans all of metropolitan Perth south of the Swan River and services approximately 37% of the Western Australian population.[17] Over the study period, the SMPHU collected enhanced surveillance data for pertussis cases in children under 5 years of age. The process involves a trained public health nurse interviewing the treating doctor and caregiver of the notified case, in order to obtain further information such as the likely source of infection and any high risk contacts. Enhanced surveillance defines a source of pertussis as a contact of the notified case who had either prolonged coughing illness or known pertussis infection, who was in contact with the notified case during the latter's incubation period (from 6 to 21 days prior to symptom onset). In the case of multiple possible sources, the source was assumed to be the individual who first became symptomatic, provided that the source's infectious period coincided with the notified case's incubation period.

Enhanced surveillance data for notified cases in infants 6 months of age and under were examined retrospectively, as well as pertussis notification data recorded on the Western Australian Notifiable Infectious Disease Database (WANIDD) for all age groups. All confirmed and probable cases meeting the case definition for pertussis were included if the optimal date of onset of pertussis occurred any time from 1 January 2008 to 31 December 2012, and residential postcode was within the SMPHU catchment area. The optimal date of onset refers to the earliest date recorded on WANIDD reflecting disease onset. In some situations, such as those where the caregiver of the notified case could not be contacted by telephone, enhanced surveillance data were not available. Notified cases and sources were defined as being fully vaccinated for age if on the optimal date of onset of illness they had received all pertussis vaccinations recommended by the Western Australian immunisation schedule for their age. This would potentially include vaccinations given within the 14 days preceding disease onset. The dates of vaccination for the source were not available so any such cases would be misclassified as being fully vaccinated for age at disease onset. Notified cases from the 2008–2010 and 2011–2012 periods were compared because this distinction allowed comparison of the pre-cocooning period with the cocooning period, and the early epidemic period with the peak epidemic period. Differences in age specific risk of infection as well as source of infant pertussis in the 2 periods were assessed.

Denominator data for notification rates were obtained from the Epidemiology Branch of the WA Department of Health. All analyses were performed in SPSS version 21. All comparisons were performed using chi-squared analyses or Fisher's exact test for categorical variables, and Mann-Whitney U testing for continuous variables. The study was approved by the Curtin University Human Research Ethics Committee (protocol approval SPH-16-2013). Ethics approval was not sought elsewhere, as this study formed part of the core business of the SMPHU.

Results

There were 3,611 cases of pertussis notified to the SMPHU from 2008 to 2012, with this period demonstrating a dramatic increase in notifications in comparison with previous years (Figure 1). Of these cases, 37.3% (n = 1348) occurred in children 12 years of age or under. At the peak of the epidemic in the December 2011 quarter, notification rates were markedly higher in children in age categories 14 years of age and under in comparison with the remainder of the population (Figure 1, Figure 2). The notification rate for the 5–9 years age group in the December 2011 quarter was 341.4 per 100,000, and 243.0 per 100,000 for the 10–14 years age group. Notification rates peaked in adults in this quarter also, but the amplitude of the peak was much less marked (56.0 per 100,000). Notification rates in children 4 years of age and under did not peak until the following quarter, at 206.8 per 100,000.

Of the 115 cases of pertussis in infants 6 months of age and under, enhanced surveillance data were available for 106 (92.2%). The optimal date of onset was the date of symptom onset for 111 of 115 cases, and the laboratory specimen date for the remaining four. There were no significant differences between those who had undergone enhanced surveillance and those who had not, comparing gender ($p = 0.74$), age ($p = 0.56$), ethnicity ($p = 1.00$) and hospitalisation status ($p = 0.48$).

The source was identified in 65 of 106 cases (61.3%). Two potential sources were identified for two of these cases, and one for the remaining 104 cases.

Figure 1: Notification rates of pertussis, south metropolitan Perth, 2008 to 2012, by quarter and age group

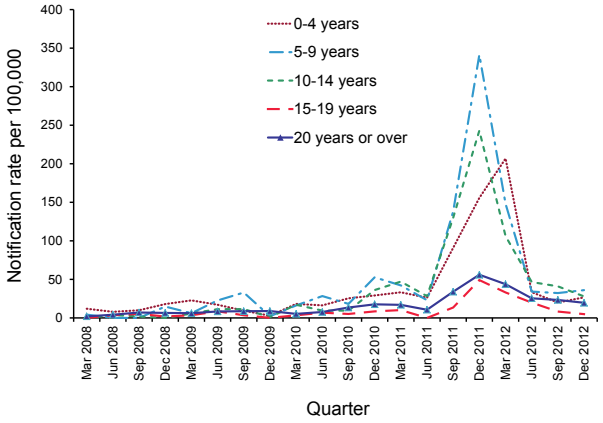
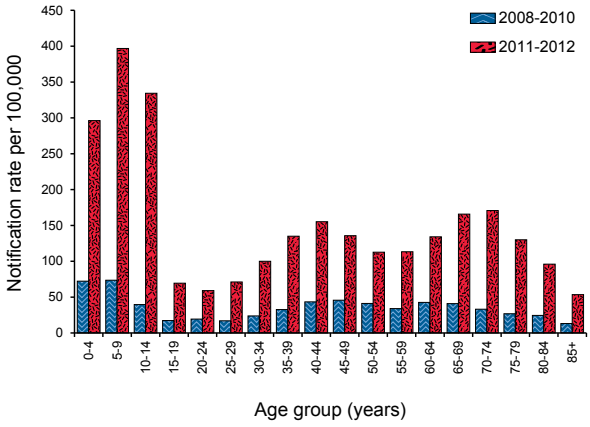


Figure 2: Notification rate of pertussis, south metropolitan Perth, 2008 to 2010 compared with 2011 to 2012, by age group



The proportion of sources whose diagnosis was confirmed with laboratory testing was unknown. Over the 5-year period, the source was a parent in 38.5% (n = 25) of cases and a sibling in 35.4% (n = 23) of cases. The most likely source of pertussis differed in the 2008–2010 period compared with the 2011–2012 period (Table). The proportion of parents as a source was lower in the 2011–2012 period (32.4%, n = 12 versus 46.4%, n = 13). However this difference was not statistically significant (p = 0.25). In contrast, the proportion of sources that were siblings was significantly higher in the 2011–2012 period (51.4%, n = 19 versus 14.3%, n = 4; p = 0.002).

During the 2011–2012 peak epidemic period, the ages of 14 of 19 sibling sources were known. Eight of these sources were aged from 2 to 4 years with five being fully vaccinated, one partially vaccinated, one unvaccinated, and one of unknown vaccination status. The true number of children in the 2–4 years age group may have been higher as the ages of 5 children were not recorded. Three sources were aged 6–11 years, and three were aged 12–19 years. Of all children in south metropolitan Perth diagnosed with pertussis in 2008–2012 and aged from 7 months to 4 years, 78.1% (n = 267) were fully vaccinated for age.

Discussion

Recent studies have shown an increasing incidence of pertussis in children but the implications of this for the source of infant pertussis have not been fully described. Identifying the source of pertussis in infants 6 months of age and under is crucial for the development of effective preventive strategies in this age group. However, the most likely source of infection will reflect local epidemiology, and if

Table: Source of pertussis in infants 6 months of age and under, south metropolitan Perth, 2008 to 2010 compared with 2011 to 2012

	2008-2010			2011-2012			Total		
	n	Known source %	Notified cases %	n	Known source %	Notified cases %	n	Known source %	Notified cases %
Parent	13	46.4	24.5	12	32.4	19.4	25	38.5	21.7
Sibling	4	14.3	7.5	19	51.4	30.6	23	35.4	20
Other household contact	3	10.7	5.7	2	5.4	3.2	5	7.6	4.3
Grand parent	3	10.7	5.7	3	8.1	4.8	6	9.2	5.2
Cousin	3	10.7	5.7	0	0	0	3	4.6	2.6
Other household contact	2	7.1	3.8	1	2.7	1.6	3	4.6	2.6
Total known source	28			37			65		
Notified cases with available enhanced surveillance data	45			61			106		
Notified cases 6 months of age and under	53			62			115		

the age specific risk of infection changes during epidemics, the source of pertussis in infants could vary at different points in the epidemic cycle. This study demonstrates changes in the source of infant pertussis corresponding with changing age specific risk of infection during an epidemic period.

Notification rates were highest in children in this epidemic, particularly at its peak in the 2011–2012 period. This correlated with a dramatic rise in the proportion of sibling sources. There are several possible explanations for the high notification rates in children. Recent studies suggest that acellular pertussis vaccine immunity wanes more rapidly than that of the whole cell pertussis vaccine.[8,10,13–15] The vaccine effectiveness of the whole cell pertussis vaccine previously administered in Australia was estimated at 91% (95% CI 85.5%–94.4%) in infants aged 8–23 months, and 84.5% (95% CI 78.3%–88.9%) in the 2–4 years age group.[19] In contrast, a recent Australian study reported the vaccine effectiveness of acellular vaccine to be 83.5% (95% CI 79.1%–87.8%) in infants aged 6–11 months, falling to 70.7% (95% CI 64.5%–75.8%) in children aged 2 years, and 59.2% (95% CI 51.0%–66.0%) in children aged 3 years.[20] In the whole cell pertussis vaccine effectiveness study, children had received 5 doses of pertussis vaccine by age 5 (2, 4, 6, 18 months and 4 years). In contrast, the acellular pertussis vaccine effectiveness for the children aged 2 and 3 years was calculated for children receiving 3 doses of vaccine, reflecting the current pertussis vaccination schedule of 2, 4, 6 months and 4 years.[20]

The high notification rates in children and the higher percentage of sibling sources could also be epidemic specific features, given the timing of this study. This is feasible as studies of contact patterns have shown high levels of assortative mixing in children.[21] Age specific infection risk and infant pertussis source types may be different in the inter-epidemic period. This would be congruent with the findings of this study, given that proportions of sources that were parents and siblings in the 2008–2010 period were comparable with those reported in previous literature.[16] Even if high incidence of pertussis in children and high proportions of siblings as sources are purely epidemic specific features, there are still implications for infant pertussis control measures during epidemics.

Cocooning programs are challenging to implement and there is no definitive evidence that they are successful in reducing the incidence of infant pertussis.[22,23] Parents remain susceptible to pertussis for 14 days following immunisation, due to the time taken to mount an immune response.[24] The earlier parental immunisation is performed post-natally, the better protected infants will be, making hospital-based vaccination ideal. Barriers to this have been identified, including legal issues related to vaccinating fathers (who are not hospital patients), and the need to provide after-hours services.[25] In Western Australia in 2011, an estimated 60% of mothers and 41% of fathers of newborns had been administered government funded pertussis vaccine, although the timing of this vaccination post-natally is unknown (2012 data not available at the time of publication).[26] These rates were similar to coverage rates reported in Victoria for the duration of their state wide cocooning program, where it was found that of those eligible, 68% of mothers and 49% of fathers were vaccinated.[22] In metropolitan areas of Victoria, 6% of mothers and 10% of fathers were vaccinated in the maternity hospital, compared with 70% of mothers and 42% of fathers in rural areas, suggesting that (particularly in metropolitan areas) vaccination may not have been given early enough in the neonatal period.[22] In this study, although the proportion of sources that were parents was lower in the cocooning period (2011–2012) compared with the pre-cocooning period (2008–2010), this observation did not reach statistical significance. While this may be a real finding, there were insufficient numbers in this study to determine that. If the difference in the proportion of source cases that were parents in the 2 periods were real, cocooning may explain this reduction, but it is likely to be insufficient to explain the observed increase in the proportion of sibling sources.

The increasing proportion of sibling sources over time reflected the increasing proportion of pertussis notifications in children 12 years of age and under over the 2008–2012 epidemic. In the peak epidemic period, sibling sources of infection were most likely to be aged 2 or 3 years. This suggests that the impact of high notification rates was greatest in the youngest siblings, despite the greatest numbers of cases occurring in children aged 7–11 years. Possible reasons for this include that siblings tend to be close in age, and that younger children are generally less able to control respiratory secretions. The only other recent Australian study of infant pertussis sources had similar findings, demonstrating that siblings aged 3 and 4 years were particularly important sources of infant pertussis during the 2009 epidemic in New South Wales.[27] Dutch research published in 2010 speculated that the high proportion of infant pertussis sources that were siblings (41%) in their study may have been related to the introduction of acellular pertussis vaccine in the Netherlands, as well as prior use of a less effective whole cell vaccine.[24] In that study, the source was a sibling aged 1–4 years in 18% of cases (95% CI 12%–25%), a sibling aged 5–8 years in 15% of cases (95% CI 9%–21%), and a sibling aged 9–13 years in

8% of cases (95% CI 4%–13%). The vaccination schedule for that population involved vaccination at 2, 3, 4 and 11 months, with a booster at 4 years introduced 5 years prior to the commencement of the study. There is a possibility that with the introduction of acellular pertussis vaccine, the interval between primary vaccination and booster doses in both the Dutch and Australian populations is now too long, resulting in waning immunity before the booster at 4 years. Even if all household contacts of newborns (including siblings) could be routinely fully vaccinated, the issue of breakthrough disease prior to the booster at 4 years would leave a certain proportion of siblings as possible infant pertussis sources, limiting the effectiveness of cocooning.

Vaccination in the 3rd trimester of pregnancy is an alternative measure for prevention of infant pertussis, with the benefit of placental transfer of maternal IgG to the infant. The vaccine effectiveness of the maternal antenatal vaccination program in the United Kingdom was estimated at 91% (84%–95% CI) for infants aged 3 months or less.[28] Following the introduction of the program, significant reductions in infant pertussis mortality, numbers of confirmed cases and numbers of hospitalisations were reported.[28] Adverse event surveillance has not detected any significant complications of maternal vaccination to date,[29] but further investigation is required into the possibility of infant immune response blunting.[28] Neonatal vaccination is an alternative possible means of infant pertussis control but similar concerns exist regarding immune blunting, requiring further study.[30] More research is also required to determine whether these observed antibody responses translate into lower incidence of pertussis in infants.

This study is a retrospective review of the data collected as part of the routine surveillance of pertussis, meaning there are several limitations. The source of pertussis was unable to be identified in 38.7% (n = 41) of cases who underwent enhanced surveillance. Previously published Australian studies on the source of infant pertussis have been unable to identify a source in 31%[27] and 49%[31] respectively. This could be due to the source being an asymptomatic or mildly unwell household contact, or a contact from outside the household unknown to the notified case or caregiver undergoing interview. If previously vaccinated adults are more likely to experience mild or asymptomatic illness, the proportion of infant pertussis sources that were parents could be underestimated in studies relying on the recall of the notified case and epidemiologic linkage rather than laboratory testing. However, siblings were the most common source of infant pertussis in a recently published study, which performed laboratory testing on all household contacts in order to identify the source.[24]

Another reason for the higher proportion of siblings noted in the 2011–2012 period could be that as the epidemic progressed, clinician awareness of pertussis in younger children increased, with a concurrent increase in laboratory testing. If this were the case, previous reports of sibling sources of infant pertussis may have underestimated the true proportion of sources attributable to siblings. Regardless, there are still implications for infant pertussis prevention and control measures.

This study has shown that a rapid increase in notification rates in children at the peak of the 2008–2012 epidemic in south metropolitan Perth was accompanied by a significant increase in siblings as sources of pertussis in young infants. In the face of widespread vaccination with a less effective acellular pertussis vaccine, it seems likely that notification rates will remain high in children. Fully vaccinated siblings aged 2 and 3 years were the most important infant pertussis sources in the peak epidemic period of this study, suggesting that immunity may wane in this age group before the vaccine booster at 4 years . Even if it were possible to fully cocoon infants through a combination of parental vaccination and ensuring siblings were fully vaccinated, the possibility of transmission via breakthrough disease in siblings would persist. The risk of sibling transmission to infants would be significantly reduced through the addition of a pertussis vaccine booster at 18 months and maternal antenatal vaccination, for which evidence of effectiveness at preventing pertussis in infants 3 months of age or less is mounting.

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Horizontal transmission of live vaccines

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Dear Editor,

Horizontal transmission has been rarely reported with of many live attenuated vaccines. Different mumps vaccines have shown rarely such transmission.[1–5] A study in US reported evidence of the transmission of rubella vaccine virus from vaccinees to two susceptible contacts.[6]

With live varicella vaccines, there are at least three reports. The brother of a 3-y-old vaccinated girl developed fever and a rash; horizontal transmission of vaccine virus was later confirmed.[7] A pregnant mother contracted the vaccine virus after her 12-mo-old boy received varicella vaccine.[8] Horizontal transmission was reported in 15 (17%) susceptible healthy siblings after varicella vaccination of 156 children with leukemia.[9] The package insert of live varicella vaccine (Varivax, Merck) states that "Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported."[10]

There are two reports with rotavirus vaccines. A randomized, double-blind study on human rotavirus vaccine (Rotarix™, Glaxo) in 100 pairs of healthy twins found that the transmission rate among placebo recipients was 18.8%.[11] In another case, rotavirus vaccine (RotaTeq, Merck) transmission was reported from a vaccinated infant to an older, unvaccinated sibling, resulting in symptomatic rotavirus gastroenteritis.[12]

A study on live attenuated influenza vaccine (FluMist, MedImmune) in a Finnish day care showed that one child in the placebo group had transiently detectable vaccine virus, indicating transmission from a vaccinated child; the child remained asymptomatic.[13]

Despite these reports, these live vaccines are used in millions of doses across the world. Clearly, the benefit of vaccination outweighs the very low risk of vaccine virus transmission.

Conflict of Interest

Go to:

All three authors are employed by Serum Institute of India Ltd.

Footnotes

Go to:

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Post-vaccine measles in a child with concomitant influenza, Sicily, Italy, March 2015

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We describe the occurrence of measles in an 18 month-old patient in Sicily, Italy, in March 2015, who received the first dose of a measles-containing vaccine seven days before onset of prodromal symptoms. Measles virus infection was confirmed by PCR and detection of specific immunoglobulin; viral genotyping permitted the confirmation of a vaccine-associated illness. The patient had a concurrent influenza virus infection, during a seasonal epidemic outbreak of influenza.

Case description

In early March 2015, measles-mumps-rubella-varicella zoster (MMRV) vaccine was administered to an apparently healthy 18-month-old child living in Sicily, Italy. Seven days later, the child presented to the family paediatrician with fever (40.1°C), catarrhal cough, runny nose and eyelid oedema. Macular rash appeared over the body two days later, starting on the trunk and then spreading to the neck and face. By day 13, the rash was fading, but due to the persistence of symptoms, the child was admitted to a children's hospital and reported as a possible case of vaccine-related measles to the Epidemiology Department of the Regional Public Health.

The local health authority carried out an epidemiological investigation: a standard measles notification form was sent to the regional health authorities and immediately forwarded to the Ministry of Health and to the Infectious Diseases Epidemiology Unit of the National Institute of Health. No direct link was identified with other measles cases in the community and the family had no history of travel outside Sicily. Moreover, contact investigation revealed no household members or pre-school contacts with symptoms consistent with measles. One of the child's parents developed influenza-like illness (ILI) symptoms (fever (›38°C) and cough, which lasted for three consecutive days) one day after administration of MMRV vaccine to the patient.

Urine and throat swab specimens were collected from the child and submitted to the Regional Reference Laboratory in Palermo for nucleic acid-based testing for measles, mumps, rubella and varicella zoster viruses and genotyping of any detected viruses. Given that this patient with suspected vaccine-associated measles developed symptoms during a seasonal epidemic outbreak of influenza viruses, and taking into account reports of morbilliform rash associated in patients with influenza B who tested negative for measles virus infection [1,2], testing was also requested for influenza and other respiratory viruses.

While no viruses could be detected in the urine specimen, measles, influenza A(H3N2) and respiratory syncytial viruses were detected in the throat swab.

On day 17, the patient's symptoms resolved without complications and the patient was discharged from hospital (Figure).

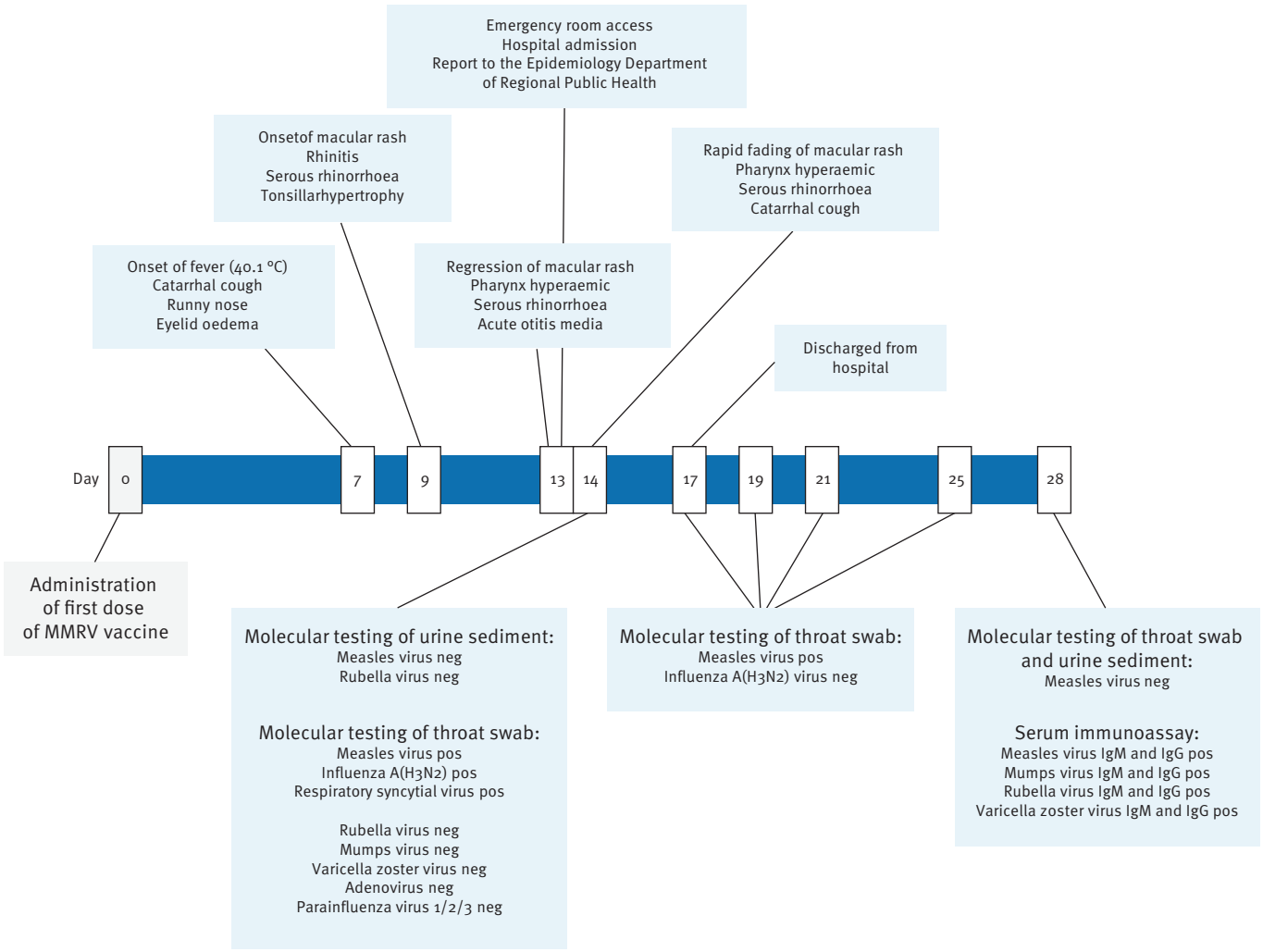
Measles virus was detected in throat swabs taken on days 17, 19, 21 and 25, but no influenza or other respiratory viruses were detectable in these specimens.

Measles virus was not detected on day 28 from a throat swab and urine specimen. A blood sample was taken at this time for serological testing for measles, mumps, rubella and varicella zoster viruses. A time line of events is shown in the Figure.

Seroconversion following MMRV immunisation was evaluated through the detection of specific measles, rubella, mumps and varicella zoster IgM and IgG antibodies by chemiluminescent immunoassay (CLIA) (measles virus: IgM = 3.1 arbitrary units (AU)/mL, IgG ›300

Figure

Time line of symptoms and physical signs in a child with post-vaccine measles and concomitant influenza, case management, specimen collection and laboratory results, Sicily, Italy, March 2015



MMRV: measles-mumps-rubella-varicella zoster; neg: negative; pos: positive.

AU/mL; mumps virus: IgM = 1.3 AU/mL, IgG = 78.9 AU/mL; rubella virus: IgM = 1.97 AU/mL, IgG = 18.0 international units (IU)/mL; varicella zoster: IgM = 0.71 AU/mL, IgG = 271.8 mIU/mL).

The measles virus was determined to be the Schwarz vaccine strain, genotype A, MVs/Palermo.ITA/12.15 [A] (VAC) [3] by sequence analysis of the genome.

Laboratory investigations

Serological and nucleic acid-based tests were performed for surveillance of measles and rubella, and genotype determination at the Regional Reference Laboratory of Palermo, formerly a member of the national network for influenza surveillance and genotyping (INFLUNET).

For the detection of specific measles, rubella, mumps and varicella zoster IgM and IgG antibodies, commercial CLIA tests were used (LIAISON (DiaSorin) and VITROS (Ortho Clinical Diagnostics)), which have the following cut-off values: measles IgM ≥ 1.0; measles IgG ≥ 13.5; mumps IgM ≥ 1.0; mumps IgG ≥ 10.0; rubella IgM ≥ 1.2; rubella IgG ≥ 15.0; varicella zoster IgM ≥ 1.0; varicella zoster IgG ≥ 100.0.

Throat swabs and the sediment of urine samples were tested using a real-time PCR instrument (QuantStudio 7 Flex Real-Time PCR system, Applied Biosystems), using specific primer/TaqMan probe sets for measles [4], mumps [5], rubella [4] and varicella zoster [6,7] viruses after extraction of total RNA using QIAmp Viral RNA Mini Kit (Qiagen).

Measles genotyping was conducted to distinguish wild-type from vaccine-associated measles viral strains. PCR products, targeting either the N gene or the H gene [8], were obtained from throat swab and sequenced using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems).

SuperScript One-Step RT-PCR kit with Platinum Taq (Invitrogen) were used for both endpoint reverse transcription RT-PCR and real-time RT-PCR reactions.

Sequences were confirmed as measles virus following comparison with the BLAST algorithm and they were phylogenetically analysed to assign genotype and cluster. The sequences were identified as Schwarz vaccine strain (genotype A) and were submitted to GenBank (accession numbers KR262162 (gene N) and KR262161 (gene H)).

Background

In Italy, vaccination against measles is included in the national vaccination schedule. Two doses of measles-mumps-rubella (MMR) vaccine have been recommended in all regions since the early 1990s [9], sometimes in association with varicella vaccination. The first dose is given at 13–15 months-old and the second at the age of 5–6 years [10].

In accordance with the national measles elimination plan [11], an enhanced surveillance system was introduced in 2007 [12] with the aim of improving timeliness, completeness of case reporting and case investigation, including laboratory confirmation of diagnosis and viral genotyping.

As the incidence of wild-type measles decreases in countries with high levels of vaccination coverage, vaccine-associated cases could be misreported [13,14], suggesting that there is a need to improve the ability to distinguish between vaccine-associated measles and 'true' wild-type measles virus infection [15].

Post-marketing surveillance of vaccines is mandatory in Italy and adverse reactions observed after the administration of vaccines are reported through the national pharmacovigilance network. According to the latest data available [16], these are mainly represented by fever, skin rash and febrile seizures, while post-vaccination viral shedding is a very uncommon event, which has been rarely documented so far [17,18].

Discussion

With an estimated more than 500 million doses administered in over 60 countries since the 1970s, the benefit of measles vaccination in preventing illness, disability and death appear unchallengeable [19,20].

Moreover, vaccine safety is annually validated by accurate post-marketing surveillance of adverse reactions conducted by the Italian Medicines Agency (AIFA). As for other live attenuated vaccines, adverse reactions following MMR or MMRV immunisation rarely present with clinically significant illness [16]: such illness is indistinguishable from wild-type measles. In this context, the reference laboratory for molecular surveillance plays a fundamental role in measles virus characterisation, through viral sequencing and genotyping, in order to promptly differentiate between wild-type and vaccine-related strains [14,18].

In this report, we documented the pharyngeal excretion of the Schwarz measles vaccine virus in an apparently healthy child with a febrile rash after measles vaccination and with laboratory-confirmed influenza A(H3N2) coinfection.

On the basis of our data, some points can be noted.

Firstly, although unlikely, measles after MMRV vaccination is possible, and this can mimic wild-type infection, leading to potential measles case misclassification. The application of molecular techniques for viral genotyping is helpful to correctly classify a case and to drive the decisions of public health authorities at the local level.

Secondly, this is the first report of a measles case with concurrent influenza and respiratory syncytial virus detection: we cannot exclude the possibility that the co-presence of other viral natural infections in a very young child, showing a slight hypogammaglobulinaemia in serum protein electrophoresis, may have favoured, or even determined, the occurrence of vaccine-related measles virus in pharyngeal secretions. Unfortunately, the parent showing ILI symptoms was not tested for influenza virus, making us unable to assess, although very likely, an intrafamilial transmission of influenza virus infection.

Notably, virus excretion was demonstrated over a 25-day period after vaccination, which is longer than previously reported [17,21,22]. Interference with other coinfecting viruses or a defective host immune response could play a role in this unexpected persistence of measles virus, although this hypothesis will require further investigation.

Thirdly, virus excretion was repeatedly detected in the throat, but not in urine sediment. This finding partially contrasts with World Health Organization (WHO) guidance for laboratory diagnosis for measles virus infection, which suggests to test preferentially for the virus in the sediment of urine samples that have been collected within at least five days after the onset of rash [23]. In the case presented here, in accordance with WHO guidance, matched urine and throat specimens were collected on the fifth day after the onset of macular rash.

Detection of measles virus in respiratory samples up to 16 days after the onset of rash suggests that other host cell pathways or viral mechanisms, potentially related to other concomitant viral infections, might be responsible for such an event. However, also in this case, further studies are necessary to better explain such an anomaly.

In conclusion, development of measles in individuals who have received MMR or MMRV vaccine is a possible,

although extremely rare, event. Therefore, especially in geographical areas with a low incidence of measles, maintenance of efficient molecular surveillance systems and the improvement of the timeliness of both case reporting and virus genotyping is of paramount importance, to ensure correct differentiation between vaccine-related illness and natural measles infection [24].

Conflict of interest

None declared.

Authors' contributions

Conceived and designed the study: FT, FV. Collected clinical and epidemiological data: PD, CD, NC. Analysed data: FT. Wrote the paper: FT, FV.

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Case of vaccine-associated measles five weeks post-immunisation, British Columbia, Canada, October 2013

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We describe a case of vaccine-associated measles in a two-year-old patient from British Columbia, Canada, in October 2013, who received her first dose of measles-containing vaccine 37 days prior to onset of prodromal symptoms. Identification of this delayed vaccine-associated case occurred in the context of an outbreak investigation of a measles cluster.

In this report we describe a case of measles-mumps-rubella (MMR) vaccine-associated measles illness that was positive by both PCR and IgM, five weeks after administration of the MMR vaccine. Based on our literature review, we believe this is the first such case report which has implications for both public health follow-up of measles cases and vaccine safety surveillance.

Between 29 August and 2 September 2013, three unlinked persons from across the Fraser Valley, British Columbia, Canada, presented with rash illness consistent with clinical measles [1]. Based on the outbreak investigation by the local health authority, none of the three cases had an identified exposure to a measles case or travel history outside of Canada during the incubation period, and a source case was never identified. All three cases had the same measles genotype B3 sequence type (MVs/British Columbia.CAN/34.13, MeaNS id 39928, GenBank accession numbers KF704002 and KF704001). Measles genotype B3 is endemic in the World Health Organization's African and Eastern Mediterranean regions [2]. Two additional cases of measles due to secondary transmission from one of the above cases were identified in British Columbia in the third week of September.

Case report

In early October 2013, a two-year-old child living in the Fraser Valley presented to the family physician with fever, rash, conjunctivitis and coryza. Symptoms had begun two days before, with a runny nose, followed by fever on the day hereafter. A macular rash appeared on the day of visiting the physician, starting on the face and progressing to the rest of the body; fever measured by the parents was at 39 °C.

Clinical examination of the child by the family physician found a fever of 39.5 °C, marked bilateral conjunctivitis, and macular rash over the body. Three days later, fever had dissipated, rash was fading and symptoms resolved without complications.

Public health alerts had been issued to community physicians regarding the recent cluster of measles in September, which may have raised suspicion for measles in this case. Additionally, the child's family was aware of measles cases in the community from a relative who attended the same church as one of the original cases, but no direct link was identified and they had no travel history outside of Canada. Contact investigation revealed no ill household members or preschool contacts. The child's past medical history indicated anaphylaxis to peanuts and eggs. Primary series of immunisations were not up-to-date, as she had just received her first dose of MMR vaccine 37 days prior to the onset of illness. At the same visit, the child had received meningococcal C and pneumococcal conjugate vaccines.

Laboratory investigations

Laboratory testing for measles was performed on specimens collected on the day of rash onset. Measles RNA was detected in the nasopharyngeal swab by the RT-PCR assay [3]. Acute and convalescent measles specific IgM and IgG antibodies were detected in the blood by ELISA (Enzygnost Anti-Measles Virus IgM and IgG (Dade Behring, Marburg, Germany): IgM detectable (0.213), IgG 1294 mIU/mL, and IgM detectable (0.246), IgG 2,413 mIU/mL, respectively. Virus genotype was determined by the National Microbiology Laboratory in Winnipeg, Canada as vaccine strain, genotype A, MVs/British Columbia/39.13 [A] (VAC) [4]. Other virology testing found no detectable Parvovirus B19 specific IgG or IgM antibody, and detectable human herpesvirus

(HHV)-6 specific IgG antibody but no detectable HHV-6 DNA.

Public health measures

While genotyping results were pending, case management proceeded as for a wild-type measles infection. Public health follow-up lead to the identification of 87 contacts. As per guidelines, post-exposure prophylaxis was provided within six days of exposure to 45 susceptible contacts (41 contacts with a history of one dose of MMR vaccine received an additional MMR dose, and four contacts with no history of MMR vaccine or with contraindications to MMR vaccination, received immunoglobulin) [1]. All contacts received education on signs and symptoms of measles, and those who received immunoglobulin were recommended to subsequently receive MMR vaccine, if this was not contraindicated.

Discussion

The incubation period of measles is typically eight to 12 days from exposure to rash onset, with a range from seven to 21 days. Public health interventions are based on this established incubation period for determining the epidemiological links between cases and for estimating periods of exclusion for contacts in high risk settings [5,6]. Based on our review of the literature, this report documents the first case of MMR vaccine-associated measles, 37 days post-immunisation, well beyond 21 days and the routine 30 days post-MMR immunisation period used by the Canadian adverse event following immunization (AEFI) surveillance system.

Measles-containing vaccines are used globally, have been part of the British Columbia immunisation schedule since 1969, and have an impressive record of safety validated by careful, ongoing AEFI surveillance. Rash and/or mild clinical illness following MMR vaccine are not uncommon [7]. Clinically significant vaccine-associated illness is rare, but when it occurs it is indistinguishable from wild-type measles, except by genotyping [8]. Detection of vaccine virus has been documented up to 14 days post-immunisation by RT-PCR, and up to 16 days by immunofluorescence microscopy of urine sediment [9-12]. Complications from vaccine-associated measles have been documented in both immune-competent and compromised individuals [13,14]. Of note, only one case report of transmission from vaccine-associated measles has been identified [15,16].

Possible explanations for this prolonged shedding of measles vaccine virus include interference with the immune response by host or vaccine factors. Immunoglobulin administration early in the incubation period has been reported to extend the time to onset of symptoms, but in this child there was no such history and no known immunosuppressive illness [5]. The two-fold rise between acute and convalescent measles-specific IgG suggests the vaccine-mediated immune response had been underway prior to the onset of symptoms. Investigations clarified that there were no shipping, handling or cold-chain deviations for the specific vaccine used, and that it was administered by a public health nurse trained in immunisations. The potential immunological impact of the older age of the child at the time of receiving the first dose of MMR vaccine, 33 months versus the typical 12-15 months of age, and the co-administration of meningococcal C and pneumococcal conjugate vaccines are areas for future investigation.

It is possible that the case's symptoms were not measles-vaccine-related but an inter-current illness confounding the presentation. However, symptoms of marked conjunctivitis, continued fever with rash, and progression of macular rash from face to the whole body, are all more suggestive of measles versus other exanthems caused by viral diseases. Parvovirus and HHV-6 results were negative, and the absence of intake of medications excludes a drug reaction. Rubella serology was not done as it was expected to be positive given the recent MMR vaccine administration. Therefore, the combination of classic measles symptoms, detection of measles vaccine virus and reactive measles IgM, and lack of evidence of an alternative illness explanation, were highly suggestive of measles vaccine-associated illness.

Heightened surveillance and awareness of measles because of the ongoing outbreak likely contributed to the identification of this case. Although this is the first such reported case, it likely represents the existence of additional, but unidentified, exceptions to the typical timeframe for measles vaccine virus shedding and illness. Such cases have important public health implications for the investigation of measles clusters because while there is uncertainty about case classification (wild-type vs vaccine-type), case and contact management should proceed as if for wild-type to prevent secondary transmission. In this case, uncertainty from the presence of a measles outbreak, symptom onset on day 37 after MMR vaccine administration, and a two-week period between the RT-PCR findings and genotype determination, resulted in the initially reasonable presumption that this was a wild-type measles case and subsequent resource-intense follow-up of contacts. Awareness of the frequency of such exceptions to the typical measles timeframe and improving the timeliness of measles vaccine virus genotyping could help focus public health resources on cases of wild-type measles. Further investigation is needed on the upper limit of measles vaccine virus shedding based on increased sensitivity of the RT-PCR-based detection technologies and the immunological factors associated with vaccine-associated measles illness and virus shedding.

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Conflict of interest

None declared.

Authors' contributions

BH, FH, MM and PVB contributed to the clinical and public health management of the case. MK, MP and JH provided laboratory testing. MM drafted the manuscript; all authors critically revised and approved the final version of the manuscript.

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Transmission of varicella-vaccine virus from a healthy 12-month-old child to his pregnant mother.

Salzman MB[1], Sharrar RG, Steinberg S, LaRussa P.

Author information

Abstract

A 12-month-old healthy boy had approximately 30 vesicular skin lesions 24 days after receiving varicella vaccine. Sixteen days later his pregnant mother had 100 lesions. Varicella-vaccine virus was identified by polymerase chain reaction in the vesicular lesions of the mother. After an elective abortion, no virus was detected in the fetal tissue. This case documents transmission of varicella-vaccine virus from a healthy 12-month-old infant to his pregnant mother.

Comment in

Toddler-to-mother transmission of varicella-vaccine virus: how bad is that? [J Pediatr. 1997]

Transmission of varicella-vaccine virus: what is the risk? [J Pediatr. 1998]

PMID: 9255208

[Indexed for MEDLINE]

BRIEF REPORT

Varicella Zoster Virus DNA at Inoculation Sites and in Saliva After Zostavax Immunization

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Analysis of 36 individuals over age 60 years who were immunized with Zostavax revealed varicella zoster virus (VZV) DNA in swabs of skin inoculation sites obtained immediately after immunization in 18 (50%) of 36 subjects (copy number per nanogram of total DNA, 28 to 2.1 $\times$ 10^6) and in saliva collected over 28 days in 21 (58%) of 36 subjects (copy number, 20 to 248). Genotypic analysis of DNA extracted from 9 random saliva samples identified vaccine virus in all instances. In some immunized individuals over age 60, vaccine virus DNA is shed in saliva up to 4 weeks.

Varicella zoster virus (VZV) is a neurotropic alphaherpesvirus. Primary infection usually causes varicella (chicken pox) in children. Airborne VZV enters the nasopharynx and replicates in tonsillar T cells followed by viremia and skin lesions [1, 2]. After primary infection, VZV becomes latent in neurons of cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis. Decades later, VZV reactivates in elderly and immunocompromised individuals to produce zoster (shingles), a syndrome characterized by pain and a vesicular rash on an erythematous base in 1–3 dermatomes. Zoster is common, with ~1,000,000 cases annually in the United States. Importantly, zoster is often followed by chronic pain (postherpetic neuralgia [PHN]) as well as by meningoencephalitis, cerebellitis, cranial nerve palsies, vasculopathy, myelopathy, and multiple inflammatory diseases of the eye [3].

To prevent zoster and its attendant neurological complications, Zostavax vaccine (Merck) was approved by the Food and Drug Administration for use in individuals at least 60 years of age. Over a 3-year period, Zostavax effectively reduced the risk of zoster by 51% and PHN by 66% in nearly 20,000 healthy adults age 60 years or older [4]. Zostavax contains live attenuated VZV, and the package insert warns newly vaccinated individuals to avoid contact for an unspecified time with newborn infants, immunosuppressed individuals, and pregnant women who have not had chicken pox or have not been immunized for chicken pox. Because VZV DNA is present in saliva of zoster patients for at least 2 weeks [5] and VZV in saliva can also be infectious [6], we examined the inoculation site and saliva of Zostavax-vaccinated subjects for the presence of VZV DNA for 4 weeks after immunization.

METHODS

After informed consent and with approval of the University of Texas Health Science Center's Institutional Review Board, 36 immunocompetent subjects (19 men and 17 women), age 60–89 years (mean $\pm$ SD, 71.1 $\pm$ 7.6 years) were inoculated intramuscularly in the deltoid area with Zostavax (Merck).

Skin. Skin over the inoculation site was disinfected with alcohol before but not after immunization. Within 10 minutes after immunization, the inoculation site was swabbed with a cotton-tipped applicator (Fisher Scientific), and the skin swab sample was immediately placed in 1 mL nuclease-free sterile water overnight at 4°C and concentrated to 200 μL with a Microsep 100 K filtration unit (Filtron Technology Corporation) by centrifugation at 8000 rpm for 30 minutes. Samples were stored frozen at −20°C until processed for DNA extraction as described below.

Saliva. On day 0 before immunization and on days 1–3, 7, 14, 21, and 28 after immunization, saliva was collected upon arising and before eating or drinking using a Salivette tube (Sarstedt Inc). The polymerase chain reaction (PCR) technologist was blinded to the source of all saliva samples. Saliva was processed, and DNA was extracted and quantified by real-time PCR using Taqman 7900 (Applied Biosystems) as described elsewhere [7]. All PCR assays were performed in triplicate. VZV DNA copy number was determined by comparing the cycle threshold value (Ct) of the test samples to Ct values obtained by PCR on dilutions of VZV DNA extracted from virus nucleocapsids [8]. The

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sensitivity of detection was 10 copies of VZV DNA per nanogram of salivary DNA. A Ct value >35 indicated the presence of VZV DNA but at a concentration too low to quantify. Such values are noted as "+" on Table 1 followed by the Ct number. DNA extracted from 9 random saliva samples was analyzed for single nucleotide polymorphism sites in VZV open reading frames 38, 54, and 62 using real-time PCR as described elsewhere [9–11].

RESULTS

Inoculation site samples taken within 10 minutes after vaccination were positive for Zostavax VZV DNA in 18 (50%) of 36 subjects. The VZV DNA copy number per nanogram of total DNA ranged from 28 to 2.1×10^6 (Table 1), possibly reflecting the presence of infectious virus since no alcohol or other agent was used to wipe the skin after inoculation.

Table 1. VZV DNA at Skin Inoculation Sites and in Saliva After Immunization With Zostavax Vaccine

			Saliva after immunization, days				
Age sex	Skin swab	Saliva before immunization	13	7	14	21	28
65 F	366 (28)[a]	0	**193 (32)** [b]	100 (32)	30 (33)	+[c] (36)	0
84 M	+ (38)	0	0	0	0	0	0
84 F	0	0	**64 (30)** [b]	26 (35)	53 (26)	+ (36)	0
66 F	28 (33)	0	0	0	0	0	0
61 M	+ (35)	0	+ (37)	**56 (28)** [b]	0	68 (29)	0
71 F	0	0	+ (36)	31 (33)	+ (38)	+ (37)	0
71 F	0	0	**167 (32)** [b]	34 (29)	0	0	0
62 M	0	0	0	0	0	0	0
64 F	0	0	0	0	0	0	0
65 F	+ (39)	0	0	0	0	0	0
63 F	1178 (22)	0	0	0	0	0	0
66 F	0	0	47 (29)	30 (32)	53 (31)	+ (38)	0
66 M	+ (39)	0	110 (31)	**97 (27)** [b]	0	20 (34)	0
75 F	+ (39)	0	111 (32)	44 (29)	31 (32)	0	0
67 M	0	0	248 (32)	22 (34)	0	0	0
65 F	112426 (24)	0	0	0	0	0	0
83 F	0	0	0	0	0	0	0
70 F	0	0	58 (31)	117 (30)	24 (34)	0	+ (39)
64 F	0	0	0	0	0	0	0
76 M	+ (38)	0	79 (28)	+ (36)	0	0	0
60 M	2124138 (18)	0	150 (28)	+ (35)	+ (35)	0	0
69 M	0	0	67 (29)	+ (35)	0	24 (34)	0
73 M	262 (32)	0	40 (34)	+ (36)	0	+ (38)	0
89 M	+ (38)	0	0	0	0	0	0
79 M	+ (39)	0	**57 (32)** [b]	+ (36)	0	0	0
77 F	0	0	0	0	0	0	0
66 M	+ (38)	0	+ (38)	27 (33)	80 (29)	0	0
72 M	0	0	0	0	0	0	0
85 M	0	0	+ (37)	**47 (30)** [b]	117 (30)	0	0
79 F	0	0	+ (39)	22 (29)	0	0	0
70 M	207 (27)	0	0	0	0	0	0
70 M	40191 (27)	0	+ (35)	30 (34)	0	0	0
76 M	19602 (31)	0	30 (34)	**111 (33)** [b]	67 (32)	36 (28)	0
69 F	0	0	0	0	0	0	0
62 M	0	0	0	0	0	0	0
77 M	0	0	**50 (32)** [b]	+ (36)	44 (32)	+ (38)	+ (35)
No.positive/total	18/36	0/36	21/36	21/36	11/36	10/36	2/36
Percent positive	50	0	58	58	31	28	6

Note. [a] VZV DNA copies per nanogram total DNA (Ct value).
[b] Vaccine strain VZV DNA verified.
[c] VZV DNA present, but too few copies to quantify.

No saliva specimen collected immediately before immunization contained VZV DNA. During the first week after immunization, VZV DNA was detected in saliva of 21 (58%) of 36 subjects (13 men and 8 women). During the 28-day study period, VZV DNA was found in 11 (31%) of 36 subjects (5 men and 6 women) at day 14, in 10 (28%) of 36 subjects (6 men and 4 women) at day 21, and in 2 (6%) of 36 subjects (1 man and 1 woman) at day 28. Figure 1 shows the percent of immunized subjects who shed VZV DNA during the 28-day study period. VZV DNA copy numbers per nanogram of total DNA ranged from 20 to 248 (Table 1). Genotypic analysis of DNA from 9 random saliva samples revealed vaccine virus DNA in all instances (Table 1, bold); wild-type VZV DNA was not detected. In 15 (42%) of 36 vaccine recipients (6 men, 9 women), VZV DNA was not detected in saliva at any time during the 28-day study period.

DISCUSSION

In 2006, Zostavax vaccine was approved by the Food and Drug Administration and recommended by the Advisory Council for Immunization Practices for use in healthy individuals over 60 years of age. The development of a vaccine to prevent zoster is a major step in reducing the morbidity associated with this important public health threat. Transmission of the Oka/Merck strain of VZV has been reported after chicken pox vaccination [12, 13], but not after Zostavax immunization [13].

Herein, we detected Zostavax VZV DNA sequences in 18 (50%) of 36 skin swab samples taken within 10 minutes after immunization. We also detected Zostavax VZV DNA sequences in saliva of 21 (58%) of 36 subjects throughout the first week after immunization and in 6% of immunized subjects at 28 days. The detection of VZV DNA in saliva is one more indication of its potential use in diagnosis of VZV persistence in various clinical situations. VZV DNA has been found not only in saliva of patients with zoster at all levels of the neuraxis [5] but also in saliva of asymptomatic astronauts [7].

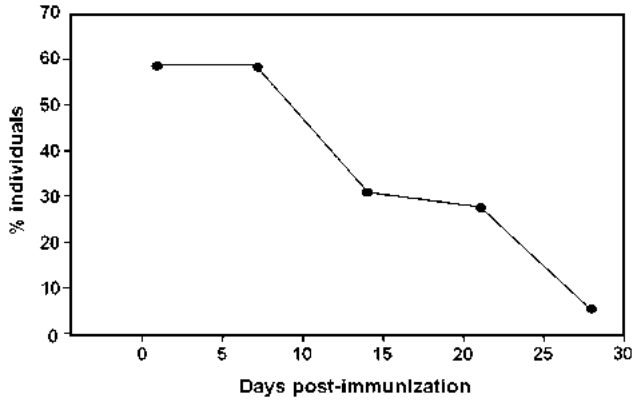

Figure 1. Percent individuals over age 60 whose saliva contained VZV DNA during the 28-day study period after Zostavax immunization.

Importantly, earlier studies revealed the presence of wild-type VZV in the vesicular fluid of a patient with zoster who had been immunized twice with varicella vaccine [14] and the presence of 2 different VZV genotypes isolated from an immunocompetent man during 2 different episodes of zoster [15]. These findings revealed that a superinfecting VZV became latent. Although we did not study latency, our finding of VZV vaccine virus in saliva supports the notion that a superinfecting VZV spreads systemically.

Finally, while transmission of vaccine virus has not been found among vaccine recipients, the detection of VZV DNA in saliva of Zostavax recipients for up to 28 days suggests that contact with saliva of recently immunized individuals represents a potential source of transmission. Because astronaut saliva contains infectious virus [6], saliva (and skin) of immunized individuals should also be studied for infectious virus.

Funding

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Comparison of virus shedding after lived attenuated and pentavalent reassortant rotavirus vaccine.

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Author information

Abstract

Transmission of rotavirus vaccine or vaccine-reassortant strains to unvaccinated contacts has been reported. Therefore, it is essential to evaluate and characterize the nature of vaccine-virus shedding among rotavirus vaccine recipients. Two groups of healthy infants who received a complete course of RotaTeq (RV5) or Rotarix (RV2) were enrolled (between March 2010 and June 2011) to compare fecal shedding for one month after each vaccine dose. Shedding was assessed using both enzyme immunoassay (EIA) and real-time reverse transcription-polymerase chain reaction (RT-PCR). Eighty-seven infants (34 girls and 53 boys) were enrolled in the study. After the first vaccine dose, the peak time of virus shedding occurred between day 4 and day 7, with positive detection rates of 80-90% by real-time RT-PCR and 20-30% by EIA. In both groups, vaccine shedding occurred as early as one day and as late as 25-28 days. Mixed effects logistic regression analysis of real-time RT-PCR data showed no significant differences between two groups when shedding rates were compared after the first vaccine dose (odds ratio [OR] 1.26; P=0.71) or after the second vaccine dose (odds ratio [OR] 1.26; P=0.99). However, infants receiving RV2 shed significantly higher viral loads than those receiving RV5 when compared after the first vaccine dose (P=0.001) and after the second dose (P=0.039). In terms of shedding rates detected by real-time RT-PCR, vaccine uptake of RV5 or RV2 among infants in Taiwan was comparable. Clinical significance of higher shedding viral loads in RV2 should be further observed.

KEYWORDS: Rotavirus vaccine; Shedding

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[Indexed for MEDLINE]

Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community

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Significance

Lack of human data on influenza virus aerosol shedding fuels debate over the importance of airborne transmission. We provide overwhelming evidence that humans generate infectious aerosols and quantitative data to improve mathematical models of transmission and public health interventions. We show that sneezing is rare and not important for—and that coughing is not required for—influenza virus aerosolization. Our findings, that upper and lower airway infection are independent and that fine-particle exhaled aerosols reflect infection in the lung, opened a pathway for a deeper understanding of the human biology of influenza infection and transmission. Our observation of an association between repeated vaccination and increased viral aerosol generation demonstrated the power of our method, but needs confirmation.

Abstract

Little is known about the amount and infectiousness of influenza virus shed into exhaled breath. This contributes to uncertainty about the importance of airborne influenza transmission. We screened 355 symptomatic volunteers with acute respiratory illness and report 142 cases with confirmed influenza infection who provided 218 paired nasopharyngeal (NP) and 30-minute breath samples (coarse >5-μm and fine ≤5-μm fractions) on days 1–3 after symptom onset. We assessed viral RNA copy number for all samples and cultured NP swabs and fine aerosols. We recovered infectious virus from 52 (39%) of the fine aerosols and 150 (89%) of the NP swabs with valid cultures. The geometric mean RNA copy numbers were 3.8×10^4/30-minutes fine-, 1.2×10^4/30-minutes coarse-aerosol sample, and 8.2×10^8 per NP swab. Fine- and coarse-aerosol viral RNA were positively associated with body mass index and number of coughs and negatively associated with increasing days since symptom onset in adjusted models. Fine-aerosol viral RNA was also positively associated with having influenza vaccination for both the current and prior season. NP swab viral RNA was positively associated with upper respiratory symptoms and negatively associated with age but was not significantly associated with fine- or coarse-aerosol viral RNA or their predictors. Sneezing was rare, and sneezing and coughing were not necessary for infectious aerosol generation. Our observations suggest that influenza infection in the upper and lower airways are compartmentalized and independent.

influenza virus aerosol airborne infection vaccination effects viral shedding

The nature of infectious contacts and the relative importance of contact, large-droplet spray, and aerosol (droplet nuclei) transmission remain controversial (**1**⇓⇓⇓⇓⇓–**6**). Nonpharmaceutical interventions have been employed to control and reduce the impact of influenza epidemics and pandemics (**7**). However, to design

effective nonpharmaceutical interventions, it is necessary to accurately define the relative and absolute contribution of each route of transmission (**8**) and implement interventions that impede those of principal importance.

Mathematical models that have been used to understand and estimate the contribution of each mode are very sensitive to estimates of unmeasured parameters (**9**, **10**), such as the viral load in exhaled breath and coughs and the frequency of sneezing by influenza cases (**8**). However, due to limitations inherent to sampling virus shedding via various routes from infected individuals, and the difficulty of distinguishing routes of transmission in observational studies, the quantitative dynamics and relative contributions of each route remain elusive (**4**, **8**). Recent reports have shown that infectious influenza virus can be recovered from exhaled aerosols (**11**⇓–**13**). These studies, based on small numbers of cases or artificial breathing maneuvers, do not provide sufficient data to quantify the extent of aerosol shedding during natural breathing, nor do they identify the contributions of spontaneous coughs and sneezes commonly thought to be the most important mechanism for viral shedding, or identify other factors that may impact viral aerosol shedding. We address these key knowledge gaps by characterizing influenza virus in exhaled breath from community-acquired influenza cases during natural breathing, prompted speech, coughing, and sneezing, and assess the infectivity of naturally occurring influenza aerosols.

Results

We screened 355 volunteers with acute respiratory illness; the 178 volunteers who met enrollment criteria provided 278 visits for sample collection. We confirmed influenza infection in 156 (88%) of the enrolled participants using qRT-PCR; 152 had at least one positive nasopharyngeal (NP) swab and 4 (3%) were confirmed based on positive aerosol samples alone. NP swab analysis was positive for 8 (33%) of 24 randomly selected volunteers from among the 177 screened who did not meet enrollment criteria; thus, sensitivity and specificity of our enrollment criteria, during the 2012–2013 season, were ~73% [95% confidence interval (CI) 62–84%] and 84% (95% CI 80–88%), respectively. In the reported analyses, we excluded 8 visits made on the day of symptom onset, 10 made >3 d after onset, 7 with missing data for cough, and 3 with incomplete qRT-PCR data (Fig. S1 and Table S1). The resulting dataset for confirmed cases with complete data on RNA copies, cough, and symptoms included 218 visits by 142 cases: 89 influenza A (83 H3, 3 pdmH1, 3 unsubtypable), 50 influenza B, and 3 dual influenza infection cases.

Our study population (**Table 1**) consisted mostly of young adults (19–21 y) with a high asthma prevalence (21%), normal body mass index (BMI, median = 22.7; 7% underweight, 20% overweight, and 8% obese) (Table S2), and a low self-reported influenza vaccination rate (22%). We observed at least one cough during 195 (89%) and one or more sneezes during 11 (5%) of the 218 visits. Cough frequency varied considerably, from 5 per 30 min at the 25th percentile to 39 per 30 min at the 75th. Most volunteers rated their upper respiratory symptoms as mild to moderate, systemic symptoms as moderate to severe, and lower respiratory symptoms as mild (**Fig. 1**).

Table 1.
Characteristics of study population

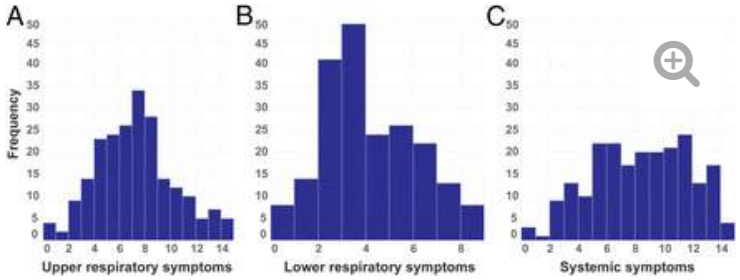

Fig. 1.
Histograms of symptom scores. (**A**) Upper respiratory symptoms (runny nose, stuffy nose, sneezing, sore throat, and earache, score range 0–15). (**B**) Lower respiratory symptoms (chest tightness, shortness of breath, and cough, score range 0–9). (**C**) Systemic symptoms (malaise, headache, muscle/joint ache, fever/sweats/chills, and swollen lymph nodes, score range 0–15).

Infectious virus was recovered from 52 (39%) fine-aerosol samples and 150 (89%) NP swabs (**Table 2**). Quantitative cultures were positive for 30% of the fine-aerosol samples, with a geometric mean (GM) for positive samples of 37 fluorescent focus units (FFU) per 30-min sample (**Fig. 2A**) and for 62% of NP swabs with GM for positive samples of 2,500. Using Tobit analysis to adjust the estimate of the GM for the presence of samples below the limit of detection, we obtained a GM 1.6 (95% CI 0.7–3.5) for fine aerosols and a GM 60.6 (95% CI 22.7–1.6 × 10^2) for NP swabs.

Table 2.
Viral shedding

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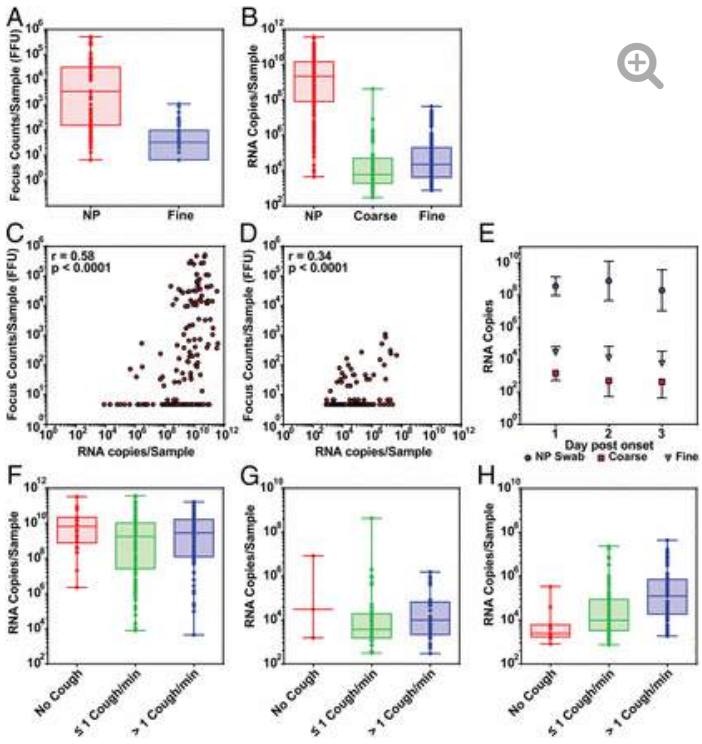

Fig. 2.
Viral shedding: (**A**) infectious influenza virus (fluorescent focus counts) in NP swabs and fine aerosols and (**B**) RNA copies in NP swabs, coarse, and fine aerosols. (**C** and **D**) Scatter plots and Spearman correlation coefficients of infectious virus plotted against RNA copies for (**C**) NP swabs and for (**D**) fine-aerosol samples. (**E**) The effect of day after symptom onset on RNA copies observed in NP swabs, coarse, and fine aerosols plotted as GM adjusted for missing data using Tobit analysis with error bars denoting 95% CIs. (**F–H**) The effect of cough frequency on RNA copies observed in (**F**) NP swabs, (**G**) coarse aerosols, and (**H**) in fine aerosols. Coarse: aerosol droplets >5 μm; Fine: aerosol droplets ≤5 μm in aerodynamic diameter.

Influenza virus RNA was detected in 76% of the fine-aerosol samples, 40% of the coarse-aerosol samples, and 97% of the NP swabs of enrolled volunteers. For the positive samples, the GM viral RNA content of fine-aerosol samples was 3.8×10^4, for coarse aerosols was 1.2×10^4, and for NP swabs was 8.2×10^8 (**Fig. 2B**). The adjusted GMs were 1.2×10^4 (95% CI 7.0×10^3 to 1.9×10^4) for fine aerosols and 6.0×10^2 (95% CI 3.0×10^2 to 1.2×10^3) for coarse aerosols. Quantitative culture was correlated with RNA copies in both NP swabs (**Fig. 2C**) (**r** = 0.58) and fine aerosols (**Fig. 2D**) (**r** = 0.34). The time course of shedding is shown in **Fig. 2E**.

Viral RNA in NP swabs was not correlated with cough frequency (number of coughs per 30 min) (**Fig. 2F** and Fig. S2**A**) (**r** = 0.02). Viral RNA in coarse aerosols was weakly correlated with cough frequency (**Fig. 2G** and Fig. S2**B**) (**r** = 0.24). However, viral RNA copy number in fine aerosols was moderately well correlated with cough frequency (**Fig. 2H** and Fig. S2**C**) (**r** = 0.45). Only 3 (13%) of 23 coarse-aerosol samples where no coughs were observed had detectable viral RNA, while 11 (48%) of the corresponding 23 fine-aerosol samples had detectable viral RNA and 8 were positive by culture. RNA copies in the fine-aerosol, no-cough samples ranged up to 3.7×10^5 (adjusted GM 1.5×10^3, 95% CI 4.2×10^2 to 5.3×10^3) and infectious virus to 1.4×10^2 FFU per 30-min sample. The few sneezes observed were not associated with greater RNA copy numbers in either coarse or fine aerosols (Fig. S3).

Results of regression analyses to identify predictors of viral RNA shedding are shown in **Table 3**, controlled for random effects of subject and repeated observations on individuals.

Table 3.
Predictors of viral RNA shedding

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The day after symptom onset (comparing day 1 postonset with days 2 and 3) was associated with a significant decline in viral RNA shed into fine aerosols (**P** < 0.05 for day 2 and **P** < 0.01 for day 3 in adjusted models), a borderline significant decline in coarse-aerosol shedding (**P** < 0.10), and was not associated with a significant change in shedding detected in NP swabs (**P** > 0.10).

In regression analyses, cough frequency was significantly associated with increased fine- (**P** < 0.001 to <0.0001) and coarse- (**P** < 0.01) aerosol shedding, but was not associated with NP shedding. Fine-aerosol shedding was significantly greater for males. Analysis of an interaction of cough with sex indicated that males produced, on average, 3.2 times more virus than did females per cough. However, females also coughed significantly (**P** = 0.005) more frequently than males: 33 (SD 39) per 30-min observation and 21 (SD 21), respectively (Fig. S4).

BMI was positively associated with shedding in fine and coarse aerosols in unadjusted models (**P** < 0.10). BMI was retained in the best-fitting adjusted models for both fine and coarse aerosols, where it was significantly associated with fine-aerosol shedding (**P** < 0.05). However, BMI was not associated with shedding detected in NP swabs (**P** > 0.10). Standard categories of BMI were not as good a fit as the continuous BMI and were not significantly associated with shedding (Table S3), although a positive trend is evident for overweight and obese individuals in the adjusted model.

Self-reported vaccination for the current season was associated with a trend (**P** < 0.10) toward higher viral shedding in fine-aerosol samples; vaccination with both the current and previous year's seasonal vaccines, however, was significantly associated with greater fine-aerosol shedding in unadjusted and adjusted models (**P** < 0.01). In adjusted models, we observed 6.3 (95% CI 1.9–21.5) times more aerosol shedding among cases with

vaccination in the current and previous season compared with having no vaccination in those two seasons. Vaccination was not associated with coarse-aerosol or NP shedding (**P** > 0.10). The association of vaccination and shedding was significant for influenza A (**P** = 0.03) but not for influenza B (**P** = 0.83) infections (Table S4).

Viral load in NP swabs was not a significant predictor of aerosol shedding (**P** = 0.16 for fine and **P** = 0.48 for coarse aerosols). Temperature measured at the time of sampling, asthma history, smoking, and influenza type were not significantly associated with the extent of measured shedding. While self-reported symptoms were not associated with aerosol shedding, they were significantly associated with shedding measured by the NP swab; only upper respiratory symptoms remained significant when adjusted for other symptoms and age. Increasing age was associated with a significant decrease in shedding in the NP swab; however, age was not associated with aerosol shedding.

Discussion

We recovered infectious influenza virus from 52 samples of fine aerosols collected from exhaled breath and spontaneous coughs produced by 142 cases of symptomatic influenza infection during 218 clinic visits. Finding infectious virus in 39% of fine-aerosol samples collected during 30 min of normal tidal breathing in a large community-based study of confirmed influenza infection clearly establishes that a significant fraction of influenza cases routinely shed infectious virus, not merely detectable RNA, into aerosol particles small enough to remain suspended in air and present a risk for airborne transmission. Because these data were collected without volunteers having to breathe through a mouthpiece or perform forced coughs, they allow us to provide estimates of average shedding rates, variability, and time course of and risk factors for shedding that can be used to provide well-grounded parameter estimates in future models of the risk of airborne influenza transmission from people with symptomatic illness.

The first published estimates of the numbers of influenza virus variants transmitted from donor to recipient host indicated that the bottleneck for transmission between humans is fairly wide and highly variable (mean 192 with 95% confidence 66–392) (**14**, **15**). Our observation that cases shed considerable quantities of virus into aerosols, GM $>10^4$ RNA copies per 30 min, and up to 10^3 infectious virus particles per 30 min, suggests that large numbers of variants could be transmitted via aerosols, especially via the short-range mode (**16**). However, longer-range aerosol transmission, as might be observed in less-crowded environments than in the initial report from Hong Kong, would be expected to usually result in lower exposures and transmission of fewer variants, consistent with the narrower bottleneck described in ferret models (**17**, **18**).

Sobel Leonard et al. (**14**) suggested that the width of the bottleneck increased with severity of illness, as indicated by a borderline significant positive association between temperature and number of variants transmitted. We did not see a significant association between measured temperature and shedding by any route. In contrast, symptoms were not a significant predictor of bottleneck size, and in our data, symptoms were not significant predictors for shedding into aerosols. Symptoms were, however, significant predictors for nasal shedding as measured in NP swabs. Thus, if aerosols were the more important route of transmission, our observations would be consistent with the currently available bottleneck analysis.

We observed that influenza cases rarely sneezed, despite having just undergone two NP swab collections (a procedure that generally makes one feel an urge to sneeze). Sneezing was not observed in the absence of cough and was not associated with greater aerosol shedding than we observed with cough alone (Fig. S3). Thus, sneezing does not appear to make an important contribution to influenza virus shedding in aerosols.

Sneezing might make a contribution to surface contamination. Because sneezes generate considerable amounts of large-droplet spray composed of many ballistic droplets not collected by our sampler, we cannot assess that possibility with our data.

Cough was prevalent and was a strong predictor of virus shedding into both coarse and fine aerosols. However, cough was not necessary for infectious aerosol generation in the ≤5-μm (fine) aerosol fraction; we detected culturable virus in fine aerosols during 48% of sampling sessions when no coughs were observed. This suggests that exhaled droplets, generated by mechanisms other than cough, are responsible for a portion of the viral load observed in the fine-aerosol fraction. Several researchers have recently shown that exhaled aerosol particles are frequently generated from normal healthy lungs by small airway closure and reopening (**19**–**21**). It has been hypothesized that during respiratory infections, airway closure and reopening frequency would be increased due to inflammation with a commensurate increase in aerosol generation and contagiousness (**22**).

Cough is thought to produce aerosols from large airways by shear forces that produce relatively coarse-aerosol droplets (**23**). Our finding that only 13% of cases not observed to have coughed during sample collection produced detectable viral RNA in their coarse aerosols is consistent with that hypothesis. The remaining aerosols may have resulted from speaking; each subject was required to recite the alphabet three times. One might expect that viral replication in the large airways combined with cough-generated coarse-aerosol droplets would produce the majority of viral aerosols. However, we observed a weak correlation of coarse-aerosol RNA copy number with cough frequency and a much stronger association of fine-aerosol copy number with cough frequency, even though cough would be expected to be the primary source of coarse aerosols. These observations suggest that cough is, at least in part, an epiphenomenon, more of a response to irritation associated with high viral loads in distal airways than a direct source of infectious aerosols.

A striking finding was the association of gender with shedding into fine aerosols. This relationship appears to have resulted from a threefold greater impact of coughing on shedding in males. We observed these gender and gender-by-cough interaction effects only for the fine-aerosol fraction. Absence of a gender effect in the coarse-aerosol fraction suggests that this is not an effect of cough on aerosol generation by shear forces in the upper airway. We did not measure lung volumes and therefore cannot control for a lung size effect. An equally plausible explanation may be that women tend to have more sensitive cough reflexes (**24**). Thus, women may have tended to cough in response to lower viral loads and coughed more frequently at a given viral load, which could have produced the observed steeper slope of viral load regressed on cough frequency in males compared with females. Consistent with this suggestion, we did observe a significantly greater cough frequency in females (**P** = 0.005) and a steeper slope of fine-aerosol viral RNA with cough in males (Fig. S4).

BMI was a borderline significant predictor of aerosol shedding in most models, was retained as an important predictor of both coarse and fine aerosols in adjusted models, and reached statistical significance for fine aerosols when adjusted for other factors; it was not a significant predictor of nasal shedding. This observation might be consistent with reports of increased inflammation in models of obesity and influenza and severity of influenza-like illness in obese persons (**25**–**30**). Alternatively, increasing BMI is associated with increased frequency of small airways closure, and the resulting increased aerosol generation during airway reopening as described above may explain the stronger association of BMI with fine than coarse aerosols and lack of association with NP swabs (**31**).

Our analysis found a clear separation of factors associated with shedding from the nose and those with shedding into aerosols, especially fine-particle aerosols. Upper airway symptoms, as would be expected, were strongly associated with shedding detected in NP swabs, and greatly reduced the size and significance of lower

respiratory and systemic symptoms in the fully adjusted model. Age was negatively associated with nasal shedding but not a predictor of aerosol shedding. More surprisingly, no symptoms, including lower respiratory and systemic systems, were strongly associated with shedding into aerosols, in this population with relatively mild lower respiratory symptoms (**Fig. 1**). Furthermore, nasal shedding was not a significant predictor of aerosol shedding and none of the strong predictors of aerosol shedding were associated with nasal shedding. Thus, we can conclude that the head airways made a negligible contribution to viral aerosol generation and that viral aerosols represent infection in the lung. Moreover, upper and lower airway infection appear to behave as though infection is compartmentalized and independent. In this context, it is notable that Varble et al. (**18**) observed that intrahost viral variants differ in the nasopharynx and lung of ferrets.

We did not observe a significant decline over time of viral load detected in NP swabs. If day 1 after onset of symptoms (used as baseline for these analyses) in our cases was equivalent to a mixture of day 1 and day 2 after experimental influenza virus inoculation in the report by Hayden et al. (**32**), then our lack of finding a clear drop in nasal shedding over the next 2 d is reasonably consistent with the pattern reported for experimental infection. There is no available data for comparison of aerosol shedding from published experimental infections. That we saw a much clearer pattern of rapid decline over time in aerosol shedding again suggests a separation of infection into upper and lower airway compartments in humans.

The association of current and prior year vaccination with increased shedding of influenza A might lead one to speculate that certain types of prior immunity promote lung inflammation, airway closure, and aerosol generation. This first observation of the phenomenon needs confirmation. If confirmed, this observation, together with recent literature suggesting reduced protection with annual vaccination, would have implications for influenza vaccination recommendations and policies.

Materials and Methods

Study Population and Sample Collection Procedures.

We recruited volunteers with acute respiratory illness on the University of Maryland–College Park campus and surrounding community from December 2012 through March 2013. The University of Maryland Institutional Review Board approved the study, and we obtained a signed consent (or assent and parental verbal assent) from volunteers who reported fever with a cough or sore throat (Fig. S5).

During the initial visit, we administered a brief screening questionnaire, measured oral temperature, height, weight, and collected two NP swabs (Copan) for each volunteer screened. One swab was used to perform QuickVue A/B rapid tests for influenza (except when results of a rapid test performed by medical provider were available). The second NP swab was used for viral culture and PCR for those meeting enrollment criteria and for PCR in a random sample of 24 of those not enrolled.

Participants were asked about sex, age, antipyretic use, vaccination status, use of steroid medications, medical and smoking history, to rate current symptoms on a four-level scale (none = 0, mild = 1, moderate = 2, severe = 3), and to rate the worst symptoms during the illness thus far. We defined symptoms as upper respiratory (runny nose, stuffy nose, sneezing, sore throat, and earache), lower respiratory (chest tightness, shortness of breath, and cough), and systemic (malaise, headache, muscle/joint ache, fever/sweats/chills, and swollen lymph nodes).

Volunteers were enrolled in exhaled breath collection if they met the following criteria: (**i**) positive QuickVue rapid test, or oral temperature >37.8 °C plus cough or sore throat, and (**ii**) presented within the first 3 d of symptom onset. Exhaled breath samples were collected using the Gesundheit-II (G-II) human source bioaerosol sampler,

as previously described (**12**, **33**). We collected exhaled breath for 30 min while the participant was seated with their face inside of the large open end of a cone-shaped inlet for the G-II. The inlet cone draws in 130 L of air per minute and allowed participants to breathe, talk, cough, and sneeze naturally throughout sample collection while maintaining >90% collection efficiency for exhaled and coughed droplets ≤100 μm. Subjects were asked to breathe normally and to recite the alphabet once at 5, 15, and 25 min. We collected "coarse" (>5 μm) aerosol droplets by impaction on a Teflon surface and "fine" droplets (≤5 μm and >0.05 μm) by condensation growth and impaction on a steel surface constantly rinsed into a buffer containing (PBS with 0.1% BSA) liquid reservoir. Audible spontaneous coughs and sneezes during breath collection were counted by direct observation in real-time (**n** = 59) or by playback of digital recordings (**n** = 159).

Participants enrolled before the third day after symptom onset were asked to come in for up to two consecutive daily follow-up visits (Fig. S5) with repeat questionnaire, NP swab, and exhaled breath collections. Final analyses included only visits for enrolled cases occurring on days 1–3 after symptom onset with complete data on cough and sneeze, symptoms, PCR results for swab and aerosol samples.

Laboratory Methods.

Detailed methods are described in the **SI Materials and Methods**. Briefly, NP swabs were eluted in 1 mL of PBS with 0.1% BSA (PBS/0.1% BSA) or universal transport medium (Copan), and Teflon impactors were scrubbed with a nylon swab saturated with PBS/0.1% BSA. The swab was eluted in 1 mL PBS/0.1% BSA. Fine-aerosol samples were concentrated to 1 mL using centrifugal ultrafiltration.

RNA was extracted from NP swab, fine- and course-aerosol samples, and whole-virion standards using an automated Qiagen system and viral RNA was quantified by one-step real-time RT-PCR using Taqman primer probe sets designed by the US Centers for Disease Control and Prevention and made available through our cooperative agreement. Standard curves were calibrated for virus copy number using plasmids containing a cDNA copy of the qRT-PCR target amplicon. Experimentally determined limits of detection and quantification for each of the qRT-PCR reactions are shown in Table S5.

Virus culture on Madin–Darby canine kidney (MDCK) cells was used to detect infectious virus in NP swab and fine-aerosol samples. Coarse-aerosol samples were not cultured for infectious virus because impaction on a dry Teflon surface was expected to reduce infectivity of those samples. Infectious influenza virus was quantified using an immunofluorescence assay for influenza nucleoprotein, and positive cells were counted as FFU by fluorescence microscopy. Details of laboratory methods can be found in **SI Materials and Methods**.

Statistical Analysis.

We entered and cleaned data using locally hosted REDCap data-capture tools (**34**) and performed data management and analyses in R (v3.2.3 R Development Core Team, Vienna, Austria) and SAS (v9.4, Cary, NC), and produced graphics with Prism Software (PRISM software v7.0; GraphPad). We used the delta method to estimate confidence limits for sensitivity and specificity. We used Spearman correlation, generalized linear models (SAS Proc GENMOD), and Tobit regression (**35**) with nested random effects of sample within subject in (SAS Proc NLMIXED) to analyze infectious virus counts, RNA copy numbers, and compute GM virus concentrations. Tobit regression accounted for uncertainty and censoring of the observations by the limit of quantification. We included all independent variables with unadjusted $\mathbf{P} < 0.10$ in initial adjusted models and selected final models using the Akaike information criterion while retaining adjustment for age and sex. Regression model results are presented as the ratio of shedding at the 75th percentile to shedding at the 25th percentile of the distribution of the independent variable, so that clinical and epidemiological meaning of the relationship can be more easily interpreted.

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The authors declare no conflict of interest.

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View Abstract

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Development, production, and postmarketing surveillance of hepatitis A vaccines in China.

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Author information

Abstract

China has long experience using live attenuated and inactivated vaccines against hepatitis A virus (HAV) infection. We summarize this experience and provide recent data on adverse events after immunization (AEFIs) with hepatitis A vaccines in China. We reviewed the published literature (in Chinese and English) and the published Chinese regulatory documents on hepatitis A vaccine development, production, and postmarketing surveillance of AEFI. We described the safety, immunogenicity, and efficacy of hepatitis A vaccines and horizontal transmission of live HAV vaccine in China. In clinical trials, live HAV vaccine was associated with fever (0.4%-5% of vaccinees), rash (0%-1.1%), and elevated alanine aminotransferase (0.015%). Inactivated HAV vaccine was associated with fever (1%-8%), but no serious AEFIs were reported. Live HAV vaccine had seroconversion rates of 83% to 91%, while inactivated HAV vaccine had seroconversion rates of 95% to 100%. Community trials showed efficacy rates of 90% to 95% for live HAV and 95% to 100% for inactivated HAV vaccine. Postmarketing surveillance showed that HAV vaccination resulted in an AEFI incidence rate of 34 per million vaccinees, which accounted for 0.7% of adverse events reported to the China AEFI monitoring system. There was no difference in AEFI rates between live and inactivated HAV vaccines. Live and inactivated HAV vaccines manufactured in China were immunogenic, effective, and safe. Live HAV vaccine had substantial horizontal transmission due to vaccine virus shedding; thus, further monitoring of the safety of virus shedding is warranted.

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Horizontal transmission of the Leningrad-3 live attenuated mumps vaccine virus.

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Author information

Abstract

Here we describe symptomatic transmission of the Leningrad-3 mumps vaccine virus from healthy vaccinees to previously vaccinated contacts. Throat swab and serum samples were taken from six symptomatic mumps cases and from 13 family contacts. Assessment of serum IgG and IgM anti-mumps virus antibodies and IgG avidity testing was performed using commercial test kits. Sera neutralizing antibodies were measured by plaque reduction neutralization assay using the L-3 vaccine mumps virus as the target. All six of the symptomatic mumps cases and three contact subjects tested positive for mumps by RT-PCR. The genomic sequences tested (F, SH and HN genes) of all nine of these samples were identical to the L-3 mumps vaccine strain. All 13 contacts were asymptomatic; however clear serological evidence of mumps infection was found in some of them. The likely epidemiological source of the transmitted L-3 mumps virus was children who were recently vaccinated at the schools attended by the six symptomatic mumps patients described here. The L-3 mumps vaccine virus can be shed and transmitted horizontally, even to subjects previously vaccinated with the same virus.

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Transmission of the L-Zagreb mumps vaccine virus, Croatia, 2005-2008.

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Abstract

We report on three cases of symptomatic transmission of the L-Zagreb mumps vaccine virus from three vaccinated children to five adult contacts. The five contact cases were parents of the vaccinated children and presented with parotitis and in one case also with aseptic meningitis. The etiology of the contacts' illness was determined by viral culture, genomic sequencing, serology and epidemiological linking. Two of the vaccinated children developed vaccine associated parotitis as an adverse event three weeks following immunization. Symptoms in contact cases developed five to seven weeks after the vaccination of the children. The five contact cases, as well as the three children with adverse events recovered completely. The children had been vaccinated with MMR vaccine produced by the Institute of Immunology Zagreb, each of them with a different lot. One of the possible explanations for these adverse events is that the very low levels of wild mumps virus circulation in the last decade, combined with waning immunity in those who received one dose of vaccine or suffered from mumps in childhood, resulted in susceptible young adults and that this unique epidemiological situation allows us to detect horizontal transmission of mumps vaccine virus.

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IPV

Inactivated poliovirus vaccine

© GAVI

Inactivated polio vaccine (IPV) was developed in 1955 by Dr Jonas Salk. Also called the Salk vaccine IPV consists of inactivated (killed) poliovirus strains of all three poliovirus types. IPV is given by intramuscular or intradermal injection and needs to be administered by a trained health worker. IVP produces antibodies in the blood to all three types of poliovirus. In the event of infection, these antibodies prevent the spread of the virus to the central nervous system and protect against paralysis.

Advantages

- As IPV is not a 'live' vaccine, it carries no risk of VAPP.
- IPV triggers an excellent protective immune response in most people.

Disadvantages

- IPV induces very low levels of immunity in the intestine. As a result, when a person immunized with IPV is infected with wild poliovirus, the virus can still multiply inside the intestines and be shed in the faeces, risking continued circulation.
- IPV is over five times more expensive than OPV. Administering the vaccine requires trained health workers, as well as sterile injection equipment and procedures.

Safety

IPV is one of the safest vaccines in use. No serious systemic adverse reactions have been shown to follow vaccination.

Efficacy

IPV is highly effective in preventing paralytic disease caused by all three types of poliovirus.

Recommended use

An increasing number of industrialized, polio-free countries are using IPV as the vaccine of choice. This is because the risk of paralytic polio associated with continued routine use of OPV is deemed greater than the risk of imported wild virus.

However, as IPV does not stop transmission of the virus, OPV is used wherever a polio outbreak needs to be contained, even in countries which rely exclusively on IPV for their routine immunization programme.
Once polio has been eradicated, use of all OPV will need to be stopped to prevent re-establishment of transmission due to VDPVs.

Related Resources

IPV and routine immunization

What is vaccine-derived polio?

Online Q&A
Updated April 2017

Q: What is vaccine-derived polio?

A: Oral polio vaccine (OPV) contains an attenuated (weakened) vaccine-virus, activating an immune response in the body. When a child is immunized with OPV, the weakened vaccine-virus replicates in the intestine for a limited period, thereby developing immunity by building up antibodies. During this time, the vaccine-virus is also excreted. In areas of inadequate sanitation, this excreted vaccine-virus can spread in the immediate community (and this can offer protection to other children through 'passive' immunization), before eventually dying out.

On rare occasions, if a population is seriously under-immunized, an excreted vaccine-virus can continue to circulate for an extended period of time. The longer it is allowed to survive, the more genetic changes it undergoes. In very rare instances, the vaccine-virus can genetically change into a form that can paralyse – this is what is known as a circulating vaccine-derived poliovirus (cVDPV).

It takes a long time for a cVDPV to occur. Generally, the strain will have been allowed to circulate in an un- or under-immunized population for a period of at least 12 months. Circulating VDPVs occur when routine or supplementary immunization activities (SIAs) are poorly conducted and a population is left susceptible to poliovirus, whether from vaccine-derived or wild poliovirus. Hence, the problem is not with the vaccine itself, but low vaccination coverage. If a population is fully immunized, they will be protected against both vaccine-derived and wild polioviruses.

Since 2000, more than 10 billion doses of OPV have been administered to nearly 3 billion children worldwide. As a result, more than 13 million cases of polio have been prevented, and the disease has been reduced by more than 99%. During that time, 24 cVDPV outbreaks occurred in 21 countries, resulting in fewer than 760 VDPV cases.

Until 2015, over 90% of cVDPV cases were due to the type 2 component in OPV. With the transmission of wild poliovirus type 2 already successfully interrupted since 1999, in April 2016 a switch was implemented from trivalent OPV to bivalent OPV in routine immunization programmes. The removal of the type 2 component of OPV is associated with significant public health benefits, including a reduction of the risk of cases of cVDPV2.

The small risk of cVDPVs pales in significance to the tremendous public health benefits associated with OPV. Every year, hundreds of thousands of cases due to wild polio virus are prevented. Well over 10 million cases have been averted since large-scale administration of OPV began 20 years ago.

Circulating VDPVs in the past have been rapidly stopped with 2–3 rounds of high-quality immunization campaigns. The solution is the same for all polio outbreaks: immunize every child several times with the oral vaccine to stop polio transmission, regardless of the origin of the virus.

– Fact sheet on vaccine-derived poliovirus published by the Global Polio Eradication Initiative (PDF)

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Vaccine. 2001 Oct 15;20 Suppl 1:S38-41.

What are the limits of adjuvanticity?

Del Giudice G[1], Podda A, Rappuoli R.

Author information

Abstract

Vaccines developed traditionally following empirical approaches have often limited problems of immunogenicity, probably due to the low level of purity of the active component(s) they contain. The application of new technologies to vaccine development is leading to the production of purer (e.g. recombinant) antigens which, however, tend to have a poorer immunogenicity as compared to vaccines of the previous generation. The search for new vaccine adjuvants involves issues related to their potential limits. Since the introduction of aluminium salts as vaccine adjuvants more than 70 years ago, only one adjuvant has been licensed for human use. The development of some of these new vaccine adjuvants has been hampered by their inacceptable reactogenicity. In addition, some adjuvants work strongly with some antigens but not with others, thus, limiting their potentially widespread use. The need to deliver vaccines via alternative routes of administration (e.g. the mucosal routes) in order to enhance their efficacy and compliance has set new requirements in basic and applied research to evaluate their efficacy and safety. Cholera toxin (CT) and labile enterotoxin (LT) mutants given along with intranasal or oral vaccines are strong candidates as mucosal adjuvants. Their potential reactogenicity is still matter of discussions, although available data support the notion that the effects due to their binding to the cells and those due to the enzymatic activity can be kept separated. Finally, adjuvanticity is more often evaluated in terms of antigen-specific antibody titers induced after parenteral immunization. It is known that, in many instances, antigen-specific antibody titers do not correlate with protection. In addition, very little is known on parameters of cell-mediated immunity which could be considered as surrogates of protection. Tailoring of new adjuvants for the development of vaccines with improved immunogenicity/efficacy and reduced reactogenicity will represent one of the major challenges of the ongoing vaccine-oriented research.

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[Indexed for MEDLINE]

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Antibodies are not required for immunity against some viruses

Date: March 1, 2012

Source: Cell Press

Summary: A new study turns the well established theory that antibodies are required for antiviral immunity upside down and reveals that an unexpected partnership between the specific and non-specific divisions of the immune system is critical for fighting some types of viral infections. The research may lead to a new understanding of the best way to help protect those exposed to potentially lethal viruses, such as the rabies virus.

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FULL STORY

A new study turns the well established theory that antibodies are required for antiviral immunity upside down and reveals that an unexpected partnership between the specific and non-specific divisions of the immune system is critical for fighting some types of viral infections. The research, published online on March 1st in the journal Ei qjpu by Cell Press, may lead to a new understanding of the best way to help protect those exposed to potentially lethal viruses, such as the rabies virus.

The immune system has two main branches, innate immunity and adaptive immunity. Innate immunity is a first line of defense that relies on cells and mechanisms that provide non-specific immunity. The more sophisticated adaptive immunity, which counts antibody-producing B cells as part of its arsenal, is thought to play a major role in the specific response to viral infections in mammals. However, adaptive immune responses require time to become fully mobilized.

"Mice infected with vesicular stomatitis virus (VSV) can suffer fatal invasion of the central nervous system even when they have a high concentration of anti-VSV antibodies in their system," explains senior study author, Dr. Ulrich H. von Andrian, from Harvard Medical School. "This observation led us to revisit the contribution of adaptive immune responses to survival following VSV infection."

The research team studied VSV infection in mice that had B cells but did not produce antibodies. Unexpectedly, although the B cells themselves were essential, survival after VSV exposure did not require antibodies or other aspects of traditional adaptive immunity."We determined that the B cells produced a chemical needed to maintain innate immune cells called macrophages. The macrophages produced type I interferons, which were required to prevent fatal VSV invasion," says co-author Dr. Matteo Iannacone.

Taken together, the results show that the essential role of B cells against VSV does not require adaptive mechanisms, but is instead directly linked with the innate immune system. "Our findings contradict the current view that antibodies are absolutely required to survive infection with viruses like VSV, and establish an unexpected function for B cells as custodians of macrophages in antiviral immunity," concludes Dr. von Andrian. "It will be important to further dissect the role of antibodies and interferons in immunity against similar viruses that attack the nervous system, such as rabies, West Nile virus, and Encephalitis."

Journal reference: Moseman et al.: "B Cell Maintenance of Subcapsular Sinus Macrophages Protects against a Fatal Viral Infection Independent of Adaptive Immunity."

Story Source:

Materials provided by **Cell Press**. Note: Content may be edited for style and length.

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https://www.ncbi.nlm.gov/pubmed/22386268

Immunity. 2012 Mar 23;36(3):415-26. doi: 10.1016/j.immuni.2012.01.013. Epub 2012 Mar 1.

B cell maintenance of subcapsular sinus macrophages protects against a fatal viral infection independent of adaptive immunity.

Moseman EA[1], Iannacone M, Bosurgi L, Tonti E, Chevrier N, Tumanov A, Fu YX, Hacohen N, von Andrian UH.

Author information

Abstract

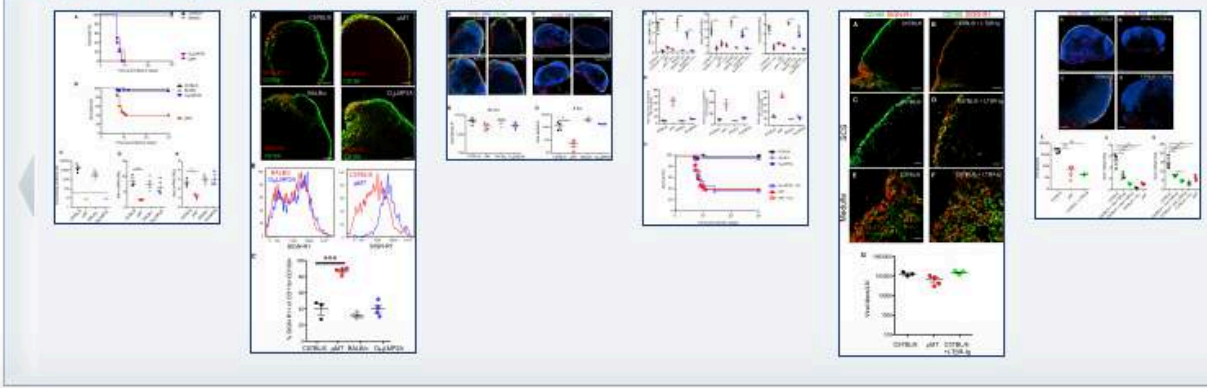
Neutralizing antibodies have been thought to be required for protection against acutely cytopathic viruses, such as the neurotropic vesicular stomatitis virus (VSV). Utilizing mice that possess B cells but lack antibodies, we show here that survival upon subcutaneous (s.c.) VSV challenge was independent of neutralizing antibody production or cell-mediated adaptive immunity. However, B cells were absolutely required to provide lymphotoxin (LT) α1β2, which maintained a protective subcapsular sinus (SCS) macrophage phenotype within virus draining lymph nodes (LNs). Macrophages within the SCS of B cell-deficient LNs, or of mice that lack LTα1β2 selectively in B cells, displayed an aberrant phenotype, failed to replicate VSV, and therefore did not produce type I interferons, which were required to prevent fatal VSV invasion of intranodal nerves. Thus, although B cells are essential for survival during VSV infection, their contribution involves the provision of innate differentiation and maintenance signals to macrophages, rather than adaptive immune mechanisms.

Comment in

B cells: An innate talent uncovered. [Nat Rev Immunol. 2012]
B cells, not just for antibody anymore. [Immunity. 2012]

PMID: 22386268 PMCID: PMC3359130 DOI: 10.1016/j.immuni.2012.01.013

[Indexed for MEDLINE] **Free PMC Article**



PubMed

Format: Abstract

Neurology. 1992 Apr;42(4):761-4.

Severe tetanus in immunized patients with high anti-tetanus titers.

Crone NE[1], Reder AT.

Author information

Abstract

Severe (grade III) tetanus occurred in three immunized patients who had high serum levels of anti-tetanus antibody. The disease was fatal in one patient. One patient had been hyperimmunized to produce commercial tetanus immune globulin. Two patients had received immunizations 1 year before presentation. Anti-tetanus antibody titers on admission were 25 IU/ml to 0.15 IU/ml by hemagglutination and ELISA assays; greater than 0.01 IU/ml is considered protective. Even though one patient had seemingly adequate anti-tetanus titers by in vitro measurement (0.20 IU), in vivo mouse protection bioassays showed a titer less than 0.01 IU/ml, implying that there may have been a hole in her immune repertoire to tetanus neurotoxin but not to toxoid. This is the first report of grade III tetanus with protective levels of antibody in the United States. The diagnosis of tetanus, nevertheless, should not be discarded solely on the basis of seemingly protective anti-tetanus titers.

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Publication type, MeSH terms, Substance

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VIROLOGY

Rapid Identification of Measles Virus Vaccine Genotype by Real-Time PCR

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ABSTRACT During measles outbreaks, it is important to be able to rapidly distinguish between measles cases and vaccine reactions to avoid unnecessary outbreak response measures such as case isolation and contact investigations. We have developed a real-time reverse transcription-PCR (RT-PCR) method specific for genotype A measles virus (MeV) (MeVA RT-quantitative PCR [RT-qPCR]) that can identify measles vaccine strains rapidly, with high throughput, and without the need for sequencing to determine the genotype. We have evaluated the method independently in three measles reference laboratories using two platforms, the Roche LightCycler 480 system and the Applied Biosystems (ABI) 7500 real-time PCR system. In comparison to the standard real-time RT-PCR method, the MeVA RT-qPCR showed 99.5% specificity for genotype A and 94% sensitivity for both platforms. The new assay was able to detect RNA from five currently used vaccine strains, AIK-C, CAM-70, Edmonston-Zagreb, Moraten, and Shanghai-191. The MeVA RT-qPCR assay has been used successfully for measles surveillance in reference laboratories, and it could be readily deployed to national and subnational laboratories on a wide scale.

KEYWORDS measles, PCR, genotyping, measles vaccine, molecular methods

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Editor Yi-Wei Tang, Memorial Sloan-Kettering Cancer Center

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Endemic transmission of measles virus (MeV) was interrupted in the Americas in 2002 (1), but since then, importations of measles from areas of endemicity have caused frequent and sometimes large outbreaks (2–6) and a recent transitory suspension of the elimination status (7). An important component of the public health response to a measles outbreak is vaccination of unimmunized contacts (8). Since approximately 5% of recipients of measles virus-containing vaccine experience rash and fever which may be indistinguishable from measles (9), it is very important to identify vaccine reactions to avoid unnecessary isolation of the patient, as well as the need for contact tracing and other labor-intensive public health interventions. Recent measles outbreaks in the Canadian provinces of Alberta and British Columbia have emphasized the need for rapid differentiation of vaccine reactions (18, 19) from reactions to infection with the wild-type virus. During the measles outbreak in California in 2015, a large number of suspected cases occurred in recent vaccinees (3). Of the 194 measles virus sequences obtained in the United States in 2015, 73 were identified as vaccine sequences (R. J. McNall, unpublished data). In contrast, only 11 of 542 cases genotyped in the National Reference Center for Measles, Mumps, and Rubella in Germany were associated with the vaccine virus.

Genotyping is used to confirm the origin of an outbreak and to exclude endemic circulation, but it is also the only way to distinguish vaccine strains from wild-type viruses. Genetic characterization of MeV is accomplished by sequencing of the 450

TABLE 1 The lower limit of detection of MeVA RT-qPCR compared to MeV RT-qPCR was determined by testing serial dilutions of synthetic MeV RNA with a known copy number

Assay	Copy no.	No. of samples with positive results/total no. of samples tested	% positive results
MeVA RT-qPCR	10^3	18/18	100
	10^2	18/18	100
	10^1	13/20	65
	10^0	1/18	6
	10^{-1}[a]	0/3	0
MeV RT-qPCR	10^3	18/18	100
	10^2	18/18	100
	10^1	18/18	100
	10^0	4/18	22
	10^{-1}[a]	0/3	0

[a]This concentration was tested only 3 times since it is undetectable by both assays and therefore was not informative in the determination of the lower limit of detection.

nucleotides (nt) coding for the COOH terminal 150 amino acids of the nucleoprotein (N-450) (10). The WHO currently recognizes 24 genotypes of measles virus, and all of the vaccine strains are in a single genotype, genotype A. Wild-type viruses of genotype A are no longer circulating (11).

It is difficult, especially during outbreaks, to perform rapid confirmation of vaccine reactions by sequencing, and there is interest in developing rapid molecular tests to detect vaccine strains (12). Here, we describe a real-time reverse transcription-PCR (RT-PCR) method that detects the vaccine genotype (MeVA RT-quantitative PCR [RT-qPCR]) and that can provide rapid discrimination between wild-type-virus infections and vaccine reactions. The method was developed initially on the Roche LightCycler 480 platform at the Canadian National Microbiology Laboratory (NML) and then independently evaluated at the Robert Koch-Institute (RKI) in Germany using the same platform and at the US Centers for Disease Control (CDC) using the Applied Biosystems 7500 platform.

RESULTS

Assay development and evaluation at the NML. The analytical sensitivity of the MeVA RT-qPCR on the Roche LightCycler 480 platform was established using the synthetic RNA standard, which was serially diluted from 10^3 to 10^{-1} copies per reaction and tested in triplicate in at least 6 separate assays in parallel with the MeV RT-qPCR. The lower limit of detection of the MeVA RT-qPCR was 10 to 100 copies per reaction, compared to a sensitivity of 1 to 10 copies per reaction for the MeV RT-qPCR (Table 1).

Eighty-eight surveillance specimens that were previously genotyped as genotype A, 96 specimens of nonvaccine measles virus genotypes (B3, C2, D3, D4, D6, D7, D8, D9, E, H1, and H2), and isolates for genotypes B2, C1, D2, D5, D6, D7, D10, G1, G2, and H2 (WHO Measles Strain Bank, US Centers for Disease Control, Atlanta, GA, USA) were tested with MeVA RT-qPCR and produced no false-positive results. The amplification curves of 33 wild-type measles virus samples, including all the genotypes listed above, did not rise significantly in comparison to the curves of samples containing vaccine strain RNA (Fig. 1). However, 3 of 88 genotype A specimens were not detected by the MeVA RT-qPCR (Table 2). These three specimens were near the lower limit of detection (crossing-point [Cp] value, >35) for the MeV RT-qPCR. The sensitivity of the MeVA RT-qPCR in relation to the MeV RT-qPCR was 97% (90% to 99%, 95% confidence interval [CI]), and the specificity was 100% (95% to 100%, 95% CI) (Table 3). Specificity was further evaluated by testing a panel of other viral agents from cell culture-derived material or clinical specimens (parvovirus B19, dengue virus serotypes 1 to 4, influenza virus H3N2, poliovirus Sabin 1 species C, enterovirus D68-2 [EV-D68-2] species D, Coxsackie virus, EV71, parechovirus, echovirus 18, herpes simplex virus 1 [HSV1], HSV2, Epstein-Barr virus [EBV], cytomegalovirus [CMV], human herpesvirus 6 [HHV-6], HHV7,

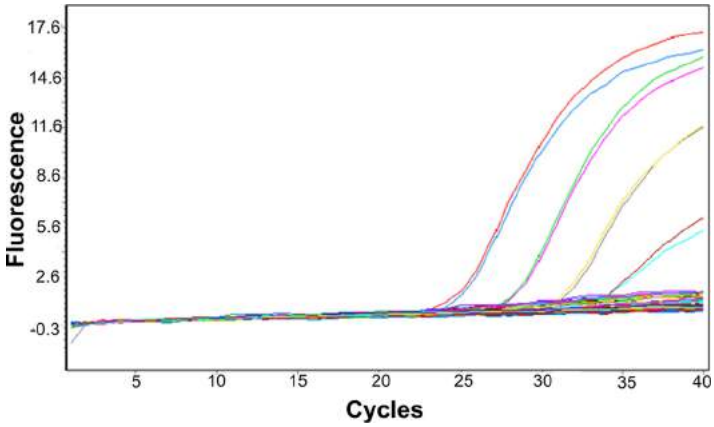

FIG 1 Amplification curve from the MeVA RT-qPCR on the Roche LightCycler 480 system. The bundle of the flat curves includes 33 wild-type measles virus specimens comprising the following genotypes: B2, B3, C1, C2, D2, D3, D4, D5, D6, D7, D8, D9, D10, G1, G2, E, H1, and H2. The amplification curves are from MeV vaccine RNA from 10^2 to 10^5 copy numbers, assessed in duplicate. The QuantiTect Probe RT-PCR kit was used for these reactions.

varicella zoster virus [VZV], rubella virus, and mumps virus). All specimens were negative by MeVA RT-qPCR.

Fifty specimens that were positive for vaccine strain A were tested in parallel by MeVA RT-qPCR and MeV RT-qPCR, and there was a good correlation of the Cp values between the two methods, with a slope of 0.88 (0.82 to 0.94, 95% CI). The slope was significantly different from 1.00, and a *y* intercept of 4.1 (2.2 to 6.0, 95% CI) confirmed that the sensitivity and limit of detection of the MeVA RT-qPCR method were lower than those of the MeV RT-qPCR (Fig. 2).

Assay evaluation at RKI. The MeVA qPCR was also independently evaluated at RKI by testing 46 archival measles virus specimens of genotype A and 112 samples containing wild-type MeV, including genotypes B3, D4, D5, D6, D8, D9, D10, G2, and H1. The same LightCycler 480 platform was used. The MeV RT-qPCR (16) includes the SuperScript III Platinum One-Step qRT-PCR kit (Invitrogen), so an evaluation was performed comparing the SuperScript III and QuantiTect reagent kits. The SuperScript III PCR kit produced suboptimal results, with significant increases of the amplification baseline of nonvaccine measles virus genotypes D10, D8, and B3 (Fig. 3A).

When the QuantiTect Probe RT-PCR kit was used for the MeVA RT-qPCRs, the test was 89% sensitive and 99.5% specific for genotype A measles virus (Table 3), with amplification curves comparable to those shown in Fig. 1. There was a single false-positive result from a genotype D5 wild-type strain, which produced amplification with

TABLE 2 Comparison of MeVA RT-PCR and MeV RT-qPCR in three reference laboratories

Reference laboratory and MeVA RT-qPCR result	No. of MeV RT-qPCR samples		Total no. of samples
	Genotype A	Not genotype A	
NML			
Positive	85	0	85
Negative	3	96	99
Total	88	96	184
CDC			
Positive	12	0	15
Negative	1	12	13
Total	13	12	28
RKI			
Positive	41	1	42
Negative	5	111	116
Total	46	112	158

TABLE 3 Summary of sensitivity and specificity of MeVA RT-qPCR for the detection of MeV genotype A

Center	No. of samples	% sensitivity (95% CI)	% specificity (95% CI)	Genotypes tested
NML	184	97 (90–99)	100 (95–100)	B3, B2, C1, D2, C2, D3, D4, D5 D6, D7, D8, D9, D10, G1, G2, E, H1, H2
RKI	158	89 (0.76–0.96)	99 (94–100)	B3, D4, D5, D6, D8, D9, D10, G2, H1
CDC	28	92 (66–100)	100 (70–100)	B3, D4, D8, D9, G3, H1, AIK, CAM-70, Edmonston-Zagreb, Moraten, Shanghai-191[a]
Overall	370	94 (88–97)	99 (97–100)	

[a]Genotypes D4 and G3 and the non-Edmonston vaccine strains, tested using synthetic RNAs and culture lysate, respectively, were not included in the sensitivity and specificity calculations.

the MeVA RT-qPCR. The region targeted by the MeVA assay was sequenced, and the sequence differed from the vaccine strain sequence by a G at position 517 in the probe region (conserved in all wild-type genotypes listed in Fig. 4), by a C at position 538 in the reverse primer region (similar to genotypes D4, D7, and D8), and by a T at position 548, at the 5′ terminus of the reverse primer (similar to genotypes B3 and D6). These genotypes did not produce any cross-reactivity with the MeVA-specific assay, and the reason for the false-positive result for this D5 specimen is unclear.

Assay evaluation at CDC on the ABI 7500 platform. The MeVA RT-qPCR method was independently evaluated at the CDC on the ABI 7500 instrument, which is a commonly used instrument in state public health laboratories and is available in many laboratories in the WHO Measles Rubella Laboratory Network (14). Similarly to the results seen with the LightCycler 480 platform, the MeVA RT-qPCR assay performed suboptimally with the SuperScript III kit with respect to the resulting amplification curves for wild-type measles virus genotypes (Fig. 3B).

The MeVA RT-qPCR and MeV qPCR were compared using the ABI 7500 platform and the QuantiTect kit, and the samples included synthetic MeV RNAs serially diluted from 10^5 to 10^1 copies per reaction. The dilutions were tested in duplicate on at least four separate assays. The results were similar to those obtained from the Roche LightCycler 480 system (Table 1) in that the lower limit of detection of the MeVA RT-qPCR assay was approximately 1 Log_{10} higher than for the MeV RT-qPCR assay.

To assess the specificity of the MeVA RT-qPCR assay on the ABI 7500 platform and to compare it to the performance of the MeV RT-qPCR assay, three sets of samples were used, i.e., synthetic RNAs containing the entire N gene open reading frames from six currently circulating wild-type genotypes (B3, D4, D8, D9, G3, and H1) (B. Bankamp, unpublished data), RNA from cell culture lysates from five vaccine strains (AIK-C, CAM-70, Edmonston-Zagreb, Moraten, and Shanghai-191), and RNA extracted from 28

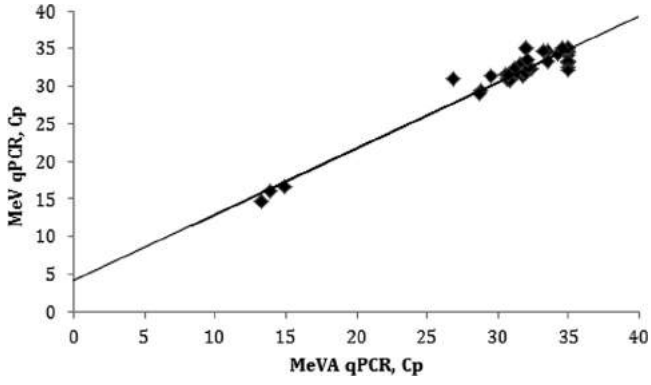

FIG 2 Correlation between Cp values of 50 genotype A measles virus specimens tested by MeVA RT-qPCR and the standard MeV RT-qPCR method. The regression line has a slope of 0.88 (0.82 to 0.94, 95% CI), a *y* intercept of 4.1 (2.2 to 6.0, 95% CI) and an R^2 value of 0.949 ($P < 0.0001$). The QuantiTect Probe RT-PCR kit was used for these reactions.

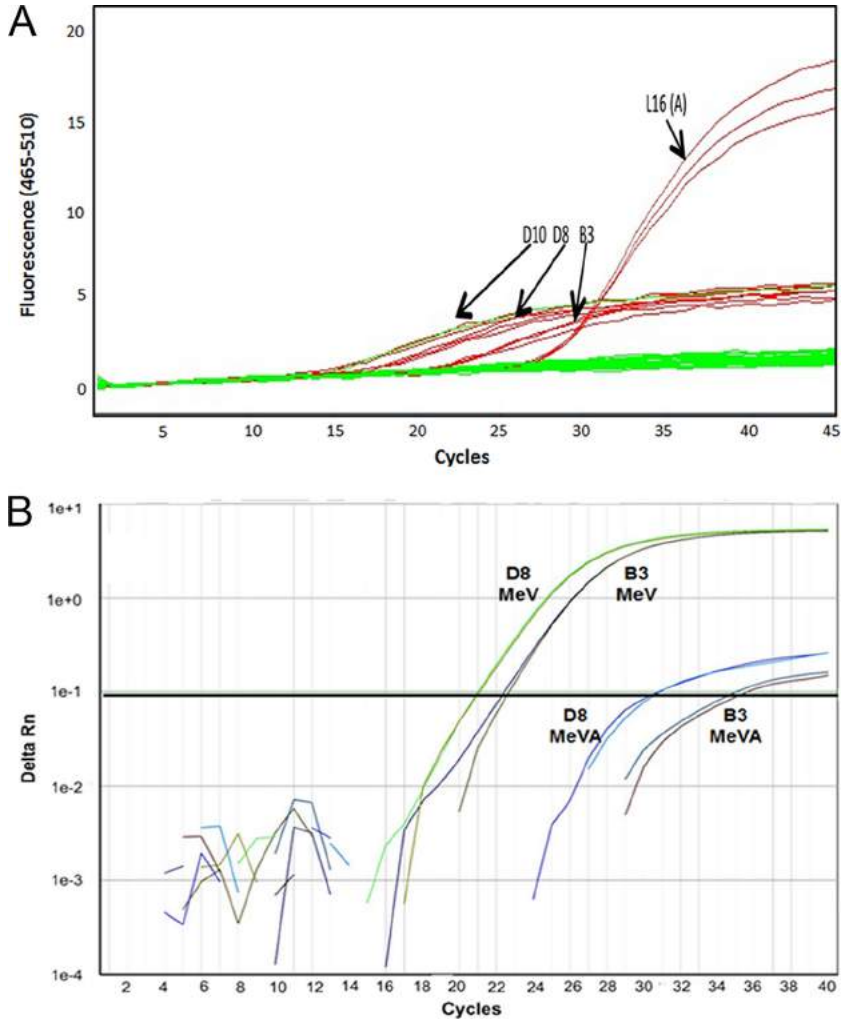

FIG 3 Negative effect of the use of the SuperScript III Platinum One-Step quantitative RT-PCR kit on the specificity of the MeVA RT-qPCR for the vaccine genotype. (A) The use of SuperScript III on the Roche LightCycler 480 platform caused a significant rise in the baseline of the amplification curves for genotype D10, D8, and B3. (B) Results of the use of SuperScript III on an ABI 7500 platform in amplification curves from wild-type measles virus RNA.

archival respiratory swabs and urine specimens that were submitted to the CDC for routine surveillance. Three archival specimens were negative by MeV RT-qPCR, and the other 25 were positive by MeV RT-qPCR and included clinical specimens from measles cases and vaccine reactions (with threshold cycle [C_T] values ranging from 14 to 36).

Of the positive archival specimens, all specimens with wild-type genotypes ($n = 12$) were negative in the MeVA RT-qPCR assay but positive in the MeV RT-qPCR assay and 12 of 13 specimens from vaccine reactions were positive in both assays (Table 2). Three of the specimens from the vaccine reactions had C_T values ranging from 38 to 40 in the MeV RT-qPCR assay and from 38 to 40 in the MeVA RT-qPCR.

The RNA from all five vaccine strains was detected in both assays with slightly lower sensitivity (C_T value, 2 to 3) in the MeVA RT-qPCR assay than in the MeV RT-qPCR assay (data not shown). In addition, the MeVA RT-qPCR assay did not produce a positive signal in samples containing high copy numbers of synthetic RNA from the six commonly circulating wild-type genotypes (Fig. 5).

If we consider all samples that were amplified within 40 PCR cycles, as was done at NML and RKI for the LightCycler platform, the sensitivity of the MeVA test on the ABI 7500 platform was 94% and the specificity was 100% (Table 3).

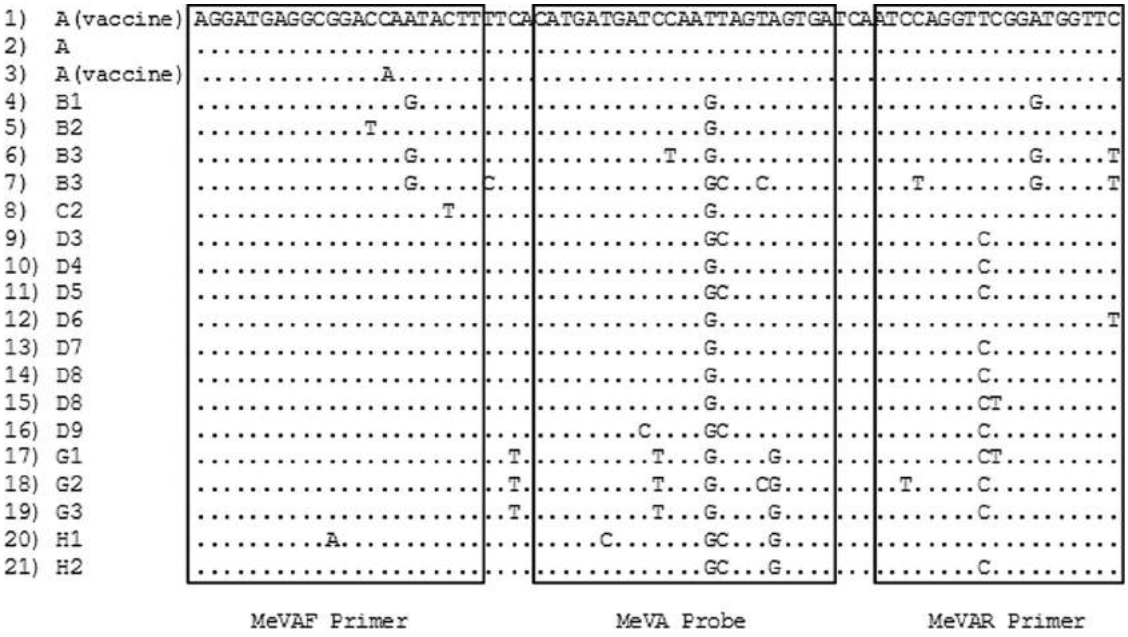

FIG 4 Alignment of the N gene region (positions 478 to 548) amplified by the MeVA RT-qPCR. The alignment includes examples of each genotype available on GenBank for this region, except for genotype D9, which was sequenced from one of our archival specimens. Row 1, 31 identical sequences from various vaccine strains; row 2, MVi/Maryland.USA/54 (A); row 3, two vaccine strains showing a 1-nt difference in the forward primer region; row 4, MVi/Yaounde.CMR/12.83 (B1); row 5, MVi/Libreville.GAB/84 (B2); row 6, MVi/Ibadan.NIE/971 (B3); row 7, MVi/New_York.USA/94 (B3); row 8, MVi/Maryland.USA/77 (C2); row 9, MVi/Illinois.USA/89/1 (D3); row 10, MVi/Montreal.CAN/89 (D4); row 11, Bankok.THA/12.93 (D5); row 12, MVi/New_Jersey.USA/94/1 (D6); row 13, MVs/Dundee.UNK/82 (D7); row 14, MVi/BritishColumbia.CAN/13.10/1 (D8); row 15, MVi/Manchester.GBR/30.94 (D8); row 16, MVs/Ontario.CAN/14.14 (D9); row 17, MVi/Berkeley.USA/83 (G1); row 18, MVi/Amsterdam.NLD/49.97 (G2); row 19, MVi/Gresik.IDN/17.02 (G3); row 20, MVi/Hunan.CHN/93/7 (H1); row 21, MVi/Beijing.CHN/94/1 (H2).

DISCUSSION

In response to the need for prompt differentiation between vaccine reactions and wild-type measles virus infection cases, laboratories have been developing methods that do not require sequencing of N-450. A method targeting a region on the hemagglutinin gene has been described and tested with a small number of vaccine and wild-type specimens or isolates (15). Here, we describe the development and validation of a measles virus genotype A-specific RT-qPCR, MeVA RT-qPCR, that targets the N gene of MeV. This assay produces rapid results and is capable of high throughput. The MeVA RT-qPCR was thoroughly tested at three global reference laboratories. Two RT-qPCR platforms and over 300 samples were included in the evaluation. Overall, our data show very high (99.5%) specificity for the A genotype, albeit with lower (94%) sensitivity than the standard MeV RT-qPCR (16). Because of the lower sensitivity, the MeVA RT-qPCR is intended to be used as a tool for rapid detection of genotype A sequences and not as a primary diagnostic test. The MeVA RT-qPCR should be performed in parallel with the MeV RT-qPCR method. Multiplexing of the two tests is in progress to increase the efficiency of this method.

We have shown that the MeVA RT-qPCR can be used on both the Roche LightCycler 480 and the ABI 7500 platforms, which are available in a large number of laboratories around the world. We also demonstrated that the QuantiTect kit gave optimal performance on both platforms.

An alignment of the nt 478 to 548 region used for the MeVA RT-qPCR (Fig. 4) shows that some wild-type strains differ only by a single nucleotide in the probe region, a G at position 517, although other mismatches that may favor specificity are present in the primer regions. This point mutation may be stable, since it results in an amino acid change (serine in wild-type strains to isoleucine in vaccine strains), but it is conceivable that wild-type strains may arise with a mutation in this position that cross-reacts with the MeVA assay. Therefore, we currently still confirm every MeVA RT-qPCR result by WHO-recommended sequencing of the N-450 region.

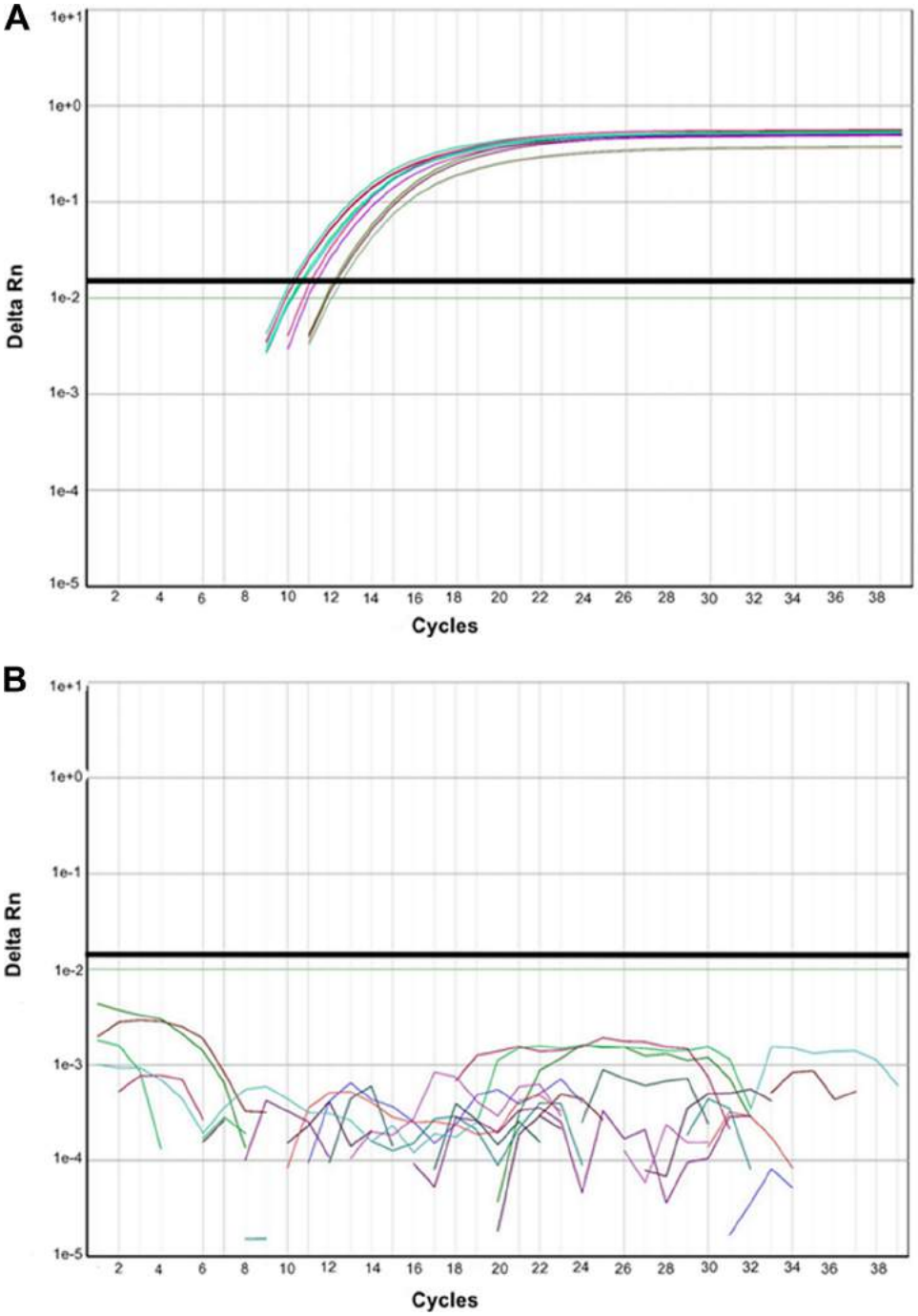

FIG 5 Specificity of the MeVA RT-qPCR assay, using an Applied Biosystems 7500 platform. Synthetic RNA from the six active wild-type measles virus genotypes (B3, D4, D8, D9, G3, and H1) was tested. Panel A shows detection of 10^7 copies of RNA/reaction in the MeV qPCR assay, and panel B shows the lack of amplification of 10^7 copies of RNA/reaction in the MeVA RT-qPCR assay. The QuantiTect Probe RT-PCR kit was used for these reactions.

The specificity of the test has been assessed on most of the measles virus genotypes currently circulating in the world (except D11 and G3) (11, 14), and there was only one genotype D5 specimen that gave a false-positive result. The sequence of the MeVA RT-qPCR target region of this genotype D5 virus differed from that of the vaccine strains by the G at position 517, conserved in all measles virus wild-type strains, and by two additional nucleotides in the reverse primer. Genotypes D4, D6, and D8 have the same sequence as this D5 strain in the probe region and one fewer difference in the reverse

primer region (Fig. 4), but they did not cross-react with the MeVA RT-qPCR. Another genotype D5 strain, tested at the NML, and 12 additional D5 strains, tested at the RKI, were not amplified by the MeVA RT-qPCR. Therefore, the reasons for this false-positive result remain unclear.

During measles outbreak investigations, rapid detection of measles vaccine reactions is necessary to avoid unnecessary public health interventions. In Canada, the NML has been using the MeVA and MeV RT-qPCRs with a turnaround time of 2 days. Therefore, local health authorities can initiate appropriate public health responses without waiting for sequencing results, which often take several days to obtain. The MeVA RT-qPCR is especially useful during large measles outbreaks, when it is difficult for laboratories to perform sequencing on a large number of specimens in a timely manner. Similarly, recent measles outbreaks in the United States have reinforced the need for rapid confirmation of vaccine reactions. In countries such as Germany, which is still experiencing frequent measles outbreaks, this RT-PCR-based method has already proven to be a valuable tool for guiding the public health responses. The MeVA RTqPCR assay is a straightforward application of real-time RT-PCR methodology, and the two platforms evaluated here are available in many laboratories. This assay could be readily deployed to national and subnational laboratories on a wide scale.

MATERIALS AND METHODS

Primers, probes, and control RNA. The primers and probe for the vaccine-specific assays were designed following analysis of 31 sequences available on GenBank from Edmonston-derived and non-Edmonston-derived vaccine strains. These sequences are identical in the target region of MeVA RT-qPCR (the 3′ region of the MeV N gene between nt 478 and nt 548 of the Edmonston strain [GenBank accession no. AF266288.2]), including the more divergent non-Edmonston-derived strains Shanghai-191 and CAM-70 (Fig. 4) (15). Two vaccine strains, Schwarz FF-8 (GenBank AB591381.1) and Edmonston AIK-C (GenBank S58435.1), have a 1-nt difference in the sequence of the forward primer, but they are identical to the other vaccine strains in the probe region (Fig. 4). The primers (Invitrogen) for reverse transcription and cDNA amplification were 5′-AGGATGAGGCGGACCAATACTT-3′ (MeVAF) and 5′-GAACCATCCGAACC TGGAT-3′ (MeVAR). Both primers were used at a concentration of 0.9 μM. Amplification was detected by a TaqMan probe (TIB Molbiol) with 6-carboxyfluorescein (FAM) as a fluorophore, at a concentration of 0.25 μM. The probe had the sequence 5′-FAM-CATGATGATCCAATTAGTAGTGA-BBQ-3′ (MeVA probe [BBQ, black berry quencher]), where the underlined characters indicate locked nucleic acid bases containing a 2′O,4-C methylene bridge which has the effect of increasing the melting temperature (T_m) and potentiating the destabilizing effect of a nucleotide mismatch (17).

As a standard for the measurement of MeV copy numbers, synthetic measles virus RNA was prepared by *in vitro* transcription, using a MEGAscript T7 transcription kit (Invitrogen, Life Technologies Inc.), either from a plasmid containing the open reading frame of the N gene of genotype A (16) or from PCR amplicons that included the T7 promoter in the forward primer (Bankamp, unpublished). DNase-treated RNA was purified with a MEGAclear transcription cleanup kit (Ambion, Life Technologies Inc.) and quantitated fluorometrically (Qubit, Life Technologies Inc.). The absence of residual DNA was verified by real-time RT-PCR (MeV RT-qPCR) (16) in the presence or absence of the reverse transcriptase.

Samples tested. For this study, 370 samples were tested to evaluate the sensitivity and specificity of the MeVA RT-PCR. The majority of these were clinical samples that were submitted to NML, CDC, or RKI as part of routine surveillance activities for measles.

Roche LightCycler 480 platform. Archival nasopharyngeal swabs and urine specimens sent to the NML for molecular surveillance were used. These specimens tested positive for measles virus by MeV RT-qPCR using a previously described method (16) and were genotyped using the N-450 target (10, 11). RNA was extracted using the QIAamp viral RNA minikit (Qiagen; catalog no. 52904) or the MagNA Pure liquid chromatograph (LC) total nucleic acid isolation kit—high performance (Roche Diagnostics; catalog no. 05323738001) on the MagNA Pure LC 2.0 instrument (Roche Diagnostics). For RT-PCR, 2 μl of extracted RNA was subjected to one-step reverse transcription and qPCR using the QuantiTect Probe RT-PCR kit (Qiagen; catalog no. 204443) according the instructions of the manufacturer. The RT-qPCR mixtures (total volume, 20 μl) were incubated at 50°C for 20 min (RT step) and 95°C for 15 min (activation of the polymerase) and subjected to 40 cycles of amplification (95°C for 5 s and 60°C for 1 min) on the Roche LightCycler 480 instrument. The RT-qPCR result was considered positive if there was amplification within 40 cycles, but crossing-point (Cp) values were recorded for only the first 35 cycles.

At the National Reference Center for Measles, Mumps, and Rubella at the RKI, archival surveillance specimens were extracted using the QIAamp viral RNA minikit (Qiagen; catalog no. 52906) and amplified by using the SuperScript III Platinum One-Step quantitative RT-PCR kit (Invitrogen; catalog no. 11732-088) or the QuantiTect Probe RT-PCR kit (Qiagen; catalog no. 20443). MeVA RT-qPCR, MeV RT-qPCR, and genotyping at the N-450 region were performed as described above. The RT-PCR result was considered positive if amplification was detected within 40 cycles.

Applied Biosystems 7500 platform. At the CDC, RNA was extracted with the QIAamp viral RNA minikit as described above. The MeV RT-qPCR was performed using the same reaction conditions and primers and probes (16). As for the Roche LightCycler 480, the SuperScript III and QuantiTect reagent kits were evaluated as described in Results. For the comparisons described in this report, the RT-qPCR result was considered positive if there was amplification within 40 cycles; however, during routine use of this assay at the CDC, specimens with threshold cycle (C_T) values between 38 and 40 are considered to represent equivocal results.

Statistical analyses. Sensitivity and specificity of MeVA RT-qPCR were calculated using the VassarStats website (13). Linear regression and related statistics were calculated using an online calculator developed by GraphPad Software, Inc. (http://www.graphpad.com/quickcalcs/linear1) and graphed using Microsoft Excel.

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The findings and conclusions in this report are ours and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Names of specific vendors, manufacturers, or products are included for public health and informational purposes; inclusion does not imply endorsement of the vendors, manufacturers, or products by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

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Why have three long-running Cochrane Reviews on influenza vaccines been stabilised?

Three Cochrane Reviews focussing on the prevention of influenza in healthy adults, healthy children, and in the elderly are long-running reviews under the same senior author team. The protocol for the oldest review was first published 20 years ago.

Over the years the reviews have progressively accumulated evidence leading to ever greater stability in their conclusions. 'Stable' is a publication flag that usually indicates that the results are unlikely to change with the inclusion of new studies, such is the certainty of the results. The influenza vaccine reviews present us with a partly different situation. Readers will notice important outcomes where we have little or no data. They may also see that for some measures of influenza and 'influenza-like illness' (ILI), we have low-certainty evidence. We have reached a point where the evidence is not showing anything different to what it has done for a number of years. We know with varying degrees of certainty about vaccination effects on influenza and ILI, but the gap in our understanding of how vaccines affect the consequences of influenza persist. For each review, the impact of single studies is documented in the summary table 1 "Studies included in the various versions of this review and their impact on our conclusions". This month the three reviews (https://www.cochrane.org/news/featured-review-three-updated-cochrane-reviews-assessing-effectiveness-influenza-vaccines) appear in their latest updated and stabilised format.[1,2,3] Whilst we do not believe that periodic updating will complete the picture, our decision to stabilise is conditional. The three reviews will not be updated again unless certain criteria are met.

First, a new trial that meets inclusion criteria becomes available. Few trials of interest have been conducted recently, as a comparison with an inactive control is considered by some to be unethical. In the elderly, the latest completed trial dates from nearly two decades ago. Our searches have failed to find relevant ongoing trials.

A second condition is the introduction of a new generation of vaccines, based on new technology. This is possible given that several new technologies are being developed, such as vaccines containing fragments of the haemagglutinin antigen "stalk" on the viral surface (so called stalk-specific vaccines).[4]

The third condition is more complex: the development and testing of a new causal paradigm for ILI and influenza. Currently, massive worldwide machinery is needed to produce new vaccines every year to address viral antigenic changes, and to address the poor persistence of the antibody response in individuals. However, the vaccination selection and production programmes are based on aetiological assumptions which are neither explanatory nor predictive, as shown in our reviews. Overall the largest dataset to have accumulated to date is from trials conducted in the population least likely to benefit from vaccines but most likely to produce immunity: healthy adults. In healthy adult trials a high serological response is matched by a very small clinical effect (71 healthy adults need to be vaccinated to prevent one of them experiencing influenza). This weak effect cannot be explained simply by the mismatch of vaccine antigens with wild virus ones. A larger effect is observed in children over the age of two (five children need to be vaccinated to prevent one case of influenza, although there is huge uncertainty around these estimates). There is little evidence on prevention of complications, transmission, or time off work. Other reviews have drawn similar conclusions.[5]

During stabilisation we updated the randomised evidence, but for the first time have decided against updating the large observational evidence base. The observational dataset still appears in the reviews, but only as a historical record of earlier versions. Observational studies were included in the reviews over a decade ago in the hope they could provide long-term and rare harms data and improve the external validity of the trial evidence. They turned out to be of such low quality that their conclusions were inconclusive or unreliable. The most important example is the

case-negative study to assess influenza vaccine effectiveness *post hoc* (i.e. after an influenza season) by harvesting data from a surveillance programme. This study design, which is similar to a case-control study, selects influenza cases (cases of ILI which have tested positive for influenza) and controls (cases of ILI which have tested negative) and calculates the relevant odds ratio (OR) of exposure to that season's vaccine. An estimate of vaccine effectiveness is derived from this OR using a standard formula (vaccine effectiveness = 1 - OR%). However, despite their institutional popularity,[6,7] case-negative designs have limited public health significance because the design does not test field effectiveness, but, rather, laboratory efficacy of the vaccine (the capacity of the vaccine to generate a negative polymerase chain reaction (PCR) result). Both cases and controls are symptomatic, so any prevention is solely focused on PCR negativity. In addition, no useful public health absolute measures of effect can be derived (such as absolute risk reduction (ARR) and its reciprocal number needed to vaccinate to prevent one case (NNV)) because the background rates of infection and viral circulation are not part of the calculation of the estimates of effect. There are also problems with the mathematical assumptions made in this design (for details see the reviews). Case-negative studies are an illustration of the narrow and retrospective focus on influenza viruses at the expense of overall ILI - the illness cluster of interest to patients and their clinicians. Retrospective calculation of relative estimates of laboratory efficacy can be of interest for future decisions on composition of vaccines, but their relevance to everyday decisions seems questionable. ILI = Influenza-like illness

The underlying assumption that influenza vaccination does not affect the risk of non-influenza is contradicted by a recent report from the follow up of a trial by Cowling et al.[8] In 115 participants, those who received trivalent influenza vaccines had higher risk of acute respiratory infection associated with confirmed non-influenza respiratory virus infection (RR, 4.40; 95% CI, 1.31–14.8) compared to placebo recipients. The agents were mainly rhinoviruses and coxsackie/echoviruses; ILI episodes occurred shortly after a peak of influenza activity.

Current yearly registration of candidate influenza vaccines is based on their ability to trigger a good antibody response. But antibody responses are poor predictors of field protection. This is another example of the use of surrogate outcomes in biomedicine, where effects on clinically important outcomes remain unmeasured or unproven from randomised trials: complications and death by influenza.

The simple answer is that we do not understand what the target is. What is the threat of influenza, and what can we ever expect of the vaccines?

The WHO Global Influenza Programme (http://www.who.int/influenza/surveillance_monitoring/en/) (GIP) with its backbone Global Influenza Surveillance and Response System (http://www.who.int/influenza/gisrs_laboratory/en/) (GISRS) is a complex network of 143 national reference centres and specialist laboratories in 113 states carrying out surveillance of circulating influenza viruses. GISRS was devised and developed to guide annual influenza vaccine production, and the emphasis is mainly on influenza viruses, their variants, and emerging strains.

However there is no reliable system to monitor and quantify the epidemiology and impact of ILI, the syndrome that presents clinically. Few states produce reliable data on the number of physician contacts or hospitalised cases due to ILI, and none tie these data to the proportion of ILI caused by influenza. We do not know for certain what the impact of ILI is, nor the impact of the proportion of ILI caused by influenza. Prospective studies apportioning positivity to the scores of viruses probably causing ILI are rare, as interest is focused on influenza. The standard quoted figure of 36,000 yearly deaths in the US is based on the "respiratory and circulatory deaths" category including all types of pneumonia, including secondary to meconium ingestion or bacterial causes. More recently, the US Centers for Disease Control and Prevention (CDC) have proposed estimates of impact ranging between 3,000 and 49,000 yearly deaths. When actual death certificates are tallied, influenza deaths on average are little more than 1,000 yearly (http://dspace.mit.edu/handle/1721.1/69811) . So, the actual threat is unknown (but likely to be small) and so is the estimation of the impact of vaccination.

The uncertainty over the aetiology of ILI, its capricious nature and the weak correlation between immunity and protection, point to possible causal or concurrent factors in the genesis of both ILI and influenza. In other words, virus

positivity may only be one of the factors necessary for a case of influenza or ILI to manifest itself.

We await to see whether anyone has the interest or the courage to develop effective ways to control upper respiratory viral syndromes. Meanwhile our reviews will remain as a testimonial to the scientific failure of industry and governments to address the most important clinical outcomes for patients.

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Tom Jefferson is Senior Associate Tutor at the University of Oxford and Centre for Evidence Based Medicine. He and his co-authors are long-time Cochrane authors and contributors. In this post they have shared their personal interpretation of the findings and relevance of three recently updated Cochrane Reviews on the effectiveness of influenza vaccines on various populations. Please also note the standard disclaimer for all Cochrane Blog posts at the bottom of this page.

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Disclosure

TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane Review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013). In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boerhinger Ingelheim. He is holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane Reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ is a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network.

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Measles virus neutralizing antibody response, cell-mediated immunity, and IgG antibody avidity before and after a third dose of measles-mumps-rubella vaccine in young adults

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Abstract

Background—Two doses of measles-mumps-rubella (MMR) vaccine are 97% effective against measles, but waning antibody immunity and two-dose vaccine failures occur. We administered a third MMR dose (MMR3) to young adults and assessed immunogenicity over 1 year.

Methods—Measles virus (MeV) neutralizing antibody concentrations, cell-mediated immunity (CMI), and IgG antibody avidity were assessed at baseline, 1-month, and 1-year after MMR3.

Results—Of 662 subjects at baseline, 1 (0.2%) was seronegative (<8 mIU/mL) and 23 (3.5%) had low (8-120 mIU/mL) MeV neutralizing antibodies. At 1-month post-MMR3, 1 (0.2%) subject was seronegative and 6 (0.9%) had low neutralizing antibodies with only 21/662 (3.2%) showing a ≥4-fold rise in neutralizing antibodies. At 1-year post-MMR3, none were negative and 10 (1.6%) of 617 subjects had low neutralizing antibodies. CMI results showed low-levels of spot-forming

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Conflict of Interest: Laura A. Coleman worked for Marshfield Clinic Research Foundation at the time of the study, but she currently works for Abbott Nutrition, Columbus, OH. All other coauthors do not report any conflict of interest.

Meetings: The MeV neutralizing antibody results were presented at the Infectious Disease Week Conference, October 8-12, 2014, Philadelphia, PA.

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cells after stimulation, suggesting T-cell memory, but the response was minimal post-MMR3. MeV IgG avidity results did not correlate with neutralization results.

Conclusions—Most subjects were seropositive pre-MMR3 and very few had a secondary immune response post-MMR3. Similarly, CMI and avidity results showed minimal qualitative improvements in immune response post-MMR3. We did not find compelling data to support a routine third dose of MMR vaccine.

Keywords

measles; third dose measles-mumps-rubella (MMR) vaccine; measles vaccine immunogenicity; vaccine preventable disease; immunization; cell-mediated immunity; measles virus antibody avidity

Background

Measles is a contagious, viral rash illness; complications including pneumonia and encephalitis can result in death[1]. High two-dose measles-mumps-rubella (MMR) vaccination coverage and improved measles control in the World Health Organization (WHO) Region of the Americas resulted in the declaration of measles elimination in the U.S. in 2000[2].

Two doses of MMR vaccine are generally sufficient to provide long-lasting protection against measles[3]. Nonetheless, measles virus (MeV) is one of three components in the MMR vaccine, and third doses have been administered during mumps outbreaks among highly vaccinated populations[4, 5] and in non-outbreak settings among healthcare personnel, military recruits, international travelers, and college students who may have been two-dose vaccinated but lacked documentation[6-8].

The immunogenicity of the MeV component of a third MMR dose has not been studied. We assessed the magnitude and duration of an aggregate MeV neutralizing antibody response, cell-mediated immune response, and IgG antibody avidity before and after a third MMR dose (MMR3) in a healthy, young adult population.

Methods

Setting

The study population comprised patients of the Marshfield Clinic, a private, multispecialty group practice with regional centers throughout central and northern Wisconsin. The Clinic maintains an electronic vaccination registry (www.recin.org) for immunizations administered by Marshfield Clinic providers, local public health agencies, and immunization providers. No measles cases were reported in the area during the study period.

Subjects

Two cohorts comprising 685 subjects were enrolled during 2009-2010. Cohort 1 (N=113 subjects) participated in a 10-year longitudinal study at the Marshfield Clinic examining immunogenicity and adverse events following the second MMR vaccine dose, hereafter

called the longitudinal study[9, 10]. To achieve adequate sample size, Marshfield's vaccination registry was used to recruit subjects from Cohort 2 who had two documented MMR doses but did not participate in the longitudinal study (N=572 subjects). Invitation letters were mailed to both cohorts and follow-up phone calls were made. Additionally, Cohort 1 subjects who participated in the measles cell-mediated immunity (CMI) sub-study during the longitudinal study were asked to participate in the current CMI sub-study.

Although only 16 (14.2%) Cohort 1 subjects had low or negative MeV antibody concentrations during the longitudinal study, 93/113 Cohort 1 subjects with ≥1 low or negative antibody concentration to measles, mumps, or rubella during the longitudinal study (defined previously[10-12]) and all Cohort 2 subjects were offered a third dose of MMR vaccine (M-M-R II; Merck & Co.). Serum was collected from all subjects immediately before (baseline), and one month and one year after MMR3.

Study design

At each visit, subjects were questioned about measles disease, exposures, vaccinations, and other health events. MMR vaccine was administered during the initial visit. Informed consent was obtained from all subjects. Institutional Review Boards of the Marshfield Clinic Research Foundation and the Centers for Disease Control and Prevention approved the study. Sample size determination and exclusion criteria were previously described[13].

Cell-mediated immunity sub-study

The 60 participants of the longitudinal measles CMI sub-study or subjects with a low or negative MeV antibody concentration on ≥1 serum specimen draw during the longitudinal study were asked to participate in the current CMI sub-study. However, only 34 (56.7%) subjects meeting these criteria were re-enrolled. A convenience sample from Cohort 2 was used to reach the recruitment goal of 60 subjects.

Laboratory Methods

Laboratory testing was performed at the end of the study. Other than each subject's unique identifier code and serum collection dates, laboratories were blinded to study information.

Plaque reduction neutralization—Plaque reduction neutralization (PRN) testing was performed using low-passage Edmonston MeV on Vero cell monolayers, as previously described[14]. Endpoints were determined for all serum samples tested and ND_{50} titers calculated using the Kärber method. Serial four-fold dilutions of serum were tested in duplicate starting at 1:8 and ending at 1:8192 against virus diluted to give 25-35 plaques/well and run in parallel with the Second WHO International Standard Reference Serum (66/202). After incubating the virus-serum mixtures at 37° C with 5% CO_2, the mixtures were transferred onto corresponding 24-well tissue culture plates containing confluent Vero monolayers; after incubating for 1 hour at 37° C, the inoculum was removed and cells overlaid with medium containing carboxymethylcellulose and returned to the incubator for 5 days prior to staining with neutral red and plaque counting. Serum samples from individual subjects were tested in the same assay run. Titers were standardized against the WHO reference serum with a titer of 1:8 corresponding to 8 mIU/mL in this assay.

Cell-mediated immunity—Cryo-preserved peripheral blood mononuclear cells (PBMCs) were thawed and cultured overnight in 5% CO_2 at 37°C with Roswell Park Memorial Institute (RPMI) media supplemented with 4% human serum type AB (Lonza), 1% penicillin/streptomycin, and 1% 200 mM L-glutamine. Following the overnight culture, IFN-γ production by T-cells was assessed using enzyme-linked immunospot assays of PBMCs (5×10^5 cells/well), as previously described[15]. PBMCs were stimulated either with a mixture of MeV hemagglutinin, fusion, and nucleoprotein proteins as 20 amino acid peptides (11 amino acids overlapping) at 1μg/mL or with a lysate from MeV-infected Vero cells (Advanced Biotechnologies) at 10μg/mL for 40 hours. RPMI media and Con A (5μg/mL) were used as negative and positive controls, respectively. After stimulation, the plates were incubated with biotin-conjugated antibodies to human IFN-γ, then developed and read, as previously described[15]. Low and positive T-cell responses were categorized as <20 and ≥20 spot-forming cells (s.f.c.)/million PBMCs, respectively.

Avidity—MeV IgG antibody avidity was evaluated to determine whether there was a correlation between neutralizing antibody concentrations and strength of antibody binding. Avidity testing occurred after neutralization results were available using the method described previously[16]. Serum samples from all 662 subjects were split into quartiles based on baseline PRN antibody concentration. Subjects with negative neutralizing antibody concentrations were negative for MeV IgG by the Captia Measles IgG enzyme immunoassay assay (Trinity Biotech, Jamestown, NY), thus avidity could not be measured. All subjects with low MeV neutralizing antibody concentrations at baseline, 1-month, or 1-year post-MMR3 were tested for MeV antibody avidity. A random number generator selected specimens from at least 10 subjects from each of the remaining 3 quartiles for avidity testing of 59 subjects. The specimen was classified as negative if at 1:21 dilution it had undetectable IgG by the Captia assay, low avidity if the end titer avidity index percentages (etAI%) were ≤30%, intermediate between 30%-70% (intermediate results were retested), or high avidity if the etAI% was ≥70%.

Data analysis

Based on previous studies[17, 18], serum samples were categorized as: (1) negative (<8 mIU/mL), susceptible to infection and disease; (2) low (8-120 mIU/mL), potentially susceptible to infection and disease; (3) medium (121-900 mIU/mL), potentially susceptible to infection but not disease; and (4) high (>900 mIU/mL), not susceptible to infection or disease. Serum samples were also dichotomized as potentially susceptible (<121 mIU/mL) and not susceptible (≥121 mIU/mL).

We combined Cohorts 1 and 2 during analysis because there were no statistically significant differences between the cohorts by sex, race/ethnicity, or age. However, Cohort 1 had significantly lower geometric mean concentrations (GMCs) of MeV neutralizing antibody at baseline (p=0.0289), so we stratified the chi-squared risk factor analysis at 1-month and 1-year post-MMR3 by baseline MeV neutralizing antibody concentrations.

Mantel-Haenszel chi-squared and Fisher's exact tests were run to assess categorical variables. Wilcoxon Rank Sum tests were used for continuous variables. Potential risk

factors for negative or low MeV neutralizing antibody levels included: sex, age at first MMR dose, time since second MMR dose (we used <15 years versus ≥15 years prior based on average age of subjects at enrollment minus the age when the second dose was recommended), and (for post-MMR3 serum samples) the binary variable of whether the subject had low or negative MeV neutralizing antibody levels at baseline. In multivariate logistic regression, a backwards selection approach that used p-values <0.4 for inclusion and <0.05 for retention identified factors independently associated with negative or low MeV neutralizing antibody levels at baseline, 1-month and 1-year post-MMR3.

For the CMI analysis, the mean number of spot-forming cells resulting from PBMC stimulation with MeV peptide and MeV lysate was determined at baseline, 1-month, and 1-year post-MMR3. The MeV-specific T-cell response was calculated by subtracting the mean spontaneous response (no stimulation) from the mean peptide or lysate response. MeV T-cell responses were correlated with MeV neutralizing antibody levels at baseline, 1-month, and 1-year post-MMR3. For the avidity analysis, end titer avidity index percentages were correlated with MeV neutralizing antibody levels at all 3 time points.

GMCs of MeV neutralizing antibody were calculated from base 2 log-transformed data. Statistical significance was assigned for P-values <0.05. Data were analyzed with SAS 9.3 (Cary, NC). Reverse cumulative distribution curves were created in Excel to compare the shift in curves from baseline, 1-month, and 1-year post-MMR3.

Results

Enrollment

We contacted 194/200 persons from the longitudinal study; 113 (58.2%) were enrolled, 45 (23.2%) refused, and 36 (18.5%) were ineligible (15 had previously received MMR3 and 21 had other reasons). To achieve adequate sample size, we contacted 1379 (76.8%) of an additional 1795 persons. Of those, 572 (41.4%) were enrolled, 664 (48.2%) refused, and 143 (10.4%) were ineligible (4 had previously received MMR3 and 139 had other reasons) (Supplementary Figure 1).

Baseline serum samples were obtained from 685 enrolled subjects. We excluded 20 (2.9%) Cohort 1 subjects who had medium or high antibody concentrations for all 3 antigens throughout the longitudinal study and were, therefore, not given MMR3. An additional 3 (0.4%) were excluded because they only had baseline samples. There were 662 (96.6%) subjects who received MMR3 and completed the 1-month draw; 617 (92.6%) completed the 1-year draw. Subjects were aged 18-28 years, (mean: 20.8 years, standard deviation: +/-2.1); 294 (44.4%) were male and 649 (98.0%) were self-declared non-Hispanic, white. The mean interval between the second and third MMR doses was 15.8 years (range: 6.7–20.4 years).

MeV neutralizing antibody concentrations pre- and post-MMR3

Of 662 subjects at baseline, 1 (0.2%) was seronegative, 23 (3.5%) had low MeV neutralizing antibody concentrations, 337 (50.9%) had medium concentrations, and 301 (45.5%) had high concentrations (Figure 1). The seronegative subject was a female aged 20 years who received her last MMR dose 18 years prior. At 1-month and 1-year post-MMR3, she had

medium MeV neutralizing antibody concentrations. Of 23 subjects with low baseline antibody concentrations, 1 was negative, 5 were low, 14 were medium, and 3 were high 1-month post-MMR3. One year post-MMR3, 19 of 23 had sera drawn; 5 had low, 14 had medium, and 0 had high MeV neutralizing antibody concentrations.

Overall, at 1-month post-MMR3, 1/662 (0.2%) subjects had no detectable MeV neutralizing antibodies, 6 (0.9%) had low, 256 (38.7%) had medium, and 399 (60.3%) had high neutralizing antibody concentrations. One year post-MMR3, all 617 subjects who returned were positive for MeV neutralizing antibodies: 10 (1.6%) had low, 299 (48.5%) had medium, and 308 (49.9%) had high neutralizing antibody concentrations.

When assessed as a continuous variable, subjects with low or negative baseline MeV neutralizing antibody concentrations were more likely to have low or negative antibody concentrations 1-month and 1-year post-MMR3. Whereas subjects with high baseline concentrations were more likely to have high neutralizing antibody concentrations at 1 month (R^2=0.54, P<0.0001) and 1 year (R^2=0.68, P<0.0001)(Figure 2).

GMCs were significantly different between baseline and 1-month post-MMR3 (727 vs. 1060 mIU/mL, P<0.0001), and between baseline and 1-year post-MMR3 (727 vs. 843 mIU/mL, P<0.05). However, the reverse cumulative distribution curves show the shift in MeV antibody concentrations from baseline to 1-month to 1-year post-MMR3 was minimal (Figure 3).

Four-fold rises

Twenty-one (3.2%) of 662 subjects had ≥4-fold rises from baseline to 1-month post-MMR3, of whom at baseline 1 was seronegative, 8 had low antibody concentrations, and 12 had medium PRN concentrations. Eight (1.3%) of 617 subjects had ≥4-fold rises from baseline to 1-year post-vaccination, of whom at baseline 1 was seronegative, 4 had low concentrations, and 3 had medium PRN concentrations.

Risk factors for negative or low MeV neutralizing antibody concentrations pre- and post-MMR3

The unadjusted odds ratios showed that those who had their first MMR dose at age 12-<15 months ([Odds Ratio] OR:3.47, [Confidence Interval] CI:1.24–9.72, p=0.01) had a higher odds of having lower or negative baseline antibody concentrations compared with those who had their first dose at age ≥15 months, and those who had their second MMR dose <15 years prior had a lower odds of having low or negative baseline MeV neutralizing antibody levels versus those who had their second dose ≥15 years prior (OR:0.22, CI:0.05–0.93, p=0.03) (Table 1).

Of 50 (7.6%) subjects who received their first dose at age 12-<15 months, 5 (10.0%) had negative or low baseline MeV antibody concentrations, versus 19/612 (3.1%) subjects who were vaccinated with their first dose at age ≥15 months. Of 190 (28.7%) subjects who received their second dose <15 years prior, 2 (1.1%) had negative or low baseline MeV antibody concentrations, versus 22/472 (4.7%) subjects who received their second dose ≥15 years prior. In multivariate analysis, having the first MMR dose at 12-<15 months of age

remained a significant risk factor at baseline (OR:3.94,CI:1.37–11.30, p=0.01), and those who had their second MMR dose <15 years prior continued to have a lower odds of having low or negative MeV antibody concentrations (OR:0.18,CI:0.04–0.80, p=0.02).

At 1-month post-MMR3, there were no significant risk factors for having low or negative MeV antibody concentrations when adjusting the chi-squared analysis by controlling for baseline GMCs. In multivariate analysis, a significant risk factor for negative or low MeV antibody concentrations 1-month post-MMR3 was whether a subject had low or negative baseline MeV antibody concentrations (OR:195.8,CI:21.8–>999.9, p<0.0001).

At 1-year post-MMR3, females had a lower odds of having low or negative MeV antibodies (OR:0.34, CI:0.06–1.80, p=0.04) versus males when adjusting the chi-squared analysis by controlling for baseline GMCs. In multivariate analysis at 1-year post-MMR3, being female remained protective (OR:0.19, CI:0.04–0.99, p=0.049) and low or negative baseline MeV neutralizing antibody concentrations were a risk factor (OR:54.95, CI:10.90–277.14, p<0.0001).

Cell-mediated immunity

Of 60 CMI sub-study subjects, 7 were excluded (6 did not receive MMR3 and 1 had insufficient blood drawn); 1 (1.9%) of 53 subjects missed the 1-month draw and 6 (11.3%) missed the 1-year draw. MeV lysate stimulation results were missing for an additional 2 subjects at baseline and 1 subject at 1 month. Positive controls were positive for all CMI subjects, indicating viable cells capable of spot-formation. The unstimulated T-cell mean spot-forming cells (s.f.c.)/million PBMCs was 0.1±0.1 at baseline, 0.1±0.1 at 1-month, and 0.2±0.2 at 1-year post-MMR3.

Of 53 CMI sub-study subjects, none had negative baseline MeV neutralizing antibody concentrations and 5 (9.4%) had low baseline concentrations, of whom, 1 had a positive baseline CMI response (≥20 s.f.c./million PBMCs) to peptide stimulation and none had a positive baseline response to lysate stimulation. Only 13/48 (27.1%) subjects with medium or high baseline MeV neutralizing antibodies had a positive baseline CMI result by peptide stimulation and 7/46 (15.2%) subjects had a positive baseline CMI result by lysate stimulation.

The spot-forming cells/million PBMCs were generally higher with peptide stimulation compared to lysate stimulation. At baseline, the MeV peptide mean spot-forming cells was 19.6±9.3 s.f.c./million PBMCs compared to 11.9±7.2 s.f.c./million PBMCs by lysate stimulation. At 1-month post-MMR3, the MeV peptide mean spot-forming cells was 18.5±7.6 s.f.c./million PBMCs, with 13/52 (25.0%) specimens positive by peptide stimulation, compared with 7.3±2.9 s.f.c./million PBMCs, with 5/51 (9.8%) specimens positive by lysate stimulation. At 1-year post-MMR3, the mean spot-forming cells was 29.7±15.9 s.f.c./million PBMCs, with 14/47 (29.8%) positive by peptide stimulation, compared with 10.3±6.4 s.f.c./million PBMCs, with 7/47 (14.9%) specimens positive by lysate stimulation.

Baseline MeV antibody concentrations did not correlate with baseline MeV T-cell responses to peptide stimulation (R^2=0.002, p=0.73) or lysate stimulation (R^2=0.0008, p=0.85)(Figure 4). MeV antibody concentrations at 1-month post-MMR3 correlated with MeV T-cell responses at 1 month by peptide stimulation (R^2=0.30, p<0.0001), but the correlation did not remain after removing the 2 outliers (R^2=0.05, p=0.13). There was no correlation between MeV antibody concentrations and lysate stimulation at 1 month (R^2=0.001, p=0.80), but after removing the outlier, there was a correlation (R^2=0.14, p=0.007). At 1-year post-MMR3, there was a significant correlation between MeV antibody concentrations and MeV T-cell responses by peptide stimulation (R^2=0.17, p=0.004), but no correlation by lysate stimulation (R^2=0.06, p=0.09).

Avidity

Overall, 38/59 (64.4%) subjects evaluated had MeV antibodies with high avidity at baseline (Table 2), including 7/24 (29.2%) subjects with low MeV antibody concentrations at baseline. The avidity results did not correlate with MeV antibody concentrations at baseline (R^2=0.07, p=0.07), 1-month (R^2=0.01, p=0.50) or 1-year (R^2=0.02, p=0.31) post-MMR3 (Figure 5).

Discussion

A modest but significant boost in MeV geometric mean neutralizing antibody concentrations occurred 1-month and 1-year post-MMR3 compared with baseline. However, almost all subjects were MeV seropositive prior to receiving MMR3, and subjects' antibody levels returned to near-baseline 1-year post-vaccination. Nonetheless, for the 24 (3.6%) subjects with low or negative baseline MeV antibody concentrations, 18 (75%) moved into medium or high categories at 1 month, of whom, 12 (67%) remained medium or high at 1 year. Among the subsets tested for CMI and avidity, we did not find compelling qualitative data to support a routine third dose of MMR vaccine.

The second MMR vaccine dose was recommended to provide measles immunity to individuals who failed to respond to the first dose[19]; two doses are 97% effective at preventing measles[20, 21]. Although 95% of vaccinated persons have detectable MeV antibodies 10-15 years after the second MMR dose[10, 22], waning immunity occurs after two doses[10][23], and two-dose failures have been documented[24].

Having a low or negative baseline MeV antibody concentration was the biggest risk factor for low or negative antibody concentrations 1-month and 1-year post-MMR3, suggesting that inherent biology may be partially responsible for a person's measles antibody levels[10, 25]. Although our results concurred with other reports that timing of administration of the first and second MMR doses significantly affected MeV antibody levels later in life[26, 27], our findings represented only a small proportion of the study population (only 50 [7.6%] subjects received their first dose at age 12-<15 months).

Most subjects did not have a positive CMI result at baseline, despite the majority of subjects having medium or high baseline MeV antibody concentrations. Nonetheless, low-levels of spot-forming cells generally occurred for most specimens after stimulation, suggesting T-

cell memory. However, this was not greatly boosted by MMR3. After removing outliers, we found mixed results at 1-month post-MMR3 with no correlation between MeV antibody response and MeV T-cell response by peptide stimulation, but a significant correlation by lysate stimulation. Although we did find a significant correlation between CMI response by peptide stimulation and MeV antibody concentration at 1-year post-MMR3, <1/3 of subjects had positive cell-mediated responses by peptide stimulation and even fewer had positive responses by lysate stimulation at 1 year. These findings could have been because transient increases in circulating MeV-specific T-cells were missed due to specimen collection timing (antigen-stimulated T-cell responses typically peak 2 weeks post-vaccination[28], whereas samples were taken 1-month and 1-year post-MMR3). Other studies assessing antibody and T-cell responses after a second MMR dose showed no correlation[29, 30]. Another possibility is that numbers of T-cells producing IFN-γ in response to MeV did not increase post-MMR3 due to lack of infection by vaccine virus in the presence of neutralizing antibodies.

The MeV IgG avidity results did not correlate with neutralization results. Most subjects reached an IgG avidity plateau. Typically, IgG avidity maturation for measles shifts from low to high 4 months following immunization or infection[16] which might negate additional increases in antibody avidity with subsequent doses of measles-containing vaccine. Nonetheless, only 29% of subjects with low baseline MeV neutralizing antibody concentrations had high avidity results at baseline. It could be interpreted that subjects with poor antibody response and intermediate avidity results were potentially susceptible prior to revaccination. However, the avidity results are an average of the measles IgG and should be interpreted cautiously, since whole MeV is used as the target antigen in the avidity assay, whereas the neutralization assay measures antibodies that bind MeV surface glycoproteins[31].

Our study had additional limitations. Subjects were not representative of the U.S. population. Selection bias may have occurred in Cohort 1, because MMR3 was only offered to those who had a low or negative measles, mumps, or rubella antibody concentration during the longitudinal study.

Overall, MeV neutralizing antibody concentrations initially increased after MMR3 but declined to near-baseline levels one year later. Although our findings showed that MMR3 increased antibody levels for the small percentage of subjects with low MeV neutralizing antibody concentration levels who were on the cusp of protection, the CMI and avidity results in the subset tested showed that MMR3 did not result in substantial improvements in the quality of the immune response. While a third MMR dose may successfully immunize the rare individual who failed to respond after two doses, MMR3 is unlikely to solve the problem of waning immunity in the U.S. A better strategy for maintaining U.S. measles elimination would be to improve vaccination coverage in pockets of unvaccinated individuals and maintain high two-dose coverage nationally with the current two-dose MMR recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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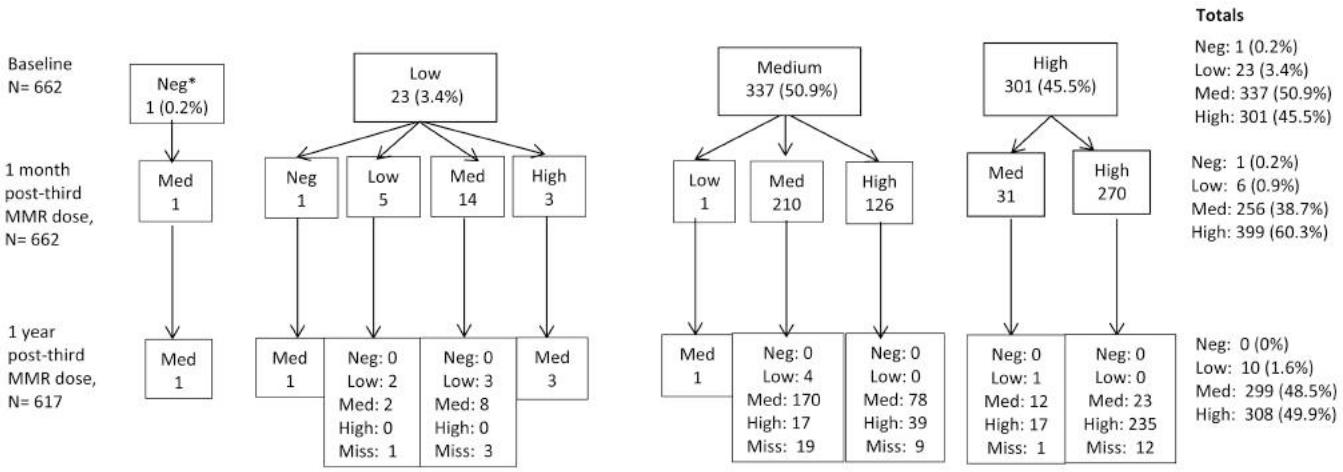

Figure 1.

Flow chart of measles virus neutralizing antibody concentration levels at baseline, 1 month, and 1 year following a third dose of MMR vaccine.

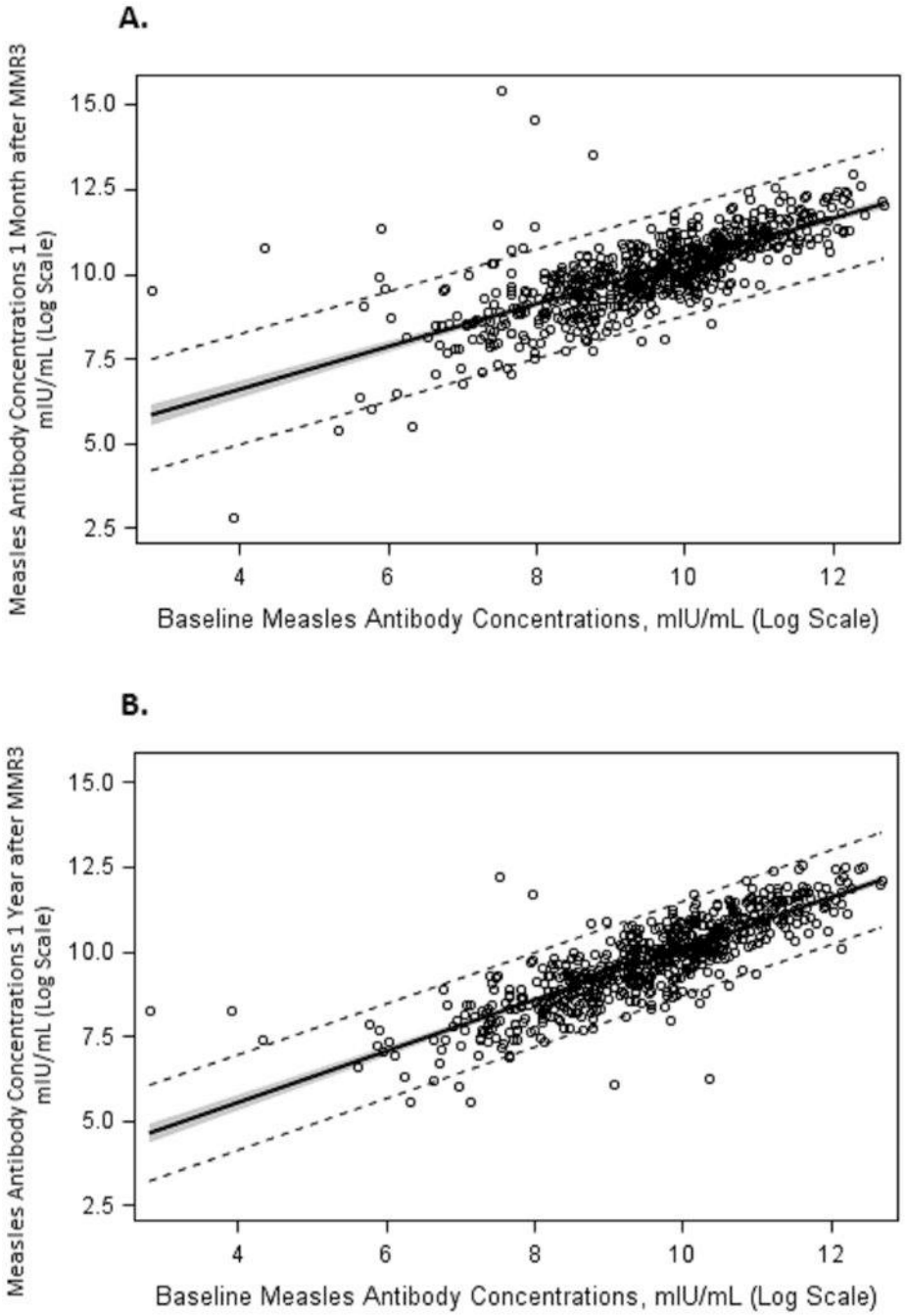

Figure 2.

A. Comparison of individual measles antibody concentration levels at baseline and 1 month following a third dose of MMR vaccine. R^2=0.54, p<0.0001. **B.** Comparison of individual measles antibody concentration levels at baseline and 1 year following a third dose of MMR vaccine. R^2=0.68, p<0.0001. For both figures, data points are represented by circles and they show the comparison result for each subject. The dark solid line represents the best-fit of the comparison. The light shading around the line represents the 95% confidence limits. The dotted lines represent 95% prediction limits.

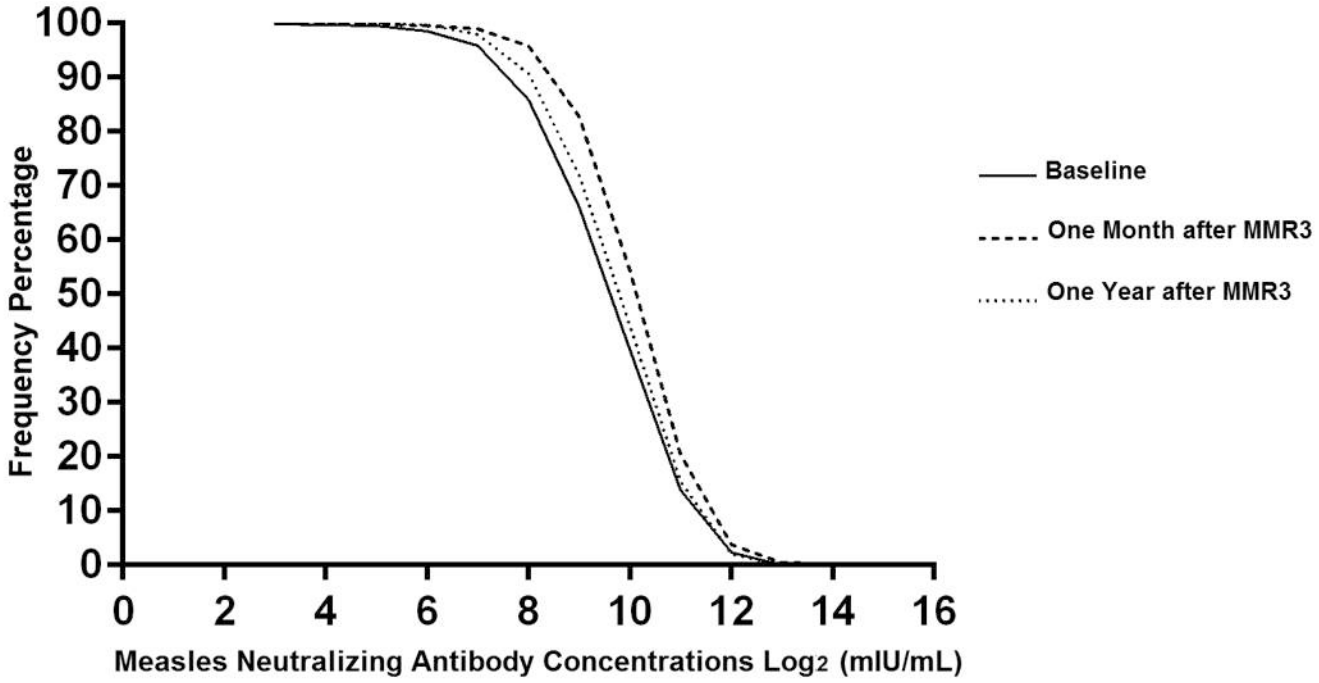

Figure 3.

Reverse cumulative distribution curve by percent of subjects who had measles virus neutralizing antibody concentrations at baseline, 1 month, and 1 year following a third dose of MMR vaccine.

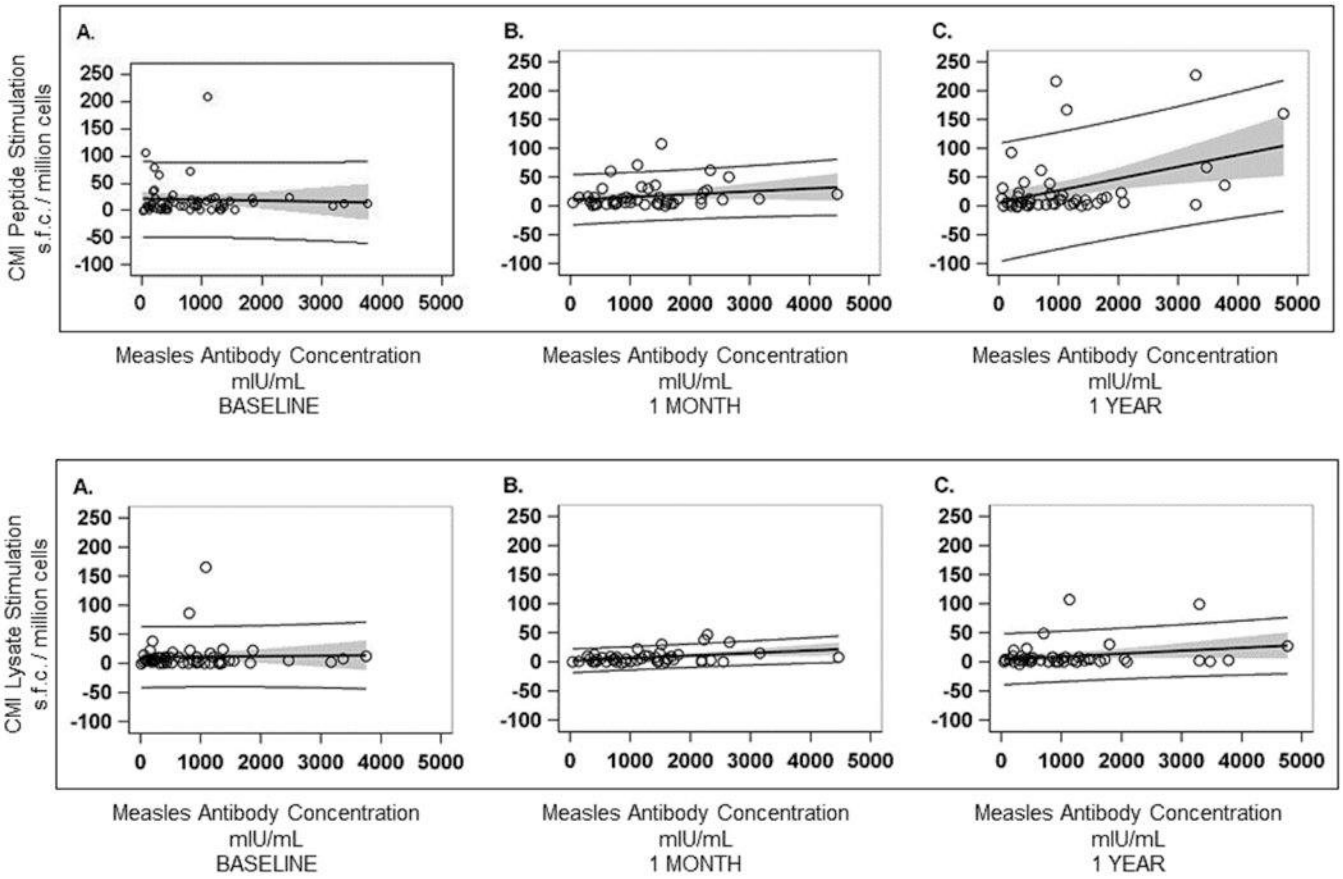

Figure 4.

Figure 4a: A. Comparison of baseline measles virus neutralizing antibody concentration levels (mIU/mL) and baseline measles virus T-cell response to measles virus peptide stimulation (spot-forming cells [s.f.c.]/ million cells), n= 53. R^2= 0.002, p=0.73. **B.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus T-cell response to measles virus peptide stimulation (s.f.c./ million cells) 1 month after receiving a third dose of MMR vaccine, n=50. R^2=0.05, p=0.13 (Note that 2 outliers were removed from the figure). When the 2 outliers were included, the results were: n=52. R^2= 0.30, p<0.0001, and the x-axis on the graph extended beyond 40,000 mIU/mL. **C.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus T-cell response to measles virus peptide stimulation (s.f.c./ million cells) 1 year after receiving a third dose of MMR vaccine, n=47. R^2= 0.17, p=0.004. For all figures, data points are represented by circles and they show the comparison result for each subject. The dark solid line represents the best-fit of the comparison. The light shading around the line represents the 95% confidence limits. The dotted lines represent 95% prediction limits.

Figure 4b: A. Comparison of baseline measles virus neutralizing antibody concentration levels (mIU/mL) and baseline measles virus T-cell response to measles virus lysate stimulation (s.f.c./ million cells), n=51. R^2= 0.0008, p=0.85. **B.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus T-cell response to measles virus lysate stimulation (s.f.c./ million cells) 1 month after receiving a third dose of MMR vaccine, n=49. R^2= 0.14, p=0.007 (Note that 1 outlier was removed from the figure;

the other outlier was already missing because of insufficient blood drawn to analyze the measles virus lysate response). When the outlier was included, the results were: n=50. R^2=0.001, p=0.80, and the x-axis on the graph extended beyond 40,000 mIU/mL. **C.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus T-cell response to measles virus lysate stimulation (s.f.c./ million cells) 1 year after receiving a third dose of MMR vaccine, n=47. R^2=0.06, p=0.09. For all figures, data points are represented by circles and they show the comparison result for each subject. The dark solid line represents the best-fit of the comparison. The light shading around the line represents the 95% confidence limits. The dotted lines represent 95% prediction limits.

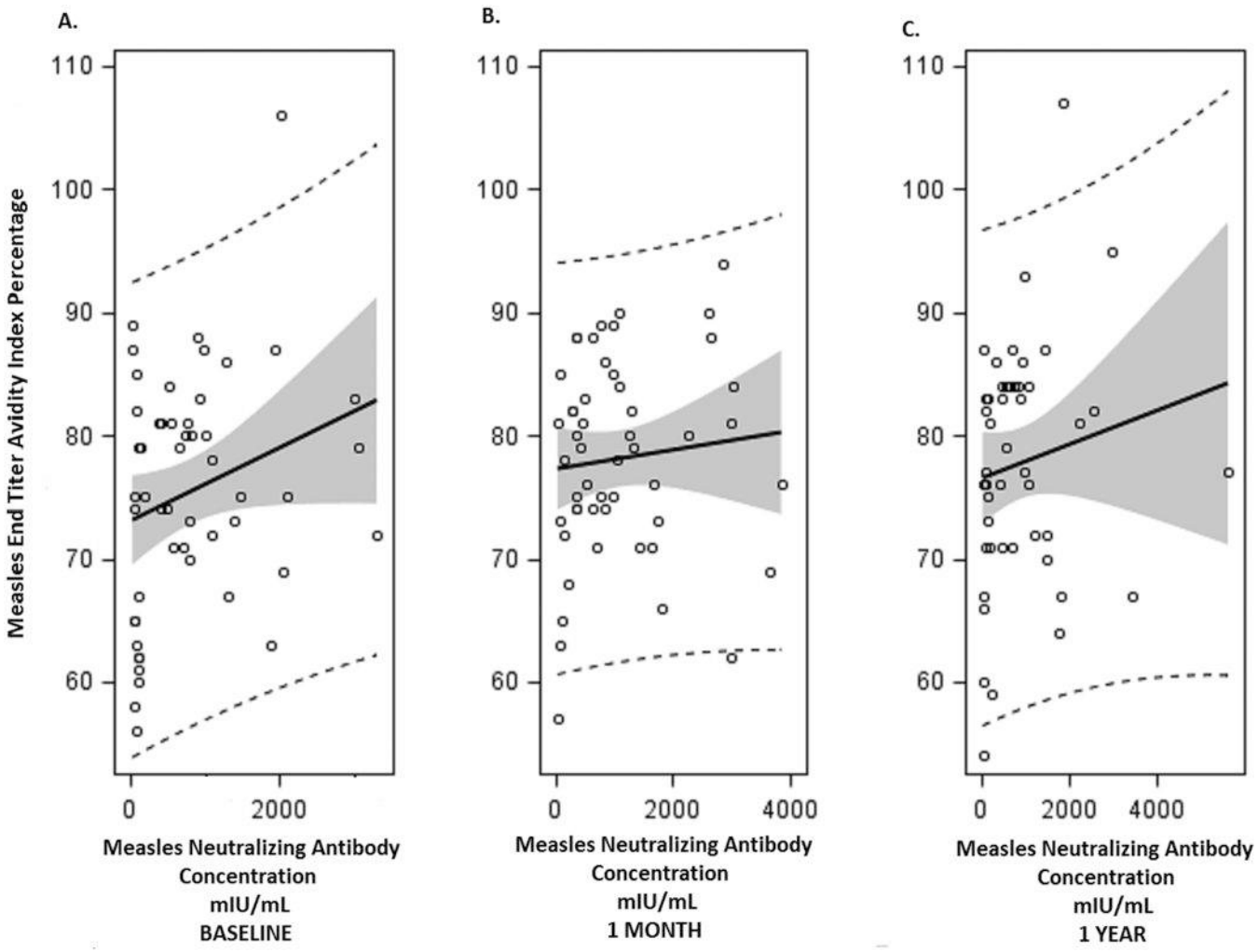

Figure 5.

A. Comparison of baseline measles virus neutralizing antibody concentration levels (mIU/mL) and baseline measles virus antibody avidity levels (end titer avidity index percentage [etAI%]), n= 51. R^2=0.07, p=0.07. **B.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus antibody avidity levels (etAI%) 1 month after receiving a third dose of MMR vaccine, n=51. R^2=0.01, p=0.50. **C.** Comparison of measles virus neutralizing antibody concentration levels (mIU/mL) and measles virus antibody avidity levels (etAI%) 1 year after receiving a third dose of MMR vaccine, n=47. R^2=0.02, p=0.31. For all figures, data points are represented by circles and they show the comparison result for each subject. The dark solid line represents the best-fit of the comparison. The light shading around the line represents the 95% confidence limits. The dotted lines represent 95% prediction limits.

Table 1

Risk factors for negative or low measles neutralizing antibody concentrations at baseline, 1 month, and 1 year after receiving a third dose of measles-mumps-rubella (MMR) vaccine

	Baseline N= 662				1 Month Post-MMR3 N= 662				1 Year Post-MMR3 N= 617			
	Unadjusted OR (95% CI)[1]	p-value[2]	Multivariate OR (95% CI)	Multivariate p-value	Adjusted OR[3] (95% CI)	p-value	Multivariate OR (95% CI)	Multivariate p-value	Adjusted OR (95% CI)	p-value	Multivariate OR (95% CI)	Multivariate p-value
Sex												
Female	0.56 (0.24-1.28)	0.16	0.53 (0.23- 1.23)	0.14	0.22 (0.03-1.45)	0.08	0.16 (0.02- 1.48)	0.11	0.34 (0.06-1.80)	0.04*	0.19 (0.04-0.99)	0.049*
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Age at 1st MMR dose												
12- <15 months	3.47 (1.24- 9.72)	0.01*	3.94 (1.37- 11.30)	0.01*	0.83 (0.09-7.57)	0.15	—	—	1.37 (0.19-9.74)	0.90	—	—
≥15 months	Reference		Reference		Reference				Reference			
Time since 2nd MMR dose												
<15 years	0.22 (0.05- 0.93)	0.03*	0.18 (0.04-0.80)	0.02*	1.75 (0.20-15.29)	0.79	—	—	2.38 (0.49-11.61)	0.26	2.64 (0.50-14.04)	0.25
≥15 years	Reference		Reference		Reference				Reference		Reference	
Baseline antibody concentrations												
<121mIU/mL	N.A.[4]	N.A.	N.A.	N.A.	N.A.	N.A.	195.8 (21.8- >999.9)	<0.0001*	N.A.	N.A.	54.95 (10.90- 277.14)	<0.0001*
≥121 mIU/mL	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Reference		N.A.	N.A.	Reference	

[1] OR= Odds Ratio, CI= Confidence Interval

[2] Statistical Significance at $p<0.05$ is represented by an asterisk.

[3] Adjusted by controlling for baseline measles antibody concentrations.

[4] N. A. means not applicable. (By default, baseline measles neutralizing antibody concentrations could not be a risk factor at baseline. We were also unable to assess baseline neutralizing antibody concentrations at 1 month or 1 year post-MMR3 during univariate analysis because this was the variable we adjusted for to account for the statistical differences between Cohort 1 and Cohort 2. This adjustment allowed us to combine the cohorts during the analysis to increase our power. However, it is of note that the *unadjusted* OR's for baseline neutralizing antibody concentrations were highly significant at 1-month and 1-year post-MMR3.)

Table 2

Measles virus neutralizing antibody geometric mean concentrations by plaque reduction neutralization in correlation with measles virus antibody avidity levels by end titer avidity index percentages at baseline, 1 month, and 1 year after receiving a third dose of measles-mumps-rubella (MMR) vaccine

		BASELINE						1 MONTH POST-MMR3						1 YEAR POST-MMR3[1]						
		Measles Neutralizing Antibody Concentrations	Avidity Index					Measles Neutralizing Antibody Concentrations	Avidity Index					Measles Neutralizing Antibody Concentrations	Avidity Index					
Quartile[2]	n	GMC (mIU/mL)[3]	Mean[4]	Neg[5] (%)	Low (%)	Int (%)	High (%)	GMC (mIU/mL)	Mean	Neg (%)	Low (%)	Int (%)	High (%)	GMC (mIU/mL)	Mean	Neg (%)	Low (%)	Int (%)	High (%)	Miss (%)
1	27	69	71	8 (29.6)	0	10 (37.0)	9 (33.3)	249	75	2 (7.4)	0	5 (18.5)	20 (74.1)	143	73	1 (3.7)	0	6 (22.2)	16 (59.3)	4 (14.8)
2	11	556	78	0	0	0	11 (100)	606	81	0	0	0	11 (100)	466	80	0	0	0	10 (90.9)	1 (9.1)
3	11	990	79	0	0	1 (9.1)	10 (90.9)	1222	78	0	0	0	11 (100)	750	79	0	0	1 (9.1)	10 (90.9)	0
4	10	2130	78	0	0	2 (20)	8 (80)	2435	78	0	0	2 (20)	8 (80)	2225	81	0	0	3 (30)	7 (70)	0
Total	59	299	75	8	0	13	38	582	77	2	0	7	50	415	77	1	0	10	43	5

[1] Five subjects were missing data at one year.

[2] Quartiles were established based on baseline plaque reduction neutralization measles antibody concentration. Subjects with the lowest baseline measles neutralizing antibody concentrations were placed in Quartile 1 and subjects with the highest baseline measles neutralizing antibody concentrations were placed in Quartile 4. The number of subjects selected from Quartile 1 is more than from the other 3 quartiles, because we tested the avidity on every subject who had a negative or low measles neutralizing antibody concentration during at least 1 time point. Of note, 24 of 27 subjects in Quartile 1 had a negative or low baseline measles antibody concentration; the remaining 3 subjects in Quartile 1 had a medium neutralizing antibody concentration at baseline (but were still in the lowest quartile).

[3] Abbreviations used: GMC means Geometric Mean Concentration, Neg means negative, Int means intermediate, Miss means missing

[4] The mean avidity index excludes the negative specimens by Captia Measles IgG enzyme immunoassay since avidity could not be run on those specimens.

[5] Negative means that at 1:21 dilution, the specimen had undetectable IgG by the Captia Measles IgG enzyme immunoassay.

Measles Outbreak Traced to Fully Vaccinated Patient for First Time

By Nsikan Akpan | Apr. 11, 2014 , 12:00 PM

Get the measles vaccine, and you won't get the measles—or give it to anyone else. Right? Well, not always. A person fully vaccinated against measles has contracted the disease and passed it on to others. The startling case study contradicts received wisdom about the vaccine and suggests that a recent swell of measles outbreaks in developed nations could mean more illnesses even among the vaccinated.

When it comes to the measles vaccine, two shots are better than one. Most people in the United States are initially vaccinated against the virus shortly after their first birthday and return for a booster shot as a toddler. Less than 1% of people who get both shots will contract the potentially lethal skin and respiratory infection. And even if a fully vaccinated person does become infected—a rare situation known as "vaccine failure"—they weren't thought to be contagious.

That's why a fully vaccinated 22-year-old theater employee in New York City who developed the measles in 2011 was released without hospitalization or quarantine. But like Typhoid Mary, this patient turned out to be unwittingly contagious. Ultimately, she **transmitted the measles to four other people**, according to a recent report in *Clinical Infectious Diseases* that tracked symptoms in the 88 people with whom "Measles Mary" interacted while she was sick. Surprisingly, two of the secondary patients had been fully vaccinated. And although the other two had no record of receiving the vaccine, they both showed signs of previous measles exposure that should have conferred immunity.

A closer look at the blood samples taken during her treatment revealed how the immune defenses of Measles Mary broke down. As a first line of defense against the measles and other microbes, humans rely on a natural buttress of IgM antibodies. Like a wooden shield, they offer some protection from microbial assaults but aren't impenetrable. The vaccine (or a case of the measles) prompts the body to supplement this primary buffer with a stronger armor of IgG antibodies, some of which are able to neutralize the measles virus so it can't invade cells or spread to other patients. This secondary immune response was presumed to last for decades.

By analyzing her blood, the researchers found that Measles Mary mounted an IgM defense, as if she had never been vaccinated. Her blood also contained a potent arsenal of IgG antibodies, but a closer look revealed that none of these IgG antibodies were actually capable of neutralizing the measles virus. It seemed that her vaccine-given immunity had waned.

Although public health officials have assumed that measles immunity lasts forever, the case of Measles Mary highlights the reality that "the actual duration [of immunity] following infection or vaccination is unclear," says Jennifer Rosen, who led the investigation as director of epidemiology and surveillance at the New York City Bureau of Immunization. The possibility of waning immunity is particularly worrisome as the virus surfaces in major U.S. hubs like **Boston**, **Seattle**, New York, and the **Los Angeles area**. Rosen doesn't believe this single case merits a change in vaccination strategy—for example, giving adults booster shots—but she says that more regular surveillance to assess the strength of people's measles immunity is warranted.

If it turns out that vaccinated people lose their immunity as they get older, that could leave them vulnerable to measles outbreaks seeded by unvaccinated people—which are increasingly common in the United States and other developed countries. Even a vaccine failure rate of 3% to 5% could devastate a high school with a few thousand students, says Robert Jacobson, director of clinical studies for the Mayo Clinic's Vaccine Research Group in Rochester, Minnesota, who wasn't involved with the study. Still, he says, "The most important 'vaccine failure' with measles happens when people refuse the vaccine in the first place."

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Vaccine development needs a booster shot

by Liz Szabo, USA TODAY

Updated 9/21/2012 6:28 PM

A new study, which finds that immunity from the whooping cough vaccine fades sharply over time, underscores the urgent need to develop new vaccines and consider additional booster shots for children, health experts say.

Authors say the study in today's New England Journal of Medicine helps explain part of the resurgence in whooping cough, or pertussis, which has sickened more than 26,000 this year -- the largest outbreak in more than 50 years.

Ted S. Warren, AP

Nurses Fatima Guillen, left, and Fran Wendt, right, give Kimberly Magdeleno a whooping cough booster shot. She is held by her mother, Claudia Solorio, May 3 in Tacoma, Wash.

The current vaccine, in use since the 1990s, doesn't protect people as long as previously believed, losing 42% of its effectiveness with each passing year, says author Nicola Klein, co-director of the Kaiser Permanente Vaccine Study Center in Oakland, Calif. So even some fully vaccinated children -- who have received all five doses recommended by age 4 to 6 -- would still be vulnerable to the disease by age 10.

The Centers for Disease Control and Prevention has reached similar conclusions, says Tom Clark, a CDC epidemiologist specializing in whooping cough. While the whooping cough vaccine protects about 98% of children in the first year, it protects only about 70% five years later, Clark says.

"We know the short-term protection is very good," Clark says. "But the protection is wearing off and that is the problem."

The findings shouldn't cause parents to stop vaccinating their children, however, Klein says. Even an imperfect vaccine is better than no vaccine, she says.

Whooping cough is typically more severe among unvaccinated children than among those who've had at least some of their shots, Clark says. Unvaccinated patients also tend to be sick longer and are often more contagious.

Doctors say they're most concerned about infants.

Newborns too young to be fully vaccinated -- whose airways can quickly swell shut -- are the most likely to die from whooping cough, says C. Mary Healy, a pediatric infectious-disease specialist at Texas Children's Hospital in Houston. Eleven of the 13 deaths from whooping cough this year were in infants; the other two deaths were in toddlers, according to the CDC.

Given the vaccine's limitations, Healy says, it's more important than ever to create a "cocoon" of protection around babies by vaccinating everyone around them. About 75% of babies with whooping cough contract the bacteria from a household member, such as a sibling, parent or grandparent.

"If a vaccine does not have 100% protection that's lifelong, then it's even more important that we have â??herd immunity' to stop the virus from circulating into the community," Healy says. "That's an unacceptable level of infant deaths, in the 21st century, in the richest country in the world."

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Ultimately, the country needs a better vaccine, says James Cherry of the University of California-Los Angeles.

But "the business of coming up with a better vaccine is not going to be a quick fix," says Edgar Marcuse, a professor of pediatrics at Seattle Children's Hospital. "We still don't fully understand immunity from pertussis."

For example, even those naturally infected with whooping cough don't develop life-long immunity, and can come down with the bacterial infection again in 10 years or less, Marcuse says.

Infection rates today, in spite of the current outbreak, are 23 times lower than in the pre-vaccine days, Cherry says. In the pre-vaccine era, up to 270,000 Americans became sick with whooping cough each year, known as the "100-day cough," and up to 10,000 died, Klein says.

The whooping cough vaccine, available beginning in the 1940s, cut infection rates dramatically. That vaccine, known as DTP, was associated with more reactions than the current vaccine.

Most of those reactions were mild, such as increased crying or sore arms and legs. Some children developed benign -- but frightening -- fever-related seizures, which occured in about one in every 1,750 doses, says Gregory Poland, a professor of infectious disease at the Mayo Clinic in Minnesota.

An analysis by the Institute of Medicine found that DTP could cause rare but more serious problems: a dangerous brain inflammation, occurring in 1 to 10 per million doses; and an unusual, shock-like state, occurring 3 to 300 times per million doses, Poland says.

Whooping cough rates began rising after the current vaccine, known as Dtap, came into widespread use in the late 1990s, Cherry says.

The experience with DTP had far-reaching effects.

Although multiple studies show that today's vaccines are safe, many parents remain nervous about immunizations, delaying or skipping some of their children's shots -- a trend that has helped to fuel outbreaks of a number of infectious diseases, says Tom Belhorn, a pediatric infectious disease specialist at the University of North Carolina-Chapel Hill.

Until researchers produce a better vaccine -- with long-lasting immunity -- health experts could consider changing the vaccine schedule to get the most protection possible from the current shot, Poland says. Researchers would have to first carefully test the safety of any changes, he says, to avoid causing bad reactions.

For example, the CDC's Advisory Committee on Immunization Practices could consider adding an additional booster shot for teens -- who have made up a large number of whooping cough patients -- at around 16 or 17, Clark says. There's not much room in the current vaccine schedule to add extra shots for little kids, and there are currently no whooping cough vaccines licensed for children ages 7 to 10.

To better protect infants, Cherry says, researchers could test the safety of giving babies their first three vaccinations by age 3 months, instead of 6 months. Vaccinating pregnant women also helps protect babies for the first month or two of life, he says.

Posted 9/21/2012 6:28 PM | Updated 9/21/2012 6:28 PM

ORIGINAL ARTICLE

Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children

Nicola P. Klein, M.D., Ph.D., Joan Bartlett, M.P.H., M.P.P., Ali Rowhani-Rahbar, M.D., M.P.H., Ph.D., Bruce Fireman, M.A., and Roger Baxter, M.D.

ABSTRACT

BACKGROUND

In the United States, children receive five doses of diphtheria, tetanus, and acellular pertussis (DTaP) vaccine before 7 years of age. The duration of protection after five doses of DTaP is unknown.

METHODS

We assessed the risk of pertussis in children in California relative to the time since the fifth dose of DTaP from 2006 to 2011. This period included a large outbreak in 2010. We conducted a case–control study involving members of Kaiser Permanente Northern California who were vaccinated with DTaP at 47 to 84 months of age. We compared children with pertussis confirmed by a positive polymerase-chain-reaction (PCR) assay with two sets of controls: those who were PCR-negative for pertussis and closely matched controls from the general population of health-plan members. We used logistic regression to examine the risk of pertussis in relation to the duration of time since the fifth DTaP dose. Children who received whole-cell pertussis vaccine during infancy or who received any pertussis-containing vaccine after their fifth dose of DTaP were excluded.

RESULTS

We compared 277 children, 4 to 12 years of age, who were PCR-positive for pertussis with 3318 PCR-negative controls and 6086 matched controls. PCR-positive children were more likely to have received the fifth DTaP dose earlier than PCR-negative controls ($P<0.001$) or matched controls ($P=0.005$). Comparison with PCR-negative controls yielded an odds ratio of 1.42 (95% confidence interval, 1.21 to 1.66), indicating that after the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year.

CONCLUSIONS

Protection against pertussis waned during the 5 years after the fifth dose of DTaP. (Funded by Kaiser Permanente).

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Pertussis is a worldwide, cyclic infection. Before widespread vaccine coverage, up to 270,000 cases of pertussis were diagnosed in the United States annually, with as many as 10,000 deaths per year, predominantly among infants.[1] Pertussis vaccines prepared from whole *Bordetella pertussis* organisms were available from the 1940s through the 1990s, protecting infants who were 2 months of age or older.[1]

Whole-cell pertussis vaccines, when administered as part of a combined diphtheria, tetanus toxoids, and pertussis vaccine, were effective, but they were associated with adverse effects[2]; this led to the development of the diphtheria–tetanus–acellular pertussis (DTaP) vaccine.[3] Beginning in the early 1990s, the United States started to make the transition from whole-cell pertussis vaccines to DTaP, and by the late 1990s, DTaP was being used for all five recommended doses.[4] DTaP is now used in many countries.

Pertussis vaccination resulted in a marked decrease in the incidence of disease,[1,5] with diagnosed cases of pertussis reaching a nadir in 1976. However, since the 1980s, despite high levels of vaccine coverage in children, outbreaks of *B. pertussis* have occurred every 3 to 5 years, with an increase in the peak incidence with each successive outbreak.[6] The reasons for the ongoing outbreaks are not well understood and are probably multifactorial.[7-9]

Receipt of five doses of DTaP is mandatory for school entry in many states, including California, with the fifth dose usually administered in children between 4 and 6 years of age. Nonetheless, in 2010, California had a large pertussis outbreak,[10] with the highest incidence rates since 1958. After this outbreak, we sought to assess and quantify the waning of DTaP protection against pertussis over time in a highly vaccinated population of school-age children who had received only DTaP rather than whole-cell pertussis vaccines.

Methods

Databases

Kaiser Permanente Northern California is an integrated health care delivery system that provides care to approximately 3.2 million members. It operates 49 medical clinics and 19 hospitals, including pharmacies and laboratories. Databases capture vaccinations and laboratory tests, as well as inpatient, emergency department, and outpatient diagnoses.

Data on race or ethnic group were available in the medical record for approximately 75% of members. For the remainder, we imputed race or ethnic group with the use of the RAND Bayesian Imputed Surname Geocoding algorithm.[11] In members for whom we imputed values for missing data on race or ethnic group (American Indian or Alaska Native, Asian or Pacific Islander, black, Hispanic, or white), the probabilities summed to 1; a single value was not assigned. Microbiologic testing was centralized in a single laboratory that has identified *B. pertussis* and *B. parapertussis* with the use of polymerase-chain-reaction (PCR) assays since 2005. PCR kits were supplied by Roche from December 2005 through May 2009 and by Cepheid beginning in May 2009.

Kaiser Permanente Northern California first introduced DTaP for the fifth dose of pertussis vaccine in 1991 and completed the transition from whole-cell pertussis vaccines to DTaP for all five doses by 1999.

Study Oversight

The institutional review board of Kaiser Permanente Northern California approved this study and waived the requirement for informed consent.

All authors vouch for the completeness and accuracy of the data and analyses presented.

Study Design and Population

In this case–control study, we selected case patients and controls for the primary analysis from all Kaiser Permanente Northern California members who received a pertussis PCR test result between January 2006 and June 2011. PCR results were positive for *B. pertussis*, positive for *B. parapertussis*, or negative for both.

Potential case patients were all children who were positive for pertussis and negative for parapertussis on PCR testing during the study period and who received a dose of DTaP between the ages of 47 and 84 months (this dose was considered the fifth DTaP dose) before the PCR test was performed. We excluded persons born before 1999 (to limit the analyses to children who exclusively received DTaP vaccines) and persons who received a vaccine with reduced pertussis-antigen content (Tdap) or any pertussis-containing vaccine after the fifth dose but before the PCR test. We also ex-

cluded children in whom a PCR test was performed within 2 weeks after receipt of the fifth DTaP dose and children who were not members of Kaiser Permanente Northern California for more than 3 months between the fifth dose of DTaP and the PCR test.

The study included two control groups. The first group consisted of children who were PCR-negative for both pertussis and parapertussis and who received a fifth dose of DTaP before receiving a negative test result (the PCR-negative controls). The second group consisted of health-plan members who were matched to each PCR-positive child (the matched controls). Matched controls were the same sex and age (year and quarter of birth), of the same race or ethnic group (with seven groups defined: six for available data on race or ethnic group and one for imputed data on race or ethnic group, to account for missing data), and attended the same medical clinic (of 49 clinics) as the PCR-positive children and were members on the date of the PCR test in the PCR-positive children (the anchor date). We retained all matched controls (with no sampling) who received a fifth dose of DTaP before their anchor date. We applied the same exclusion criteria described above to both control groups and excluded children as controls if they had previously tested positive for pertussis.

The final study population consisted of children who were 4 to 12 years of age, 58% of whom were continuously enrolled in the health plan between 1 month of age and either the date on which PCR was performed or the seventh birthday. In this subgroup, the rate of vaccine coverage with five doses of DTaP was 99% and did not differ between PCR-positive case patients and PCR-negative controls.

STATISTICAL ANALYSIS

We assessed the waning of immunity after DTaP vaccination using two analyses. The primary analysis compared PCR-positive case patients with PCR-negative controls, and the secondary analysis compared PCR-positive case patients with matched controls. We considered the comparison with PCR-negative controls to be primary because it minimized the potential biases associated with the general propensity to use health care and the specific propensity of parents and physicians to test for pertussis.

We fit conditional logistic-regression models to estimate the effect of each additional year after receipt of the fifth DTaP dose on the odds of a positive PCR test for pertussis. For the primary analysis, we conditioned the logistic model on blocks of calendar time (yearly from 2006 through 2009 before the epidemic, quarterly for the first quarter of 2010, and then monthly thereafter during the epidemic). We included covariates to adjust for age (4 to <7, 7 to <10, and 10 to 12 years), sex, medical clinic (49 clinics aggregated into 12 service areas), and race or ethnic group (in children for whom data were available or from imputed probabilities). For the secondary analysis, we conditioned the logistic model on all the matching variables (PCR test date, quarter of birth, sex, race or ethnic group, and medical clinic), and we used imputed probabilities of race or ethnic group as covariates for additional adjustment for the strata of children with imputed data. For all analyses, we used SAS software, version 9.2 (SAS Institute).

RESULTS

INCIDENCE OF PERTUSSIS

From January 2006 through June 2011, a total of 27,912 PCR assays for *B. pertussis* were performed in members of the health plan, regardless of age; of these tests, 1512 (5.4%) had a positive result. During the period from January 2010 through June 2011, when 95% of the cases of pertussis in the study population were diagnosed, the incidence of pertussis was 115 cases per 100,000 person-years among members younger than 1 year of age, decreasing to 29 cases per 100,000 person-years at 5 years of age, sharply increasing to 226 cases per 100,000 person-years at 10 and 11 years of age, sharply decreasing until 15 years of age, and remaining low in persons 15 years of age or older (Fig. 1). Ecologic data showing the percentage of persons who had received DTaP instead of whole-cell pertussis vaccines as infants, according to their current age, are shown in Figure 1.

CHARACTERISTICS OF THE STUDY POPULATION

Our study population included 277 children between the ages of 4 and 12 years who were PCR-positive for pertussis, 3318 PCR-negative controls, and 6086 matched controls. Table 1 lists characteristics of the case patients and controls.

Older age was associated with a higher percentage of positive PCR tests: 4.5% among 6-year-old children, 12.2% among 8-year-old children, and 18.5% among 10-year-old children. Increasing time since the fifth dose of DTaP was associated with an increasing percentage of positive PCR tests (Fig. 2). The time since the fifth dose of DTaP was significantly longer for PCR-positive children (1699 days; 95% confidence interval [CI], 1627 to 1772) than for PCR-negative controls (1028 days; 95% CI, 1003 to 1053) (P<0.001); case children received their fifth dose of DTaP significantly earlier than controls.

WANING OF DTaP EFFECTIVENESS

In the primary analysis comparing PCR-positive children with PCR-negative controls, with adjustment for calendar time, age, sex, race or ethnic group, and medical service area, the odds ratio for pertussis was 1.42 per year (95% CI, 1.21 to 1.66), indicating that each year after the fifth dose of DTaP was associated with a 42% increased odds of acquiring pertussis. A secondary analysis comparing PCR-positive cases with matched controls yielded similar results (Table 2).

SEVERITY OF PERTUSSIS

Cases of pertussis were mild or moderate in severity. Within 5 days before or after the PCR test, 272 of the 277 children had an outpatient encounter (98.2%), and 261 received a prescription for azithromycin (94.2%); 219 children received a diagnosis of whooping cough, cough, or pertussis exposure (79.1%); and 45 children received related diagnoses (respiratory infection, asthma, bronchitis, croup, or unspecified viral infections) (16.2%). Within 100 days before or after the PCR test, 11 of the children (4.0%) had emergency department visits related to pertussis; there were no hospitalizations or deaths related to pertussis.

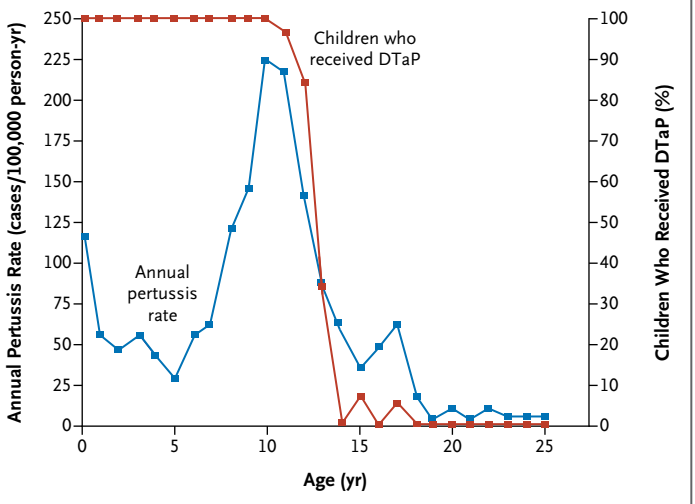

Figure 1. Annual Rate of Pertussis and Vaccination History in the Entire Health-Plan Population, According to Age, during the Pertussis Outbreak from January 2010 through June 2011.

The annual rate of pertussis (the number of cases per 100,000 person-years) for each age was calculated as follows: all cases of pertussis confirmed by a positive polymerase-chain-reaction (PCR) assay were divided by all person-years at risk and then multiplied by 100,000. Age was calculated on the date of the PCR test (for persons counted in the numerator) and on the last date of each month (for persons counted in the denominator). The percentage of members as of August 14, 2010, who were likely to have received diphtheria, tetanus, and acellular pertussis (DTaP) vaccine for all five doses (i.e., none of the doses were whole-cell pertussis vaccines) was calculated from population-based data on the timing of the transition in the health plan from diphtheria, tetanus, and whole-cell pertussis vaccines to DTaP vaccine. August 14, 2010, was the midpoint of cases (the median diagnosis date) during the 18-month period.

DISCUSSION

In the 2010 pertussis outbreak in California, a longer time since receipt of a fifth dose of DTaP was associated with an elevated risk of acquiring pertussis among children who had received all recommended acellular pertussis vaccines. In this study, the risk of pertussis increased by 42% each year after the fifth DTaP dose. If DTaP effectiveness is initially 95%, so that the risk of pertussis in vaccinated children is only 5% that of unvaccinated children, then the risk would increase after 5 years by a factor of 1.42[5] to 29% that of unvaccinated children. The corresponding decrease in DTaP effectiveness would be from 95% to 71%. The amount of protection remaining after 5 years depends heavily on the initial effectiveness. If the initial effectiveness of DTaP was 90%, it would decrease to 42% after 5 years. Regardless of the initial effectiveness, the protection from disease afforded by the fifth dose of DTaP among fully vaccinated children who had exclusively received DTaP vaccines waned substantially during the 5 years after vaccination.

The results of clinical trials evaluating the duration of protection conferred by DTaP vaccines after three or four doses suggested that protection against pertussis was sustained 5 to 6 years after

Table 1. Characteristics of PCR-Positive Children and Controls, January 2006–June 2011.*

Variable	PCR-Positive Children (N=277)	PCR-Negative Controls (N=3318)	P Value†	Matched Controls (N=6086)‡	P Value†
Male sex — no. (%)	121 (43.7)	1684 (50.8)	0.02	2659 (43.7)	1.00
Age — yr			<0.001		0.78
Mean	8.8±1.7	6.9±2.1		8.8±1.7	
Range	4–12	4–12		4–12	
Age distribution — no. (%)			<0.001		0.60
4 to <7 yr	36 (13.0)	1629 (49.1)		765 (12.6)	
7 to <10 yr	121 (43.7)	1164 (35.1)		2844 (46.7)	
10 to 12 yr	120 (43.3)	525 (15.8)		2477 (40.7)	
Year of PCR test — no. (%)			0.003		1.00
2006	2 (0.7)	97 (2.9)		44 (0.7)	
2007	1 (0.4)	102 (3.1)		22 (0.4)	
2008	6 (2.2)	107 (3.2)		132 (2.2)	
2009	6 (2.2)	155 (4.7)		132 (2.2)	
2010	201 (72.6)	2150 (64.8)		4416 (72.6)	
2011	61 (22.0)	707 (21.3)		1340 (22.0)	
Race or ethnic group — no. (%)§			<0.001		1.00
American Indian or Alaska Native	2 (0.7)	14 (0.4)		44 (0.7)	
Asian or Pacific Islander	23 (8.3)	547 (16.5)		505 (8.3)	
Black	9 (3.2)	216 (6.5)		198 (3.2)	
Hispanic	83 (30.0)	790 (23.8)		1824 (30.0)	
White	133 (48.0)	1328 (40.0)		2922 (48.0)	
Unknown and imputed	27 (9.7)	423 (12.7)		593 (9.7)	

* Plus–minus values are means ±SD. PCR denotes polymerase chain reaction.
† P values, which are based on comparisons between PCR-positive children and either PCR-negative controls or matched controls, were calculated with the use of the t-test for the continuous variable of age and with the use of the chi-square test for the rest of the variables.
‡ The controls were matched according to all the characteristics shown. The numbers and percentages in this column are weighted to indicate that the comparison of PCR-positive children with the matched controls was balanced in the analysis.
§ Race or ethnic group was determined from the medical record or was imputed in the case of missing data. The Hispanic ethnic group includes children of all races.

vaccination.[12-14] Other studies showed some waning of protection,[15-17] and several showed that increasing time since DTaP vaccination was a risk factor for vaccine failure, observations that are consistent with our findings.[17-19] Disease-free intervals after pertussis vaccination have decreased over the past two decades in Massachusetts.[20] A study in Canada showed that the transition from whole-cell pertussis vaccines to DTaP was associated with an increased incidence of pertussis among children who received only DTaP.[21] Taken together, these studies indicate that protection is less enduring with DTaP than with whole-cell pertussis vaccines.[22] The recent California epidemic provides data from a large population of children who only received acellular vaccines and for whom enough time had passed that we could quantify the extent to which DTaP protection waned.

The incidence of pertussis was highest among the population of children who were 8 to 11 years of age and who had received the full five-dose series of DTaP in childhood, suggesting that the waning efficacy of the fifth dose among school-age children played a key role in both allowing

and sustaining the recent pertussis outbreak. This observation was surprising because it is not until children reach their teenage years that they are usually considered to be a reservoir for pertussis,[23] and teenagers have been disproportionately affected in previous pertussis outbreaks.[20] Figure 1 shows that on a population basis, the incidence of pertussis decreased very sharply at 12 to 15 years of age, precisely the same ages of children who were likely to have received whole-cell pertussis vaccines as infants. These ecologic data show that the risk of pertussis was lower among older adolescents, who were likely to have previously received at least one dose of the whole-cell pertussis vaccine than among younger adolescents, who had exclusively received DTaP.

Most children in this study received their fifth dose of DTaP between 4 and 6 years of age. Thus, age and time since vaccination were highly collinear (r=0.97), and we were unable to fully separate out these two variables in the primary analysis involving PCR-negative controls. We could not entirely rule out the possibility that the incidence of pertussis among older children was higher because they were older rather than because of waning protection. The sharp increase in the incidence of pertussis among children 8 to 11 years of age, followed by a sharp decrease at 12 to 15 years (Fig. 1), is not characteristic of the epidemiology of pertussis in unvaccinated persons or in previous outbreaks. Furthermore, the secondary analyses involving controls who were closely matched for age showed that the association between the time since vaccination and the risk of pertussis was similar to that in the primary analysis. Therefore, it is more plausible to attribute the increased incidence of pertussis in children between 8 and 11 years of age to the waning effectiveness of DTaP rather than to aging.

The Centers for Disease Control and Prevention recommends routine administration of Tdap beginning at 11 years of age, with vaccination of children as young as 7 years of age in certain circumstances.[24] The limited duration of DTaP protection raises the question of whether routine administration of Tdap in younger children (e.g., 8-year-old children) is warranted. However, several issues must be clarified, including the effectiveness and duration of protection of Tdap, the possibility of increased local reactions with more frequent administration of Tdap, the increased cost and burden associated with earlier Tdap boosting (particularly since no other vaccines are routinely given at this age), and the risk of transmission to infants posed by mild-to-moderate pertussis infections that could be prevented with earlier Tdap boosting. Prevention of future outbreaks will be best achieved by developing new pertussis-containing vaccines that provide long-lasting immunity.

The large population in the health plan allowed controls to be matched to PCR-positive children on many potential confounders, and matched con-

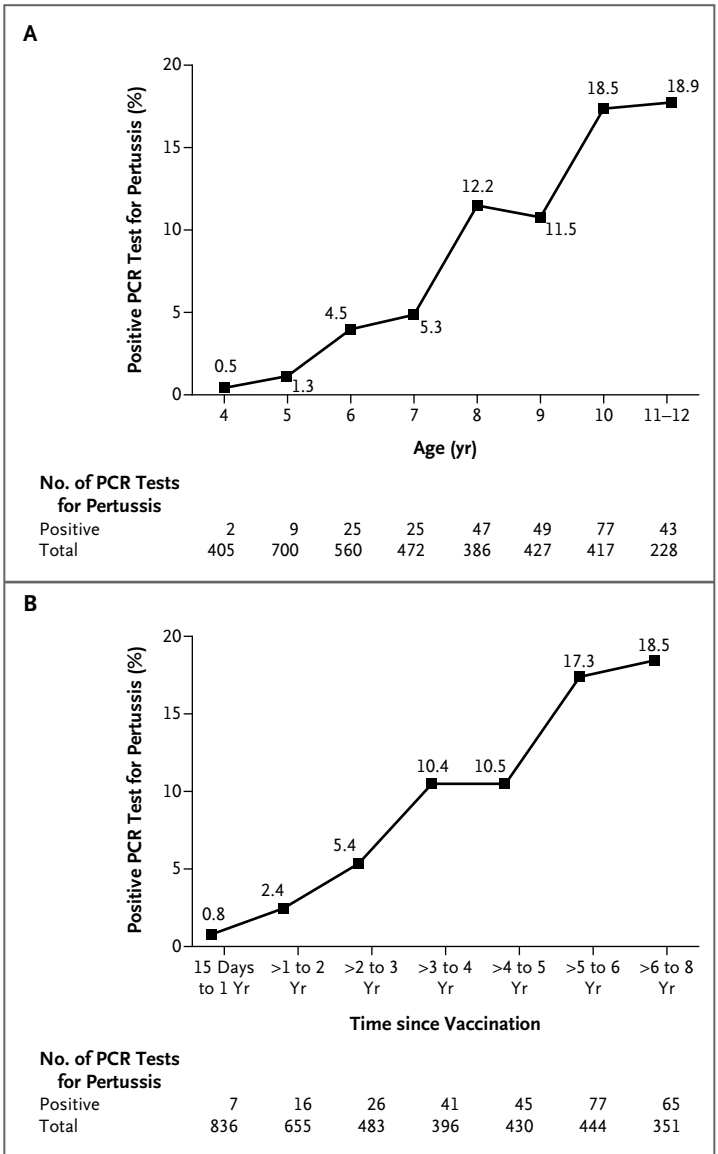

Figure 2. Percentage of PCR Tests That Were Positive for Pertussis from January 2006 through June 2011, According to Age and Time since Vaccination.

Table 2. Waning of Effectiveness per Year after Fifth Dose of DTaP Vaccine.

Group Compared with PCR-Positive Children	Odds Ratio for Pertussis (95% CI)	P Value
PCR-negative controls	1.42 (1.21–1.66)*	<0.001
Matched controls	1.50 (1.13–2.00)†	0.005

* The odds ratio was estimated on the basis of a conditional logistic-regression analysis that was stratified according to calendar time and included covariates to adjust for age, sex, race or ethnic group, and medical service area. This model deleted 10 observations for PCR-negative controls because of missing covariate data.

† The odds ratio was estimated on the basis of a conditional logistic-regression analysis that was stratified according to calendar time, age, sex, race or ethnic group, and medical clinic and included imputed probabilities of race or ethnic group as covariates to provide additional adjustment within the strata of children with imputed data.

trols were more similar to PCR-positive children than were PCR-negative controls on all measured potential confounders. However, matched controls were probably not as similar to PCR-positive children as PCR-negative controls were with respect to unmeasured potential confounders, such as the propensity to have undergone a PCR test to detect pertussis. Because we believe that such unmeasured confounders were probably a greater source of bias than the ones we were able to measure, we considered the analysis involving PCR-negative controls to be more informative.

Our study has several important strengths. One was that we compared PCR-positive children with two sets of controls and obtained similar results with each comparison. Another was that we had precise histories regarding the number of doses of vaccine received and the timing of vaccination and nearly complete demographic data for PCR-positive children and controls. Finally, we observed that older age was associated with an increasing proportion of positive PCR tests (Fig. 2); this supports our inference that the increase in the incidence of pertussis reflected a true increase in the incidence of disease rather than increased testing for pertussis.

Our study has limitations. First, although we estimated that the fifth dose of DTaP became 42% less effective each year, we could not anchor this estimate to the initial effectiveness of the vaccine because of the absence of an unvaccinated population. Second, it is possible that PCR testing misclassified a small fraction of persons (i.e., false positive and false negative tests). Since it was highly unlikely that such potential misclassification depended on the time since immunization, misclassification would imply that DTaP effectiveness may have waned even more than we estimated.

In conclusion, our evaluation of data from a large pertussis outbreak in California showed that protection from disease after a fifth dose of DTaP among children who had received only DTaP vaccines was relatively short-lived and waned substantially each year. Our findings highlight the need to develop new pertussis-containing vaccines that will provide long-lasting immunity.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ACIP votes down use of LAIV for 2016-2017 flu season

Media Statement

For Immediate Release: Wednesday, June 22, 2016
Contact: Media Relations (http://www.cdc.gov/media),
(404) 639-3286

CDC's Advisory Committee on Immunization Practices (ACIP) today voted that live attenuated influenza vaccine (LAIV), also known as the "nasal spray" flu vaccine, should **not** be used during the 2016-2017 flu season. ACIP continues to recommend annual flu vaccination, with either the inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV), for everyone 6 months and older.

ACIP is a panel of immunization experts that advises the Centers for Disease Control and Prevention (CDC). This ACIP vote is based on data showing poor or relatively lower effectiveness of LAIV from 2013 through 2016.

In late May, preliminary data on the effectiveness of LAIV among children 2 years through 17 years during 2015-2016 season became available from the U.S. Influenza Vaccine Effectiveness Network. That data showed the estimate for LAIV VE among study participants in that age group against any flu virus was 3 percent (with a 95 percent Confidence Interval (CI) of -49 percent to 37 percent). This 3 percent estimate means no protective benefit could be measured. In comparison, IIV (flu shots) had a VE estimate of 63 percent (with a 95 percent CI of 52 percent to 72 percent) against any flu virus among children 2 years through 17 years. Other (non-CDC) studies support the conclusion that LAIV worked less well than IIV this season. The data from 2015-2016 follows two previous seasons (2013-2014 and 2014-2015) showing poor and/or lower than expected vaccine effectiveness (VE) for LAIV.

How well the flu vaccine works (or its ability to prevent flu illness) can range widely from season to season and can be affected by a number of factors, including characteristics of the person being vaccinated, the similarity between vaccine viruses and circulating viruses, and even which vaccine is used. LAIV contains live, weakened influenza viruses. Vaccines containing live viruses can cause a stronger immune response than vaccines with inactivated virus. LAIV VE data before and soon after licensure suggested it was either comparable to, or better than, IIV. The reason for the recent poor performance of LAIV is not known.

Vaccine manufacturers had projected that as many as 171 million to 176 million doses of flu vaccine, in all forms, would be available for the United States during the 2016-2017 season. The makers of LAIV had projected a supply of as many as 14 million doses of LAIV/nasal spray flu vaccine, or about 8 percent of the total projected supply. LAIV is sold as FluMist Quadrivalent and it is produced by MedImmune, a subsidiary of AstraZeneca. LAIV was initially licensed in 2003 as a trivalent (three-component) vaccine. LAIV is currently the only non-injection-based flu vaccine available on the market.

Today's ACIP vote could have implications for vaccine providers who have already placed vaccine orders. The ACIP recommendation may particularly affect pediatricians and other vaccine providers for children since data from recent seasons suggests nasal spray flu vaccine accounts for about one-third of all flu vaccines given to children. CDC will be working with manufacturers throughout the summer to ensure there is enough vaccine supply to meet the demand.

CDC conducts vaccine effectiveness (VE) studies each season to estimate flu vaccine effectiveness. Today's ACIP vote highlights the importance of measuring and evaluating the effectiveness of public health interventions, which can have significant implications for public health policy. The change in the ACIP recommendation is an example of using new available data to ensure public health actions are most beneficial. Influenza is a serious disease that causes millions of illnesses, hundreds of thousands of hospitalizations, and thousands or tens of thousands of deaths each year. While the protection offered by flu vaccines can vary, the flu shot's overall VE estimate of 49 percent suggests that millions of people were protected against flu last season.

Today's ACIP recommendation must be reviewed and approved by CDC's director before it becomes CDC policy. The final annual recommendations on the prevention and control of influenza with vaccines will be published in a CDC Morbidity and Mortality Weekly Report (MMWR), Recommendations and Reports in late summer or early fall.

CDC has recommended an annual influenza vaccination for everyone ages 6 months and older since February 24, 2010. CDC and ACIP briefly had a preferential recommendation for nasal spray vaccine for young children (during 2014-2015); however, during the 2015-2016 season, influenza vaccination was recommended without any preference for one vaccine type or formulation over another.

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Potential Consequences of Not Using Live Attenuated Influenza Vaccine

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Abstract

Go to:

Introduction

Go to:

Decreased live attenuated influenza vaccine (LAIV) effectiveness in the U.S. prompted the Advisory Committee on Immunization Practices in August 2016 to recommend against this vaccine's use. However, overall influenza uptake increases when LAIV is available and, unlike the U.S., LAIV has retained its effectiveness in other countries. These opposing countercurrents create a dilemma.

Methods

Go to:

To examine the potential consequences of the decision to not recommend LAIV, which may result in decreased influenza vaccination coverage in the U.S. population, a Markov decision analysis model was used to examine influenza vaccination options in U.S. children aged 2–8 years. Data were compiled and analyzed in 2016.

Results

Go to:

Using recently observed low LAIV effectiveness values, fewer influenza cases will occur if LAIV is not used compared with having LAIV as a vaccine option. However, having the option to use LAIV may be favored if LAIV effectiveness returns to prior levels or if the absence of vaccine choice substantially decreases overall vaccine uptake.

Conclusions

Go to:

Continued surveillance of LAIV effectiveness and influenza vaccine uptake are warranted given their importance in influenza vaccination policy decisions.

INTRODUCTION

Go to:

The 2003 licensure of live attenuated influenza vaccine (LAIV), a nasal spray, introduced a new needle-sparing form of vaccine administration and led to vaccine acceptance among needle-averse individuals.[1,2] Having a choice among vaccines and administration modes may increase uptake[1–5]; offering a choice between LAIV and inactivated influenza vaccine (IIV) to adults increased uptake by 5–7 percentage points.[6] However, potential positive effects of an LAIV option have been countermanded by changing recommendations for its use resulting from varying effectiveness estimates.

Effectiveness of LAIV has been highly variable in the U.S. Meta-analyses and reviews found LAIV more effective than IIV in children aged 2–8 years,[7–10] leading the Advisory Committee on Immunization Practices (ACIP) to preferentially recommend LAIV for this age group in 2014.[11] However, in the 2013–2014 and 2014–2015 seasons, LAIV was not effective against influenza A (H1N1) owing to heat

instability.[12] Consequently, ACIP removed the LAIV preference for the 2015–2016 season.[13] The manufacturer changed the H1N1 construct for the 2015–2016 LAIV, but vaccine effectiveness remained low[14] and ACIP recommended against LAIV use in 2016.[15] Reasons for this continued loss of effectiveness in the U.S. are unclear. By contrast, LAIV effectiveness in other countries has been maintained.[16–18]

Conflicting effects between greater overall vaccine uptake with LAIV use and reduced LAIV effectiveness creates a dilemma. Using decision analysis, trade-offs among vaccine choice, uptake, and effectiveness in children aged 2–8 years were explored.

METHODS

Go to:

A Markov model of influenza vaccination in children aged 2–8 years[19] was modified to consider two strategies: one where LAIV use is eliminated and another where either vaccine can be used. Thus, trade-offs were examined between: (1) no longer recommending LAIV, with potentially decreased vaccine uptake based on preference, needle phobia, and other factors; and (2) offering both vaccines and maintaining prior uptake, but with low LAIV effectiveness that could potentially improve. The model (detailed in the Appendix), constructed using TreeAge Pro, version 2016, followed identical hypothetical cohorts over a single influenza season, with influenza vaccination and illness occurring based on the product of U.S. seasonal population averages and monthly relative likelihoods of those events.[20,21] Influenza risk with or without vaccination was tracked, based on population attack rates, protective effectiveness of each vaccine, and vaccine uptake. Influenza illness and its severity, manifestations, costs, and outcomes occurred based on medical literature data (Appendix Table 1). The primary analytic outcome was influenza risk difference between strategies. A secondary analysis examined quality-adjusted life years lost and costs.

Removing LAIV, used in 38% of children aged 2–8 years, could decrease population vaccine uptake, which was modeled as a potential decrease in vaccination rate for the IIV-only strategy. When either vaccine could be used, vaccination rates were held at 2015 levels. The base case analysis assumed no decrease in vaccine uptake with the IIV-only strategy, but potential decreases in uptake were examined in sensitivity analyses. In 2015, vaccine uptake was 51.7% for children aged <5 years and 40.7% for those aged 5–12 years. The uptake of children aged <5 years was used in the base case analysis; rates of those aged 5–12 years were used in a sensitivity analysis. LAIV effectiveness has declined to low levels in the U.S.,[14] but its effectiveness in other countries has remained relatively stable,[16–18] raising questions whether loss of effectiveness in the U.S. could be a transient phenomenon. In this analysis, the recently observed low LAIV effectiveness was modeled as the base case while examining the influence of potentially improved vaccine effectiveness in sensitivity analyses.

RESULTS

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In the base case analysis, where vaccine uptake was identical for both strategies, the model estimated that 20.9% of children aged 2–8 years had influenza illness if only IIV were used, compared with 23.5% if both vaccines continued to be used (and LAIV has low effectiveness). In one-way sensitivity analyses, the IIV-only strategy prevented fewer cases than a choice between vaccines if LAIV effectiveness is >63% (base case, 3%) or if the absolute decrease in population vaccine uptake resulting from the absence of an LAIV option was >18.7% (base case, 0%). Individual variation of all other parameters, including influenza attack rates, through ranges listed in Appendix Table 1, did not change strategy favorability.

Figure 1 shows results when varying both sensitive parameters simultaneously in a two-way sensitivity analysis. When baseline influenza vaccination uptake was 51.7% (top panel), having both vaccines available prevented more influenza cases than the IIV-only strategy if overall vaccination uptake decreased by 5 percentage points and LAIV effectiveness was >46.5%, or if vaccine uptake decreased by 10 percentage points and LAIV effectiveness was >30.4%. When baseline vaccine uptake was set at 40.7% (bottom panel), having both vaccines available was favored if LAIV effectiveness was >42.1% or >21.8% and the IIV-only strategy decreased vaccination by 5 or 10 percentage points, respectively.

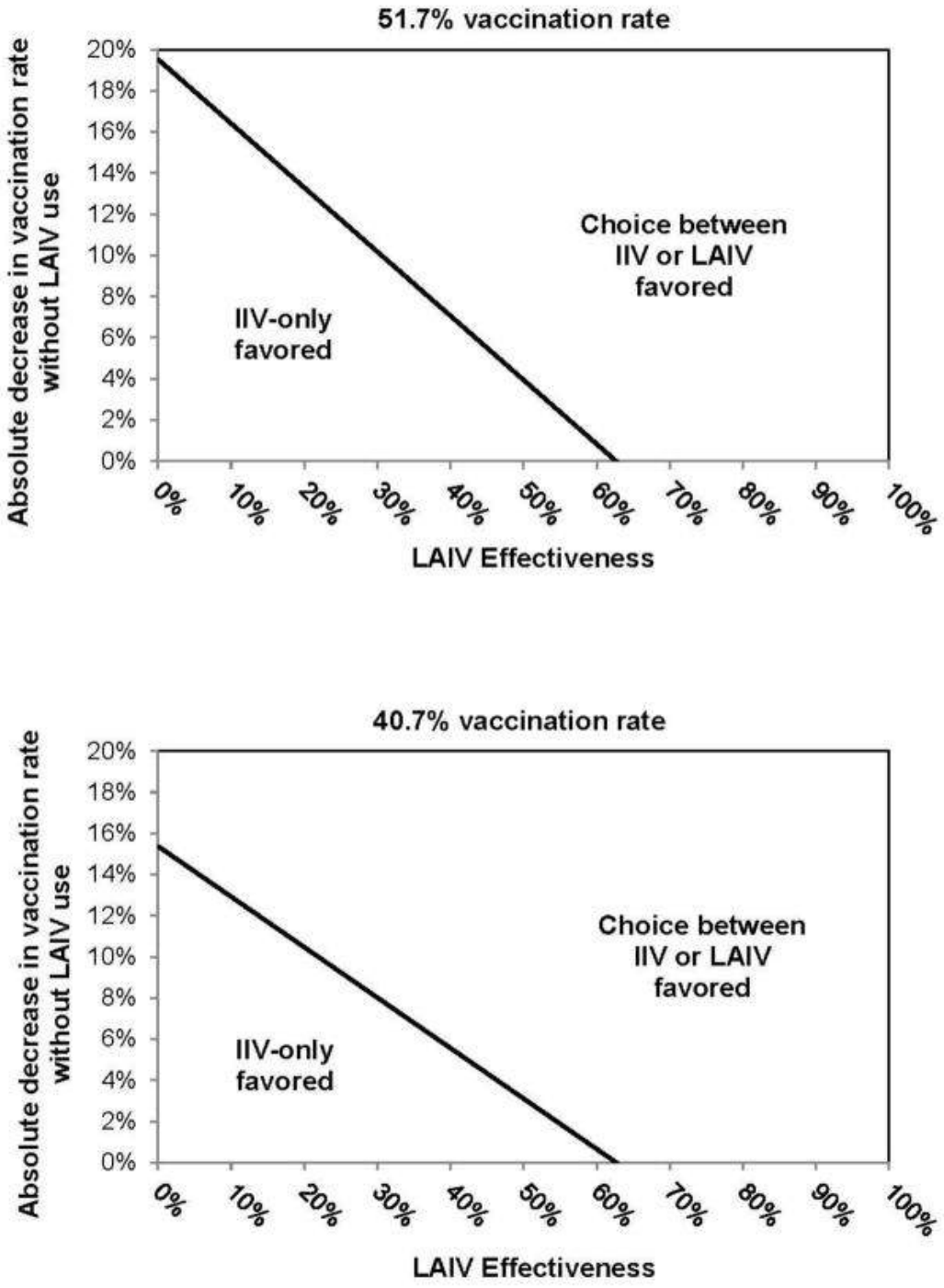

Figure 1

Two-way sensitivity analysis.

Notes: Varying LAIV effectiveness (x-axis) and the absolute decrease in vaccination rates when LAIV is not used (y-axis) for prior population vaccination rates of 51.7% (observed influenza vaccine uptake for children aged <5years, top panel) and 40.7% (uptake for children aged 5–12 years, bottom). Within each panel, areas depict where strategies are favored due to fewer influenza cases compared to the other strategy. The option to use either vaccine was favored when LAIV effectiveness is high or when the decrease in vaccination rate is high after LAIV is no longer an option. At the base case LAIV effectiveness of 3%, the vaccination rate would have to decrease by almost 19% (top) or 15% (bottom) as a result of removing LAIV for the both vaccines option to be favored.

LAIV, live attenuated influenza vaccine; IIV, inactivated influenza vaccine

A secondary cost-effectiveness analysis compared costs and quality-adjusted life years between strategies. In the base case, which assumes unchanged vaccination rates, the IIV-only strategy was less costly and more effective than a strategy where either vaccine could be used (Appendix Table 2). Two-way sensitivity analyses varying LAIV effectiveness and potential decreased vaccine uptake showed somewhat greater ranges where IIV-only was favored (compared with Figure 1) when a $100,000 per quality-adjusted life year gained threshold was used (Appendix Figure 2); that area decreased when higher thresholds were used.

DISCUSSION

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This analysis generally supports the ACIP decision to recommend against LAIV use, while showing how changes in overall vaccine uptake or LAIV effectiveness could undermine that decision. Decreased influenza vaccine uptake that could result from LAIV unavailability leads to higher disease burden, as does continuing to offer a low-effectiveness LAIV. Complicating the decision is the possibility of future improved LAIV effectiveness.

Although it is unlikely that a substantial change in just one of these parameters' values will occur and lead to continued LAIV use being favored, smaller changes in each parameter occurring jointly could plausibly lead to more illness under the new ACIP recommendations. In any case, this analysis highlights the importance of timely vaccine effectiveness estimates via influenza surveillance, as well as the usefulness of examining reasons for vaccine acceptance or refusal and the effects of policy choices on vaccine uptake. In addition, this analysis shows the potential value of decision analytic techniques, along with surveillance data, in informing and assisting policy deliberations.

This analysis did not account for herd immunity, likely an important component of LAIV effectiveness.[18,22] However, this omission's effect is probably low when LAIV effectiveness is low and when herd immunity can occur with IIV use. Absence of LAIV options in other age groups, which was not accounted for in this analysis, could have greater or lesser effects than those observed in children aged 2–8 years. Use of cohort simulation limits the ability to account for population heterogeneity. It is felt that the most likely cause of poor LAIV protection is reduced replicative effectiveness of H1N1 strains in LAIV,[25] but definitive reasons for regional effectiveness differences are not yet available. Decision analysis models depend on parameter estimates; this analysis was based on a published model[19] incorporating vaccine effectiveness data from the same data source that informed Centers for Disease Control and Prevention recommendations.[14] Continued surveillance of LAIV effectiveness and influenza vaccine uptake is warranted, given their importance and influence in future influenza vaccination policy choices.

Table 1

Key Parameter Values Examined in the Model

Parameter	Base case (range)	Source
Relative likelihood of LAIV use (vs. IIV)	38% (0–50%)	23
Vaccination likelihood		
Base case (6 months–4 years)	51.7% (+/− 6.1%)	24
Alternative case (5–12 years)	40.7% (+/− 3.6%	24
Vaccine effectiveness – Age 2–17 years		
LAIV	3% (0–70%)	14
IIV	63% (40–80%)	14

LAIV, live attenuated influenza vaccine; IIV, inactivated influenza vaccine

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CDC vaccine panel brings back FluMist for 2018-19 season

Filed Under: **Influenza Vaccines** (/infectious-disease-topics/influenza-vaccines)
Lisa Schnirring | News Editor | CIDRAP News (/ongoing-programs/news-publishing/news-publishing-staff) | Feb 21, 2018

A US Centers for Disease Control and Prevention (CDC) vaccine advisory group today voted to include FluMist in the vaccine line-up for the 2018-19 flu season, returning the vaccine to the US market after a two-season hiatus.

Intense discussions swirled around how to weigh the latest scientific data on the nasal-spray vaccine, how keeping the vaccine on the sidelines might reduce vaccine uptake, and challenges healthcare providers may face in communicating the policy change to parents and patients. But in the end, the CDC's Advisory Committee on Immunization Practices (ACIP) approved restoring the live attenuated influenza virus (LAIV) by a 12-to-2 margin.

Today's action marks the latest turnaround for a vaccine, first licensed in 2003, that has offered a needle-free option—a plus for children and a formulation that has been useful in school-based flu immunization campaigns.

In 2014, ACIP made a preferential recommendation for FluMist in healthy kids ages 2 to 8, because it seemed to provide better protection. However, it reversed the decision in 2015 because of disappointing performance against the 2009 H1N1 strain, a puzzling development given that scientists in other countries where FluMist is used didn't seem to find the same gap in protection.

Company presents new data

AstraZeneca, the company that makes FluMist, has been working to identify reasons for the reduced effectiveness and has said it might be linked to reduced fitness of the H1N1 vaccine component. Other research groups have also been trying to tease out the problem with the vaccine, with some suggesting the problem might stem from changes in patient immunity. Since the vaccine was last used in the United States, the company has swapped out the previous 2009 H1N1 vaccine component with a different type (A/Slovenia).

In the meanwhile, an ACIP working group, led by the CDC's Lisa Grohskpof, MD, MPH, has been churning through data on the vaccine from the United States and other countries, which led to today's proposal and committee vote.

At today's ACIP meeting, the company presented findings from a US study in children ages 2 to 4 on shedding and antibody responses of the H1N1 strain in the latest version of the quadrivalent vaccine. It said the results showed that the new 2017-18 post-pandemic 2009 H1N1 LAIV strain (A/Slovenia) performed significantly better than the 2015-16 post-pandemic LAIV strain (A/Bolivia). AstaZeneca officials said the new H1N1 strain prompted an antibody response similar to the highly effective H1N1 LAIV strain that was a component of the vaccine before the 2009 H1N1 pandemic.

Gregory Keenan, vice president of US medical affairs at AstraZeneca, said today in a press release from the company, "This study validates the improvements we've made to our strain selection process and confirms an improved H1N1 LAIV strain was included in the 2017-2018 formulation. We are pleased that the ACIP has voted in support of a renewed recommendation FluMist Quadrivalent in the US and look forward to continuing to work with public health authorities to optimize protection against influenza."

Experts tread cautiously before giving OK

During the committee discussion in the lead-up to the votes, some members said they worried if the new data on shedding were strong enough evidence of protection, compared with traditional vaccine effectiveness studies.

Henry Bernstein, DO, professor of pediatrics at Zucker School of Medicine at Hoftstra/Northwell and Cohen Children's Medical Center, said he had a number of concerns. But the part that worried him most was the chance that the vaccine wouldn't perform well in an H1N1-dominated season and that such a failure might undercut flu vaccination coverage, in general.

"I have real mixed emotions about this," he said. "We want to protect as many people as we can, especially kids."

Other ACIP members aired concerns that flu vaccine effectiveness often crops up as a serious issue with flu vaccines, in general, and they wondered if the committee was holding FluMist to a different standard. Some said adding FluMist back to the line-up of vaccines might make it difficult to explain the changes to patients and their families.

Bringing FluMist back into the mix is also likely to create some practical problems for clinicians, given that the ordering process for next year's vaccine has already begun. At the CDC, contracts have already been completed for the Vaccines for Children (VFC) program, which provides free vaccines to children whose families don't have health insurance or can't afford the vaccine.

Ed Belongia, MD, director of the Center for Clinical Epidemiology & Population Health at Marshfield Clinic Research Institute in Marshfield, Wisc., said today's vote is not an easy decision, and the committee was challenged by making a decision with incomplete data, but the expert are weighing their decision with the best science available. He added that the manufacturer made a good faith effort to find the root cause of the problem, and that with the body of evidence, they've made a reasonable case, short of running a vaccine effectiveness trial.

He said if enough FluMist is on the market for the 2018-19 season and there's enough 2009 H1N1 circulating, the US Influenza Vaccine Effectiveness Network should be able to evaluate how well FluMist performed.

See also:

Feb 21 AstraZeneca press release (https://www.astrazeneca-us.com/media/press-releases/2018/astrazeneca-announces-renewed-recommendation-and-availability-of-flumist-quadrivalent-vaccine-in-the-us-02212018.html)

ACIP web page (https://www.cdc.gov/vaccines/acip/index.html)

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Update: ACIP Recommendations for the Use of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) — United States, 2018–19 Influenza Season

Weekly / June 8, 2018 / 67(22);643–645

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View suggested citation

Intranasally administered live attenuated influenza vaccine (LAIV) was initially licensed in the United States in 2003 as a trivalent formulation (LAIV3) (FluMist, MedImmune, LLC). Quadrivalent live attenuated influenza vaccine (LAIV4) (FluMist Quadrivalent, MedImmune) has been licensed in the United States since 2012 and was first available during the 2013–14 influenza season, replacing LAIV3. During the 2016–17 and 2017–18 influenza seasons, the Advisory Committee on Immunization Practices (ACIP) recommended that LAIV4 not be used because of concerns about low effectiveness against influenza A(H1N1)pdm09-like viruses circulating in the United States during the 2013–14 and 2015–16 seasons (*1*,*2*). On February 21, 2018, ACIP recommended that LAIV4 be an option for influenza vaccination of persons for whom it is appropriate for the 2018–19 season (*3*). This document provides an overview of the information discussed in the decision-making process leading to this recommendation. A description of methodology and data reviewed will be included in the background materials that will supplement the 2018–19 ACIP Influenza Recommendations, which will replace the 2017–18 ACIP influenza statement (*2*), and which will also contain guidance for the use of LAIV4.

Before the 2009 influenza A(H1N1) pandemic, three randomized trials noted superior relative efficacy of LAIV3 compared with trivalent inactivated influenza vaccine (IIV3) among children (*4*–*6*). However, LAIV4 demonstrated no statistically significant effectiveness against influenza A(H1N1)pdm09-like viruses among children aged 2 through 17 years in U.S. studies conducted during the 2013–14 and 2015–16 seasons (*7*–*12*), during which these viruses predominated. This lack of effectiveness was postulated as attributable to decreased replicative fitness of the influenza A(H1N1)pdm09-like viruses included in LAIV4 during those seasons (A/California/7/2009 for 2013–14 and A/Bolivia/559/2013 for 2015–16) (*13*). Investigations into the potential cause of this reduced effectiveness against influenza A(H1N1)pdm09 revealed that these LAIV viruses exhibited reduced replication in human nasal epithelial cells, compared with prepandemic influenza A(H1N1) LAIV viruses. For the 2017–18 season, a new influenza A(H1N1)pdm09-like virus (A/Slovenia/2903/2015) was included in LAIV4, replacing A/Bolivia/559/2013. However, LAIV4 was not recommended for use in the United States during 2017–18, and no U.S. effectiveness estimates were available.

Methods

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Data from three sources were presented to ACIP for discussion. These included 1) an analysis of the effectiveness of LAIV4 and inactivated influenza vaccines for the 2013–14 through 2015–16 seasons among children aged 2 through 17 years, using pooled data from five U.S. observational studies (*3*); 2) a systematic review of published literature regarding the effectiveness of LAIV3 and LAIV4 among children during the 2010–11 through 2016–17 seasons (*3*); and 3) a study conducted by the manufacturer that evaluated viral shedding and immunogenicity associated with LAIV4 containing the new influenza A(H1N1)pdm09-like virus (A/Slovenia/2903/2015) among U.S. children aged 24 months through <4 years (*14*).

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Summary of Data Reviewed

Review of LAIV effectiveness data for previous seasons in the United States confirms low to no significant effectiveness of LAIV against influenza A(H1N1)pdm09-like viruses. However, LAIV was generally effective against influenza B viruses and was of similar effectiveness to IIV against influenza A(H3N2) viruses. No effectiveness estimates were available for the current formulation of LAIV4 containing A/Slovenia/2903/2015 against influenza A(H1N1)pdm09-like viruses at the time of the review (*3*).

Data presented by the manufacturer indicated that the new LAIV4 influenza A(H1N1)pdm09-like virus, A/Slovenia/2903/2015, was shed by a higher proportion of children during days 4 through 7 following the first of 2 doses of vaccine. A/Slovenia/2903/2015 induced significantly higher antibody responses than its predecessor, A/Bolivia/559/2013. Seroconversion rates to A/Slovenia/2903/2015 were comparable to those obtained in response to prepandemic influenza A(H1N1) LAIV strains used during seasons in which the vaccine was observed to be effective against A(H1N1) influenza viruses (*14*).

The manufacturer also summarized information from previous presentations to ACIP concerning new candidate vaccine virus evaluation techniques that were employed in their investigation to identify the cause of low LAIV4 effectiveness, and how these techniques will be used going forward (*14*,*15*). Specifically, it was reported that two additional methods will be employed in the evaluation and selection of candidate vaccine viruses for inclusion in LAIV4, and these data will be shared each year with the Food and Drug Administration. Replicative fitness of candidate strains will be evaluated in human nasal epithelial cell culture. Previous methods using eggs and Madin-Darby canine kidney (MDCK) cell culture were found not to be predictive of replication of influenza A(H1N1)pdm09-like LAIV viruses in human cells. In addition, infectivity of vaccine viruses will be quantified using both 50% tissue culture infective dose ($TCID_{50}$) and fluorescent focus assay (FFA), instead of FFA only. Whereas FFA measures expression of viral antigens on the cell surface and does not require multiple rounds of viral replication, $TCID_{50}$ measures the spread of vaccine virus between cells through sustained replication cycles. Evaluation of influenza A(H1N1)pdm09-like viruses used in the 2013–14 (A/California/7/2009) and 2015–16 (A/Bolivia/559/2013) vaccines revealed that viral titers obtained via $TCID_{50}$ were substantially lower than those obtained via FFA, indicating that these viruses were less able to sustain multiple rounds of replication. For A/Slovenia/2903/2015, the titers obtained via these two methods are similar and were comparable to those associated with prepandemic influenza A(H1N1) viruses with known efficacy (*15*).

Discussion

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Analyses of data from 2010–11 through 2016–17 indicate that LAIV was effective against influenza B viruses, and effectiveness against influenza A(H3N2) viruses was similar to that of inactivated influenza vaccines. During this period, LAIV was poorly effective among children aged 2 through 17 years against influenza A(H1N1)pdm09 viruses in the United States. Shedding and immunogenicity data provided by the manufacturer suggest that the new influenza A(H1N1)pdm09-like virus included in the current LAIV4, A/Slovenia/2903/2015, has improved replicative fitness over previous LAIV4 influenza A(H1N1)pdm09-like vaccine strains. However, no published effectiveness estimates for this formulation of the vaccine against influenza A(H1N1)pdm09 viruses were yet available because influenza A(H3N2) and influenza B viruses have predominated during the 2017–18 Northern Hemisphere season.

Effectiveness of influenza vaccines varies and is affected by many factors, including age and health status of the recipient, influenza type and subtype, prior influenza vaccination history, and degree of antigenic match between the vaccine and circulating viruses. It is possible that the vaccine effectiveness also differs among different individual vaccine products (for example, different IIVs); however, product-specific comparative effectiveness data are lacking for most vaccines. Although U.S. national influenza vaccination coverage among children did not decline substantially overall during the 2016–17 season (the first season in which it was recommended that LAIV not be used) (*3*), overall vaccination coverage remains suboptimal. Additional options for vaccination of children, including use of noninjectable vaccines such as LAIV4, might provide a means to improve coverage, particularly in school-based settings.

Recommendation of the ACIP

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For the 2018–19 U.S. influenza season, providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, recombinant influenza vaccine [RIV], or LAIV4). LAIV4 is an option for those for whom it is otherwise appropriate. No preference is expressed for any influenza vaccine product. ACIP will continue to review data concerning the effectiveness of LAIV4 as they become available. Providers should be aware that the effectiveness of the updated LAIV4 containing A/Slovenia/2903/2015 against currently circulating influenza A(H1N1)pdm09-like viruses is not yet known.

Conflict of Interest

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Emmanuel B. Walter reports grants from Novartis V&D, Novavax, and Merck & Co, outside the submitted work. No other conflicts of interest were reported.

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Suggested citation for this article: Grohskopf LA, Sokolow LZ, Fry AM, Walter EB, Jernigan DB. Update: ACIP Recommendations for the Use of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) — United States, 2018–19 Influenza Season. MMWR Morb Mortal Wkly Rep 2018;67:643–645. DOI: http://dx.doi.org/10.15585/mmwr.mm6722a5 (http://dx.doi.org/10.15585/mmwr.mm6722a5) .

Live Attenuated Influenza Vaccine [LAIV] (The Nasal Spray Flu Vaccine)

For the 2018-2019 U.S. influenza season, CDC and its vaccines advisory committee (ACIP) recommend that providers use any licensed, age-appropriate influenza vaccine (Inactivated influenza vaccines (IIV), Recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV4) with no preference expressed for one vaccine over another. (LAIV4 is again a recommended option for people for whom it is otherwise appropriate.) Learn more.

On This Page

What flu viruses does the nasal spray vaccine protect against?

All nasal spray flu vaccines for the 2018-2019 season will contain four flu viruses: an influenza A (H1N1) virus, an influenza A (H3N2) virus and two influenza B viruses.

Are any of the available flu vaccines recommended over the others?

For the 2018-2019 flu season, the Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for everyone 6 months and older with any licensed age-appropriate flu vaccine including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV4) or live attenuated influenza vaccine (LAIV4) with no preference expressed for any one vaccine over another.

Who can be vaccinated with the nasal spray flu vaccine?

The nasal spray is approved for use in non-pregnant individuals, 2 years through 49 years of age. People with some medical conditions should not receive the nasal spray flu vaccine.

Who should not be vaccinated with the nasal spray flu vaccine?

Some people should not get the nasal spray flu vaccine:

- Children younger than 2 years
- Adults 50 years and older
- Pregnant women
- People with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine
- Children 2 years through 17 years of age who are receiving aspirin- or salicylate-containing medications.
- People with weakened immune systems (immunosuppression)
- Children 2 years through 4 years who have asthma or who have had a history of wheezing in the past 12 months.
- People who have taken influenza antiviral drugs within the previous 48 hours.
- People who care for severely immunocompromised persons who require a protected environment (or otherwise avoid contact with those persons for 7 days after getting the nasal spray vaccine).

In addition, the following conditions are precautions to the use of the nasal spray influenza vaccine:

- Asthma in people aged 5 years and older.
- Other underlying medical conditions that can put people at higher risk of serious flu complications. These include conditions such as lung disease, heart disease (except isolated hypertension), kidney disease (like diabetes), kidney or liver disorders, neurologic/neuromuscular, or metabolic disorders. See "People at High Risk of Developing Flu–Related Complications."
- Moderate or severe acute illness with or without fever.
- Guillain-Barré Syndrome within 6 weeks following a previous dose of influenza vaccine.

How effective is the nasal spray seasonal flu vaccine?

Influenza vaccine effectiveness (VE) can vary from year to year, among different age and risk groups, by vaccine type, and even by virus type and subtype. While data from 2010-2011 through 2016-2017 indicated that LAIV lacked effectiveness among 2 through 17-year-olds against H1N1pdm09 influenza viruses (2009 H1N1) in the U.S., LAIV was effective against influenza B viruses, and was similarly effective against H3N2 viruses as inactivated influenza vaccines. For the 2018-2019 season, the manufacturer of LAIV4 has included a new H1N1 vaccine component. Some data suggest this will result in improved effectiveness of LAIV4 against H1N1. However, no published effectiveness estimates for this vaccine component against H1N1 viruses are yet available. ACIP and CDC voted to resume the recommendation for the use of LAIV4 based on evidence suggesting that the new H1N1 component will result in improved effectiveness of LAIV against these viruses. There is no expressed preference for any flu shot or the nasal spray vaccine.

For more information about vaccine effectiveness, visit How Well Does the Seasonal Flu Vaccine Work? Learn more about the 2017-18 flu season and vaccine composition for the 2018-19 flu season.

Should the nasal spray flu vaccine be given to patients with chronic diseases?

There is a precaution against giving the nasal spray flu vaccine to people with certain chronic health conditions because the safety and effectiveness of this vaccine in people with those conditions has not been established.

Should pregnant and postpartum women avoid contact with people who were recently vaccinated with the nasal spray vaccine?

Pregnant and postpartum women do not need to avoid contact with persons recently vaccinated with the nasal spray flu vaccine. However, the nasal spray flu vaccine should not be given to women who are pregnant. Postpartum women can receive a flu shot or the nasal spray flu vaccine.

Are there any contraindications to giving breastfeeding mothers the nasal spray vaccine?

Breastfeeding is not a contraindication for the nasal spray vaccine. Breastfeeding mothers younger than 50 years can get the nasal spray flu vaccine as long as they do not have any contraindication to getting that vaccine. See Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2015-2016 Influenza Season – August 7, 2015 for a list of contraindications and precautions for the nasal spray vaccine.

Can the nasal spray flu vaccine be given to patients when they are ill?

The nasal spray flu vaccine can be given to people with mild illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, nasal congestion might limit delivery of the vaccine to the nasal lining. Delaying vaccination with LAIV until the nasal congestion is reduced should be considered. People with moderate or severe illness, with or without fever, should generally wait to be vaccinated until they have recovered. Your healthcare provider can provide advice about when to get vaccinated if you are feeling ill.

Can nasal spray flu vaccine give me flu?

Flu vaccines do not cause flu illness. The nasal spray flu vaccine does contain live viruses. However, the viruses are attenuated (weakened), so that they will not cause influenza illness. The weakened viruses are also cold-adapted, which means they are designed to only multiply at the cooler temperatures found within the nose. The viruses cannot infect the lungs or other areas where warmer temperatures exist.

While a flu vaccine cannot give you flu illness, there are different side effects that may be associated with getting a flu shot or a nasal spray flu vaccine.

These side effects are mild and short-lasting, especially when compared to symptoms of bad case of flu.

What are the side effects that could occur?

The viruses in the nasal spray vaccine are weakened and do not cause severe symptoms often associated with influenza illness. Side effects from the nasal spray may include:

- Runny nose
- Wheezing
- Headache
- Vomiting
- Muscle aches
- Fever
- Sore throat
- Cough

If these problems occur, they usually begin soon after vaccination and are mild and short-lived. Almost all people who receive influenza vaccine have no serious problems from it. However, on rare occasions, flu vaccination can cause serious problems, such as severe allergic reactions. People who think that they have been injured by a vaccine can file a claim for compensation from the National Vaccine Injury Compensation Program (VICP).

More information about the safety of flu vaccines is available at Influenza Vaccine Safety.

Note: There is no recommendation for pregnant women or people with pre-existing medical conditions to get special permission or written consent from their doctor or health care professional for influenza vaccination if they get vaccinated at a worksite clinic, pharmacy or other location outside of their physician's office. For more information, visit Misconceptions about Seasonal Flu and Flu Vaccines.

LA Countywide Outbreak Of Whooping Cough Hits Exclusive Harvard-Westlake Hard

February 27, 2019 at 4:04 pm **Filed Under:** Harvard Westlake, Outbreak, Whooping Cough

STUDIO CITY (CBSLA) — An exclusive private school has been hit with dozens cases of whooping cough, which has sickened a large number of teenagers across Los Angeles County.

Health officials say they are monitoring three large clusters of highly contagious whooping cough among 11- to 18-year-olds. The county Department of Health issued a health alert to pediatricians and other health care providers about the uptick in whooping cough last week.

Harvard-Westlake's Studio City campus. (credit: CBS)

Harvard-Westlake, which has campuses in Studio City and Beverly Crest, was hit particularly hard, with 30 students coming down with whooping cough since November, according to the Hollywood Reporter.

Of about 1,600 students attend Harvard-Westlake, where tuition is close to $40,000 a year, only 18 opted out of vaccinations for medical reasons. None of the 30 students who contracted whooping cough were not vaccinated.

School officials say they have done all they can to control the outbreak, including sending students home, sanitizing classrooms, and implementing a new protocol that requires students who stay home sick must be tested at a hospital for whooping cough before they can return to class.

Whooping cough, also known as pertussis, gets its name from the distinctive cough that sounds like a whoop. It is highly contagious and can be fatal for infants.

Parents are being urged to take students with flu-like symptoms to get them tested at a hospital before allowing them to return back to school.

Pediatrics. 2004 Mar;113(3 Pt 1):455-9.

Chickenpox outbreak in a highly vaccinated school population.

Tugwell BD[1], Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR.

Author information

Abstract

OBJECTIVE: We investigated a chickenpox outbreak that started in an Oregon elementary school in October 2001, after public schools began phasing in a varicella vaccination requirement for enrollment. We sought to determine the rate of varicella vaccination and effectiveness and risk factors for breakthrough disease.

METHODS: A chickenpox case was defined as an acute maculopapulovesicular rash without other explanation occurring from October 30, 2001 through January 27, 2002 in a student without a prior history of chickenpox. We reviewed varicella vaccination records and history of prior chickenpox, and we calculated vaccine effectiveness. We evaluated the effects of age, gender, age at vaccination, and time since vaccination on risk of breakthrough disease (ie, chickenpox occurring >42 days after vaccination).

RESULTS: Of 422 students, 218 (52%) had no prior chickenpox. Of these, 211 (97%) had been vaccinated before the outbreak. Twenty-one cases occurred in 9 of 16 classrooms. In these 9 classrooms, 18 of 152 (12%) vaccinated students developed chickenpox, compared with 3 of 7 (43%) unvaccinated students. Vaccine effectiveness was 72% (95% confidence interval: 3%-87%). Students vaccinated >5 years before the outbreak were 6.7 times (95% confidence interval: 2.2-22.9) as likely to develop breakthrough disease as those vaccinated </=5 years before the outbreak (15 of 65 [23%] vs 3 of 87 [3%]).

CONCLUSIONS: A chickenpox outbreak occurred in a school in which 97% of students without a prior history of chickenpox were vaccinated. Students vaccinated >5 years before the outbreak were at risk for breakthrough disease. Booster vaccination may deserve additional consideration.

Comment in

Chickenpox outbreak in a highly vaccinated school population. [Pediatrics. 2004]
Chickenpox outbreak in a highly vaccinated school population. [Pediatrics. 2004]

PMID: 14993534

[Indexed for MEDLINE]

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™
Morbidity and Mortality Weekly Report (MMWR)

Influenza Outbreak in a Vaccinated Population — USS Ardent, February 2014

Weekly
October 24, 2014 / 63(42);947-949

Theodore L. Aquino, DO1, Gary T. Brice, PhD2, Sherry Hayes, MPH3, Christopher A. Myers, PhD2, Jaqueline McDowell, MD3, Brenda White, MSPH, MPH2, Rebecca Garten, PhD4, Daniel Johnston5 (Author affiliations at end of text)

On February 10, 2014, the USS Ardent, a U.S. Navy minesweeper, was moored in San Diego, California, while conducting training. Over the course of 3 days, 25 of 102 crew members sought medical care because of influenza-like illness (ILI). Nasal swab specimens were collected from each patient, and initial rapid influenza testing indicated 16 cases of influenza A. Ultimately, polymerase chain reaction (PCR) testing conducted by the Naval Health Research Center determined that 20 specimens were influenza A, of which 18 were subtype H3N2. Two specimens could not be subtyped. The HA gene sequence of an outbreak isolate was 99% identical to strains circulating during the 2013–14 influenza season and antigenically similar to the H3N2 component of the 2013–14 influenza vaccine. At the time of the outbreak, 99% of the crew had received influenza vaccine. Through the duration of the outbreak, the minesweeper squadron medical officer collaborated with Navy Environmental and Preventive Medicine Unit Five, higher-level Navy authorities, and County of San Diego Public Health Services to implement the outbreak response, which included disseminating outbreak information to surrounding Navy units, disinfecting the ship, sending home infected crew members, identifying family members at high risk, and providing antiviral medications and guidance. No crew member had onset of symptoms >6 days after the first crew member became ill. This outbreak highlights the risk for an H3N2 influenza outbreak among vaccinated and otherwise healthy young persons.

ILI was defined as illness with two or more of the following symptoms: fever >100.4°F (>38.0°C), chills, sore throat, cough, shortness of breath, congestion, headache, body aches, and nausea. Twenty crew members reported sick on February 10, one on February 11 and four more on February 12. Symptom onset dates were February 5–11 (Figure). All ILI patients were interviewed and examined aboard ship by both an independent duty corpsman (i.e., shipboard medical provider) and a physician. Two nasal swab specimens were taken from each ILI patient by staff members from the Naval Health Research Center. Nasal swab specimens and influenza A and B rapid influenza tests were used for immediate influenza testing. The remaining nasal swab specimens were screened by the Naval Health Research Center for influenza A and B using the CDC PCR assay (1), and DNA sequencing of the HA1 portion of the hemagglutinin gene was performed as previously described (2). Data on demographics and symptomatology were collected using questionnaires and personal interviews.

All 25 crew members with ILI symptoms were otherwise healthy men aged 21–44 years. ILI cases occurred in all ranks, departments, job types, and work shifts. The ship had been in port since being transported from Bahrain to San Diego 2 months before the outbreak. No sailors reported any recent travel. Rapid influenza testing indicated 16 cases of influenza A and nine negative results. Nasal swab specimens from 20 of the 25 ILI patients were positive by PCR for influenza A, with 18 specimens confirmed as A (H3) and two as A (untyped). Influenza A virus was isolated from seven of 11 nasal swab specimens selected for viral culture. These seven specimens had HA1 protein sequences that were identical to each other and differed from the 2013–14 influenza A (H3N2) A/Texas/50/2012 vaccine strain by 5 amino acid substitutions (N128A, R142G, N145S, P198S, and V347K). Sequence analysis (3) of the HA1 portion of the hemagglutinin gene showed 99% homology to typical H3N2 strains circulating in the United States and worldwide during the 2013–14 northern hemisphere influenza season and were found to be antigenically similar to A/Texas/50/2012 (4). Ninety-nine of 102 USS Ardent crew members, 24 of the 25 with ILI symptoms, and 17 of 18 crew members with confirmed influenza A (H3N2) infection had received the 2013–14 influenza vaccine ≥3 months before the outbreak. Vaccinations had been administered at local naval health clinics and at a vaccination fair conducted by Naval Medical Center San Diego. Of the 25 crew members with ILI symptoms, 16 were vaccinated via intradermal injection, eight via intranasal mist, and one had not received vaccination.

Interviews revealed a possible source of the outbreak to be an Ardent crew member (patient A), aged 26 years, who had been evaluated at a local emergency room for fever and cough on January 30, 11 days before the first ILI case was diagnosed. A chest radiograph and computed tomographic scan were performed because of suspicion of pulmonary embolism; both were negative. The patient had been receiving treatment for pyelonephritis, and the clinical impression was that the cough was related to the pyelonephritis. No testing for influenza was performed, and the patient was discharged. Patient A's roommate in a shore apartment, also a USS Ardent sailor, experienced ILI symptoms on February 5. Because patient A's roommate was the first of the 25 crew members to experience ILI, and no other probable cause for the outbreak was found, it is possible that patient A actually had influenza. Since patient A did not board USS Ardent because he was ill, it is likely he infected his roommate, who then spread influenza to other USS Ardent crew members.

In an effort to reduce spread and impact of disease, oseltamivir (75 mg twice a day for 5 days) was prescribed to each ILI patient who reported that symptoms had developed within 48 hours of their medical visit, regardless of their vaccination status and rapid influenza testing results. In addition to antiviral medication, rapid identification of the influenza outbreak, and immediate isolation of affected persons (crew members with ILI symptoms were sent off ship to their homes for 48 hours), additional steps to control the outbreak were taken: thorough cleaning of spaces throughout the ship by the crew and use of the ship's public address system to instruct personnel to wash hands frequently, use hand sanitizer, cover their mouths when coughing, and

report for medical evaluation if they were experiencing ILI symptoms. Similar announcements were made aboard three other minesweepers sharing the same pier as USS Ardent. Following a policy implemented by the independent duty corpsman, all patients experiencing ILI symptoms were required to wear an N95 filtering facepiece respirator while shipboard until 5 days after onset of symptoms. Cleaning of spaces was done by regularly disinfecting all commonly touched surfaces with disinfecting wipes and mopping all decks with an iodophor disinfectant diluted to 150 ppm of iodine. E-mails and reports regarding the outbreak, with an emphasis on rapidly identifying patients with ILI, were distributed to all ships on Naval Base San Diego and to high-level Navy officials and County of San Diego Public Health Services. No additional cases were identified after February 14. A total of 43 working days were lost by the 25 ILI patients.

Discussion

USS Ardent, an Avenger class minesweeper, is one of the smallest ships in the U.S. Navy. It has one shared space in which the entire crew eats meals. Work areas are spread throughout the ship, and there are nine sleeping spaces. Military populations, especially those living and working in confined settings, are susceptible to respiratory disease outbreaks (5). Shipboard personnel are at especially high risk because of constant close quarter exposure to a large number of crew members (6). Virtually all areas onboard ships are shared, and movement frequently requires touching handrails, door knobs, and other objects that can be contaminated with nasal secretions. In addition, ventilation systems can circulate infectious pathogens throughout a ship (7).

As the ship was moored in San Diego, the entire crew worked onboard during the day, and 25% remained onboard through each night. The roster of crew members who remained onboard at night rotated daily. There were 16 cases of confirmed influenza A (H3N2)infection in San Diego County (Brit H. Colanter, MPH, Health and Human Services Agency County of San Diego, personal communication, 2014) during the 6 weeks leading to the ship outbreak, making it likely that the virus was acquired from the local community.

Since the 1950s, a policy of mandatory annual vaccination against influenza for active duty personnel has been largely successful in limiting influenza epidemics in the military (8). The current U.S. Department of Defense influenza vaccination policy mandates that all uniformed personnel receive seasonal influenza vaccination, unless medically exempt, or face punishment under the Uniform Code of Military Justice. The policy specifically directs all Navy operational units to be at least 90% vaccinated. However, despite vaccination measures, influenza outbreaks can still occur in highly vaccinated military populations (9,10).

1Mine Counter Measures Squadron Three, U.S. Navy; 2Naval Health Research Center, U.S. Navy; 3Navy Environmental and Preventive Medicine Unit Five, U.S. Navy; 4World Health Organization Collaborating Center for Influenza, CDC; 5Independent Duty Corpsman, USS Ardent (Corresponding author: Theodore L. Aquino, taquino@health.usf.edu, 850-284-1046)

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What is already known on this topic?

The single best way to prevent influenza infection is to receive vaccination every year. Some organizations have a mandatory vaccination policy. Despite this, influenza outbreaks can occur in highly vaccinated populations, especially in confined settings.

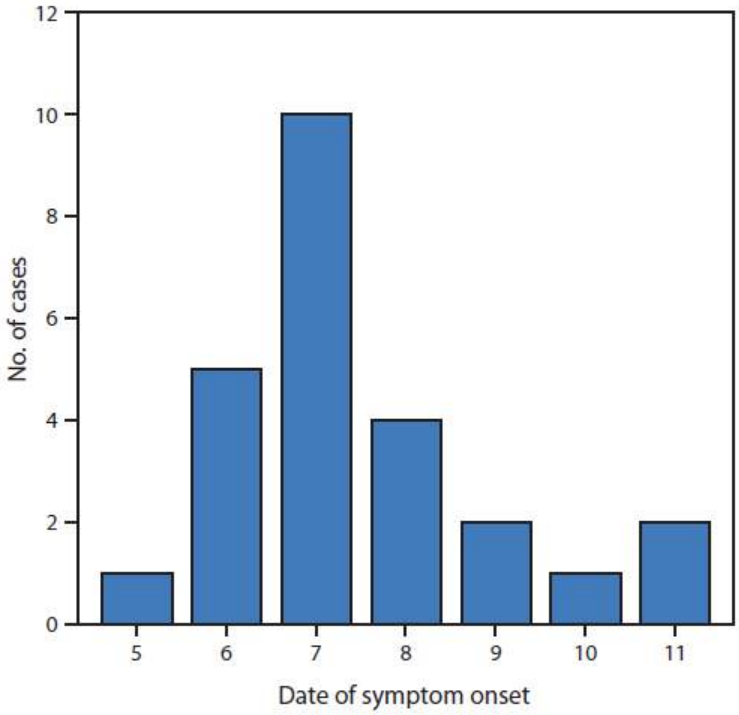
What is added by this report?

In February 2014, a total of 25 of the 102 crew members of a U.S. Navy minesweeper sought medical care because of influenza-like illness attributed to an influenza A (H3N2) virus antigenically similar to the H3N2 component of the 2013–14 vaccine. Among the crew members, 99% had received influenza vaccination, including 24 of 25 ill persons. Outbreak management included use of an antiviral medication, exclusion of the ill from the ship for 48 hours, disinfection, hand washing, and cough etiquette. No crew member had onset of symptoms >6 days after the first crew member had symptoms.

What are the implications for public health practice?

This influenza outbreak highlights the risk for an outbreak of influenza A (H3N2) in a cohort of vaccinated and otherwise healthy young persons.

FIGURE. Number of cases (N = 25) of influenza-like illness, by date of symptom onset — USS Ardent, February 5–11, 2014



Alternate Text: The figure above is a bar chart showing the number of cases (N = 25) of influenza-like illness, by date of symptom onset on the USS Ardent during February 5–11, 2014. Twenty crew members reported sick on February 10, one on February 11, and four more on February 12. Symptom onset dates were February 5–11.

PubMed

Format: Abstract

Can J Public Health. 1991 May-Jun;82(3):189-90.

[Major measles epidemic in the region of Quebec despite a 99% vaccine coverage].

[Article in French]

Boulianne N[1], De Serres G, Duval B, Joly JR, Meyer F, Déry P, Alary M, Le Hénaff D, Thériault N.

Author information

Abstract

The 1989 measles outbreak in the province of Quebec has been largely attributed to an incomplete vaccination coverage. In the Quebec City area (pop. 600,000) 1,363 confirmed cases of measles did occur. A case-control study conducted to evaluate risk factors for measles allowed us to estimate vaccination coverage. It was measured in classes where cases did occur during the outbreak. This population included 8,931 students aged 5 to 19 years old. The 563 cases and a random sample of two controls per case selected in the case's class were kept for analysis. The vaccination coverage among cases was at least 84.5%. Vaccination coverage for the total population was 99.0%. Incomplete vaccination coverage is not a valid explanation for the Quebec City measles outbreak.

PMID: 1884314

[Indexed for MEDLINE]

Publication type, MeSH terms

LinkOut - more resources

PubMed

Format: Abstract

Full text links

NEJM FULL TEXT

N Engl J Med. 1987 Mar 26;316(13):771-4.

Measles outbreak in a fully immunized secondary-school population.

Gustafson TL, Lievens AW, Brunell PA, Moellenberg RG, Buttery CM, Sehulster LM.

Abstract

An outbreak of measles occurred among adolescents in Corpus Christi, Texas, in the spring of 1985, even though vaccination requirements for school attendance had been thoroughly enforced. Serum samples from 1806 students at two secondary schools were obtained eight days after the onset of the first case. Only 4.1 percent of these students (74 of 1806) lacked detectable antibody to measles according to enzyme-linked immunosorbent assay, and more than 99 percent had records of vaccination with live measles vaccine. Stratified analysis showed that the number of doses of vaccine received was the most important predictor of antibody response. Ninety-five percent confidence intervals of seronegative rates were 0 to 3.3 percent for students who had received two prior doses of vaccine, as compared with 3.6 to 6.8 percent for students who had received only a single dose. After the survey, none of the 1732 seropositive students contracted measles. Fourteen of 74 seronegative students, all of whom had been vaccinated, contracted measles. In addition, three seronegative students seroconverted without experiencing any symptoms. We conclude that outbreaks of measles can occur in secondary schools, even when more than 99 percent of the students have been vaccinated and more than 95 percent are immune.

PMID: 3821823 DOI: 10.1056/NEJM198703263161303

[Indexed for MEDLINE]

MeSH terms, Substance

LinkOut - more resources

Whooping cough outbreak on Long Island

none

June 22, 2011 4:16:51 AM PDT

Eyewitness News

SMITHTOWN, N.Y. -- Officials on eastern Long Island are reporting an outbreak of whooping cough, also known as pertussis. Thirteen students in three schools in Smithtown have been confirmed with the contagious bacterial infection.

Health officials in Suffolk County said Tuesday they had alerted area pediatricians and had given advice to school officials on how to control the outbreak.

Pertussis causes an uncontrollable, violent cough lasting several weeks or even months. It may begin with cold-like symptoms or a dry cough that progress to episodes of severe coughing. It is spread from person to person.

Officials say all of the Smithtown students had been immunized, helping to reduce the severity of their illness.

The three schools with ill children are St. James Elementary School, Tackan Elementary School and Nesaquake Middle School.

Fordham University mumps outbreak jumps campuses

Dr. Sapna Parikh reports

February 21, 2014 8:35:57 AM PST

Eyewitness News

NEW YORK -- The outbreak of the mumps at Fordham University has spread from one campus to another.
There are now 13 reported cases, 12 at the Rose Hill campus in the Bronx and one at the Lincoln Center campus in Manhattan.

The symptoms are similar to the flu, but the virus can also cause painful swelling.

All of the infected patients had the mumps vaccine, but doctors say it's not 100 percent effective.

Infected students have been either isolated or sent home.

- UHS saw 1 case in January, 4 cases on Feb. 18; 3 cases on Feb. 19 and 5 cases on Feb. 20.

- All the students with suspected mumps infections have either returned home or have been isolated from other residents during the infectious phase of the illness.

- All Fordham students are required to have full vaccinations before attending the University, including the vaccination for mumps, measles, and rubella (MMR).

- All of the students who were tentatively diagnosed with mumps had been vaccinated. Vaccinations do not offer 100 percent protection, however, vaccination is still strongly recommended.

- Typically mumps patients are contagious for two days prior to the outbreak of symptoms and five days after.

Mumps is a viral infection. The symptoms are:

- Fever

- Headache

- Muscle aches

- Tiredness

- Loss of appetite

- Swollen and tender salivary glands under the ears or jaw on one or both sides of the face (parotitis)

Mumps is spread from person to person through contact with respiratory secretions, e.g., saliva and sneeze droplets, from an infected person. Items used by an infected person, such as cups, utensils, etc., can also be contaminated with the virus and should not be shared.

LINK: **MORE FROM CDC**

http://www.burnettcountysentinel.com/news/flu-season-continues-to-be-widespread-throughout-country/article_4bd056da-0c21-11e8-b6ae-533d3d165845.html

Flu season continues to be widespread throughout country

Jonathan Richie EDITOR@BURNETTCOUNTYSENTINEL.com Feb 8, 2018

Clarification: **Last week's article "Influenza potentially made stronger by vaccines" may have been misleading. The article's main source, Anna Treague, is not a nurse with the Centers for Disease Control (CDC). Treague, who was quoted, is a nurse with Burnett County Public Health. We regret the error and apologize for any confusion, inconvenience or misunderstanding it may have caused.**

The flu season has been in full swing for a few months. The seasonal disease has mutated over the years, and professionals say it has been made stronger as medicine continues to process vaccines.

According to the Centers for Disease Control and Prevention(CDC) this season's flu is widespread in 49 states, Wisconsin and Minnesota are covered in high levels of the flu.

"I believe that the low effective rate of the vaccine this year is due to the mutations that the virus made in the processing of the vaccine itself," said Anna Treague, nurse for Public Health. "That is at least part of the reason that influenza cases are so widespread this year."

The flu or influenza is a seasonal contagious respiratory disease that is caused by influenza viruses. The CDC says the dominant strain this year is H3N2, which tends to be more severe and causes more severe symptoms than most other strains.

Treague said that symptoms include fever, chills, headache, dry cough and aching of muscles and joints. They usually appear 1 to 3 days after being infected with most people recovering within a week.

"The H3N2 strain also has proven to not be as impacted by the vaccines as other strains," Treague said.

That being said, Treague still suggests everyone should get a flu shot.

"If you are able, get the flu shot," Treague said. "Even if the flu vaccine isn't as effective as it has been in year's past it does help. Some protection is better than no protection."

A number of different influenza vaccines are produced every year. The most common uses a chicken egg to grow the virus, which is why people with an egg allergy need a special type of vaccine. Some vaccines are trivalent (containing 3 virus strains) or quadrivalent (containing 4 virus strains.)

Treague said the flu shot is a inactive/killed virus and the nasal spray from in alive, but weakened strain.

Typically production for the next year's flu shots are developed before the current season of the flu ended.

Treague explained that there are two main viruses associated with the flu, type A and type B. It spread through droplets of moisture that go from person to person when they sneeze, cough, or talk. Those droplets are then inhaled by another person and that is how it spreads.

“I think it is important that people know how serious influenza can be for certain people, especially those who are very young and the older population,” Treague said.

She said this is because at the beginning and end of one’s life their immune system is not as strong and their bodies have to work harder to fight off viruses and compensate for the symptoms of influenza.

“Fortunately, in Wisconsin to date there has been no influenza-associated pediatric deaths reported, whereas nationwide there have been 37,” Treague said.

Treague said anyone experiencing symptoms should see their doctor immediately so it can be caught in the early stages and treated with antiviral medication. She also stressed proper hand hygiene and covering one’s mouth when coughing is instrumental in not spreading the flu.

“Another thing to help avoid spreading influenza, if you are sick, stay home,” Treague said “Please take a break from daily errands and rest, don’t venture out unless needed, if you have to venture out wear a mask, to prevent the spreading of the virus through those moisture droplets.”

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Articles

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Herd Immunity and Compulsory Childhood Vaccination: Does the Theory Justify the Law?

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ABSTRACT

Compulsory childhood vaccination is a cornerstone of U.S. public health policy. All fifty states compel children to vaccinate against many infectious diseases to achieve so-called herd immunity, a scientific theory that attempts to explain how societies protect themselves against infectious disease.

This Article explores both the theory and practice of herd immunity. The authors evaluate the scientific assumptions underlying the theory, how the theory applies in law, a game theory approach to herd immunity, and a possible framework for rational policymaking. The Article argues that *herd immunity* is unattainable for most diseases and is therefore an irrational goal. Instead, the authors conclude that *herd effect* is attainable and that a voluntary vaccination marketplace, not command-and-control compulsion, would most efficiently achieve that goal.

The Article takes on the bugaboo of the citizen "free rider" who is out to game the system, how a vaccination marketplace might work, and what factors policymakers must take into account in developing sound policies. The Article concludes that it is time for states to adopt more realistic and cost-efficient laws to achieve attainable herd effect, not illusory herd immunity.

INTRODUCTION

Many state and federal laws compel childhood vaccination based on the theory of herd immunity.[1] The theory describes a form of indirect protection in which non-immune individuals are protected from those that have acquired a disease and recovered.[2] Promoters of

Natural Immunity

[1] *See* James G. Hodge, Jr. & Lawrence O. Gostin, *School Vaccination Requirements: Historical, Social, and Legal Perspectives*, 90 KY. L.J. 831, 833 (2002) ("Each state has school vaccination laws which require children of appropriate age to be vaccinated for several communicable diseases." (citation omitted)); *see also State Information*, IMMUNIZATION ACTION COALITION, http://www.immunize.org/laws (last visited Mar. 6, 2014) (showing vaccination mandates by state, and while the Immunization Action Coalition is solely responsible for this website, its information is based on government sources, and the website is funded in part by the Centers for Disease Control and Prevention).

[2] *See, e.g.*, Paul Fine et al., *"Herd Immunity": A Rough Guide*, 52 CLINICAL INFECTIOUS DISEASES 911 (2011) [hereinafter Fine, *Rough Guide*]; Paul E.M. Fine, *Herd Immunity: History, Theory, Practice*, 15 EPIDEMIOLOGIC REVS. 265 (1993) [hereinafter Fine, *History*]; John P. Fox et al., *Herd Immunity: Basic Concept and Relevance to Public Health Immunization Practices*, 94 J. EPIDEMIOLOGY 179 (1971).

universal vaccination adopted this theory, suggesting that it applies to vaccine-induced immunity as well.[3] Today, herd immunity is the central rationale for compulsory vaccination, and the U.S. Supreme Court has long upheld the right of states to mandate vaccines under certain circumstances.[4] Vaccine proponents in the United States argue that the theory justifies vaccination of all children against vaccine-targeted diseases, except those few children with lawful exemptions.[5] Today, at or above ninety percent of all U.S. children have been vaccinated against routine childhood diseases, including measles, mumps, and pertussis.[6]

But the theory of herd immunity alone does not justify compulsion. The leap in logic from herd immunity theory to compulsory vaccination programs requires three fundamental assumptions: (1) that herd immunity is a valid and obtainable objective of vaccination policy; (2) that without compulsion, unvaccinated individuals, or their guardians, will seek to "free ride" on the immunity of the community; and (3) that individuals have an implied duty to society to be vaccinated to achieve herd immunity.[7] This Article looks at the underpinnings of the herd immunity theory and at the ties binding the theory to compulsory laws. Is herd immunity obtainable with modern vaccines? Are the assumptions of the theory relevant in the real world? Is there a free rider problem? Do members of society, and children in particular, have an obligation to accept vaccines "for the good of the herd"?

This Article concludes that herd immunity has only limited application in the world of policy. Given contemporary, imperfect vaccine technology and geographical and age-stratified vaccination mandates, herd immunity does not exist and is not attainable. Therefore, policy should seek to maximize attainable benefits, not unattainable ones, by relying on herd effect and the optimal use of scarce resources.

A game theory approach suggests that a market based on individual vaccination choices would best protect society. Game theory refutes

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[3] *Id.*

[4] *See* Jacobson v. Massachusetts, 197 U.S. 11 (1905).

[5] *See* Hodge, Jr. & Gostin, *supra* note 1.

[6] Ctrs. for Disease Control & Prevention, *National, State, and Local Area Vaccination Coverage Among Children Aged 19–35 Months—United States, 2009*, 59 MORBIDITY & MORTALITY WKLY. REP. 1171, 1171–73 (2010), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5936a2.htm.

[7] *See* Douglas S. Diekema, *Choices Should Have Consequences: Failure to Vaccinate, Harm to Others, and Civil Liability*, 107 MICH. L. REV. FIRST IMPRESSIONS 90 (2009).

the free rider problem by showing that a unique equilibrium point exists that best balances vaccination benefits and disease harms. The Article finds that market-based, not regulatory, solutions better fit vaccination decision making.[8] This market approach suggests that in the long term, individuals will appropriately balance the relative costs of vaccination and infection, leading people to vaccinate voluntarily in light of the cost-benefit analysis. Although the equilibrium vaccination coverage is in almost all cases lower than the herd immunity threshold, "soft" regulation can achieve aggregate health benefits for society without imposing inefficient marginal costs on individuals and the healthcare system.[9] We therefore argue that personal choices in a market with adequate information would better allocate scarce healthcare resources, better protect the public health, and better respect individual autonomy. Our viewpoint may help explain why many developed countries, including those with political systems closest to our own, have only voluntary childhood vaccination programs. Vaccination uptake and disease levels in these countries, including Canada, the United Kingdom, Australia, and New Zealand, are comparable to those in the United States.[10]

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[8] Such market-based approaches have been well described in the literature of administrative and regulatory law. *See generally* OFFICE OF MGMT. & BUDGET, CIRCULAR A-4, at 7-9 (2003), *available at* http://www.whitehouse.gov/omb/circulars_a004_a-4 (outlining alternatives to federal regulation, including specification of performance as opposed to design standards, use of economic incentives, and informational measures); Bruce A. Ackerman & Richard B. Stewart, *Reforming Environmental Law*, 37 STAN. L. REV. 1333, 1336–37 (1985) (describing the "massive information-gathering burdens" on administrators attempting to impose command-and-control emissions regulations).

[9] *Cf.* Exec. Order No. 12,866 § 1(b)(3), 58 Fed. Reg. 190 (Oct. 4, 1993) ("Each agency shall identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as . . . providing information upon which choices can be made by the public."); *id.* at § 1(b)(6) ("Each agency shall assess both the costs and the benefits of the intended regulation and . . . propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs."); *see also* Exec. Order No. 13,563 § 1(b), 76 Fed. Reg. 14 (Jan. 21, 2011) (supplementing Exec. Order No. 12,866 and reaffirming general principles of regulatory policy).

[10] There is no mandatory vaccination in the United Kingdom. *Childhood Immunisation: A Guide for Healthcare Professionals*, BRIT. MED. ASS'N (June 2003), http://www .worcslmc.co.uk/upload/Childhood_Immunisation_June_03.pdf. Scandinavia and Germany also rely on voluntary vaccination rather than compulsion. *Id.* There are some vaccination requirements in Australia, but there is a broad right of conscientious objection. *Id.* Some provinces in Canada require vaccines but allow conscientious objection, and the country as a whole does not mandate vaccination. *Vaccine Safety Frequently Asked Questions*, PUB. HEALTH AGENCY OF CAN., http://www.phac-aspc .gc.ca/im/vs-sv/vs-faq16-eng.php (last modified Aug. 27, 2012). In 2012, the United Kingdom, with a

Every state in the United States currently mandates roughly twenty-five to thirty-five doses of vaccines to preschoolers and school-aged children, with limited rights of exemption.[11] While there are other vaccination mandates in the United States for military personnel, hospital workers, and university students, to name a few, this Article focuses exclusively on state mandates for preschoolers and schoolchildren. Today, if children do not comply with state vaccination mandates and do not have valid exemptions, they lose their ability to attend school, a fundamental right and obligation of citizenship.[12] Further, state agents may charge the parents with medical neglect and potentially remove children to foster care for failure to vaccinate.[13] Even if a state offers limited medical, religious, and philosophical exemptions, we consider its vaccination mandate to be compulsory for purposes of this Article. We do so because in the majority of states, exemptions are extremely limited,[14] and even in those states where they exist, there are strong legislative efforts to curtail them.[15] We note at the outset that many vaccine-related issues are beyond the scope of this Article. While further considerations of

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population of roughly 63 million, had 0 reported cases of diphtheria, 2092 reported cases of measles, and 3178 reported cases of mumps. *WHO Vaccine-Preventable Diseases: Monitoring System. 2014 Global Summary*, WORLD HEALTH ORG., http://apps.who.int/immunization_monitoring/globalsummary/ (select "United Kingdom of Great Britain and Northern Ireland (the)" from the dropdown menu) (last updated July 15, 2014). Similarly, Australia, with a population of roughly 23 million, had 0 reported cases of diphtheria, 199 reported cases of measles, and 195 reported cases of mumps in 2012. *Id.* (select "Australia" from the dropdown menu). In 2012, the United States, where choice is more limited, with a population of roughly 317 million, had 1 reported case of diphtheria, 55 reported cases of measles, and 229 reported cases of mumps. *Id.* (select "United States of America (the)" from the dropdown menu).

11 *See States with Religious and Philosophical Exemptions from School Immunization Requirements,* NAT'L CONF. STATE LEGISLATURES (Dec. 2012), http://www.ncsl.org/research/health/school-immunization-exemption-state-laws.aspx (showing that only Mississippi and West Virginia do not have religious exemptions).

12 *See, e.g.*, N.Y. PUB. HEALTH LAW § 2164 (Consol. 2011).

13 *See* Kim Mack Rosenberg, *Forced Child Removal*, *in* VACCINE EPIDEMIC: HOW CORPORATE GREED, BIASED SCIENCE, AND COERCIVE GOVERNMENT THREATEN OUR HUMAN RIGHTS, OUR HEALTH, AND OUR CHILDREN 238 (Louise Kuo Habakus & Mary Holland eds., 2012).

14 *See* Y. Tony Yang & Vicky Debold, *A Longitudinal Analysis of the Effect of Nonmedical Exemption Law and Vaccine Uptake on Vaccine-Targeted Disease Rates*, 104 AM. J. PUB. HEALTH 371 (2014) (stating that fewer than ten percent of all children have exemptions).

15 *See, e.g.*, First Warning Letter from Jane R. Zucker, Assistant Comm'r, N.Y.C. Dep't of Health & Mental Hygiene, to Principals (Nov. 8, 2012), *available at* http://schools.nyc.gov/NR/rdonlyres/1B9F9BF4-34AE-49B9-8C45-B0176A0CA970/0/FirstWarningLetter.pdf (threatening principals if they do not achieve 98.8% vaccination compliance).

personal autonomy, vaccine safety, and vaccine injury are all critical and interrelated, we do not consider those issues in depth here.[16]

Part I defines and analyzes herd immunity and the closely related but distinct concept of herd effect. It contrasts disease eradication and elimination with control, highlighting the limits of what modern vaccination programs can achieve. It then explores the real world of disease outbreaks in vaccinated and unvaccinated populations. Part II introduces the Feudtner-Marcuse framework for "just" vaccination policy. This systematic approach highlights seven objectives of vaccination programs, including mandatory ones. Part III reviews game theory to understand the factors that drive people to choose or decline vaccination. We discuss a social equilibrium point that maximizes net public health gains. The Article ends by summarizing our conclusions and recommendations for U.S. vaccination policies.

I
HERD IMMUNITY AND ITS ASSUMPTIONS

Herd immunity depends on the time a disease persists within an infected host and the rate at which the disease spreads.[17] In a population of only susceptible individuals, the introduction of a single infected person will result in indiscriminate transmission to all others whom the infected person contacts until those infected people die or recover.[18] The average number of people in such a susceptible population who become infected is the so-called *basic reproduction number* R_0.[19] Each of those people who contracted the disease from the initial infected individual is able to transmit the disease to other susceptible contacts; this process repeats itself until the entire

16 Other sources provide more in-depth considerations of these issues. *See generally* VACCINE EPIDEMIC: HOW CORPORATE GREED, BIASED SCIENCE, AND COERCIVE GOVERNMENT THREATEN OUR HUMAN RIGHTS, OUR HEALTH, AND OUR CHILDREN, *supra* note 13; *see also* Mary Holland et al., *Unanswered Questions from the Vaccine Injury Compensation Program: A Review of Compensated Cases of Vaccine-Induced Brain Injury*, 28 PACE ENVTL. L. REV. 480 (2011).

17 *See* J.M. Heffernan et al., *Perspectives on the Basic Reproductive Ratio*, 2 J. ROYAL SOC'Y INTERFACE 281 (2005).

18 *See* Fine, *History*, *supra* note 2, at 273 fig.5 (showing one hundred percent transmission from one individual to all other individuals with whom he or she has effective contact in an entirely susceptible population).

19 Heffernan et al., *supra* note 17.

population is infected.[20] This model of disease transmission exhibits *epidemic* dynamics.[21]

A. Herd Immunity Threshold

By contrast, consider the case where a certain fraction θ of the population has immunity to the disease. If a single infected individual comes into the population, the average number of secondary infections from transmission is then $R_0(1-\theta)$.[22] If $R_0(1-\theta) < 1$, then the disease on average will not spread to other susceptible people.[23] This means that the disease is likely to die out either through the host's death or recovery before further spread.[24] The threshold θ_H of immune individuals to create these circumstances is $\theta_H = 1-1/R_0$, or the *herd immunity threshold*.[25] The underlying rationale for mass vaccination policies is to ensure that the fraction of immune individuals in society is above the herd immunity threshold, thus eliminating the disease from the population.[26] The moral of the herd immunity story, though, is that not every individual needs to be immune to provide protection to the society as a whole.[27]

B. Herd Effect

The concept of herd immunity refers to the complete removal of a disease from society; so long as *any* member of the population has immunity to the disease, however, the disease's ability to spread

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[20] *See* Fine, *History*, *supra* note 2 (showing the complete spread of infection in an entirely susceptible society).

[21] *See id.* at 269 (defining the epidemic threshold for a simple mass-action model of infectious dynamics).

[22] To derive this relationship, note that within a susceptible population of size N, a single infectious individual will infect on average R_0 persons. If N_V members of the population have immunity to the disease, however, then transmission is only possible within a subpopulation of size $N-N_V$. The resulting average number of secondary infections then decreases to $(R_0/N)(N-N_V) = R_0(1-N_V/N) = R_0(1-\theta)$.

[23] *See* Heffernan et al., *supra* note 17, at 281–87.

[24] *Id.*

[25] *See generally* Fine, *History*, *supra* note 2, at 269 (providing one example of use of the herd immunity threshold); Fine, *Rough Guide*, *supra* note 2, at 912 fig.1 (providing another example of use of the herd immunity threshold).

[26] *See* Fine, *Rough Guide*, *supra* note 2 (discussing the success of vaccination programs against measles, mumps, rubella, etc. in delaying or averting epidemics by keeping the amount of susceptible individuals below the threshold); *see also* Fine, *History*, *supra* note 2 (discussing the success of the global smallpox eradication program).

[27] *See* Fine, *History*, *supra* note 2.

lessens.[28] This decrease in the rate of epidemic transmission is the *herd effect*.[29] Even if herd immunity itself is not achievable, society still benefits from a "buffer" of immune individuals in order to mitigate disease.[30] Although the concepts of herd immunity and herd effect are sometimes interchangeable, they describe different aspects of the immunity puzzle—whereas herd immunity aims to *eliminate* a disease from society, herd effect refers to infection *control*.[31] Since the 1960s, compulsory state vaccination programs have achieved herd effects for specific diseases, but none has achieved herd immunity. We maintain the analytic distinction between these terms in the discussion below.

C. The Free Rider Problem

Why are universal mandatory vaccination policies necessary if we can achieve herd immunity by vaccinating only a fraction of the population? Proponents of compulsion argue that if vaccination is not mandatory, then herd immunity is generally unattainable due to a *free rider problem*.[32] From the perspective of an individual weighing the decision to vaccinate, it is in her best interest not to vaccinate because she is unlikely to become sick if all others are immune and are unlikely to transmit disease.[33] This decision-maker could then "free ride" on the immunity of others.[34]

If all individuals in a population attempt to free ride, then they all run the risk of illness. If the expected risks of vaccine injury outweigh those of illness, then no one will choose to vaccinate.[35] This situation

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28 *See* T. Jacob John & Reuben Samuel, *Herd Immunity and Herd Effect: New Insights and Definitions*, 16 EUR. J. EPIDEMIOLOGY 601, 601 (2000) (defining herd effect).

29 *See id.* (distinguishing herd effect and herd immunity).

30 *See* Fine, *Rough Guide*, *supra* note 2, at 912 (discussing the importance of "selective vaccination"—specifically, vaccinating groups that play an important role in transmission, either in slowing transmission or reducing incidence among the entire population).

31 *See infra* Part I.F. (discussing definitions of "control" and "elimination" in the context of vaccination policy).

32 *See* Fine, *Rough Guide*, *supra* note 2, at 914.

33 *See id.*

34 *See id.*

35 It is essential to distinguish between *perceived* and *absolute* costs of vaccination and infection. In general, individuals in society operate under limited information as to the probabilities of vaccine-related harm and infection and thus make individual estimations of expected costs consistent with such incomplete information. If all members of society had perfect information, absolute costs of vaccination and infection could be determined. In practice, such perfect information is never available. *See infra* Part III.

represents a *tragedy of the commons*, in which society loses an important benefit because of competing individual interests.[36] As the rate of infection decreases, individuals may perceive the risks of infection as declining, inducing some individuals to forego vaccination. This scenario has led some to decry that vaccines are the "victim[s] of their own success."[37] Compulsory vaccination is then one solution to the potential free rider problem because it forces all children to assume part of the collective responsibility to prevent infectious disease.[38]

D. Assumptions Underlying Herd Immunity Theory

The potential social costs of the free rider problem are severe in the face of a highly infectious, life-threatening disease and the failure to reach the herd immunity threshold.[39] Under what conditions, however, is herd immunity actually possible? Many of the underlying assumptions of herd immunity may be irrelevant in the real world, as authoritative scientists have acknowledged.[40] We address the following core assumptions of the theory[41]:

1. Population homogeneity;
2. Well-mixing of the population;
3. Random vaccination of individuals;
4. Perfect vaccine efficacy; and
5. Age uniformity in the population.

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36 *See* Chris T. Bauch et al., *Rapid Emergence of Free-Riding Behavior in New Pediatric Immunization Programs*, 5 PLOS ONE 1, 1 (2010).

37 *See* Matthew Janko, *Vaccination: A Victim of Its Own Success*, 14 VIRTUAL MENTOR 3, 4 (2012).

38 Dagobert L. Brito et al., *Externalities and Compulsory Vaccinations*, 45 J. PUB. ECON. 69, 69–70 (1991) (quoting J.E. STIGLITZ, ECONOMICS OF THE PUBLIC SECTOR 210 (2d ed. 1988)).

39 *See, e.g.*, V.A.A. Jansen et al., *Measles Outbreaks in a Population with Declining Vaccine Uptake*, 301 SCIENCE 804, 804 (2003) (relating the decline in measles vaccinations to "a number of large measles outbreaks").

40 *See* Fine, *History*, *supra* note 2, at 276.

41 *See id.* (naming an incomplete list of assumptions); *see also* Fine, *Rough Guide*, *supra* note 2, at 912–14 (discussing probable complexities that would upset the core assumptions).

1. The Assumption of Population Homogeneity

Population homogeneity involves two related but distinct concepts: (1) compositional homogeneity and (2) spatial homogeneity.[42] Compositional homogeneity means that all individuals belong to a single identifiable group.[43] Persons within this group transmit the disease among themselves as if all group members are the same.[44] Compositional homogeneity ignores racial, sociological, economic, and genetic differences, all of which in the real world may affect resistance to an infectious disease.[45]

Spatial homogeneity, by contrast, refers to the degree of uniform spread over a geographic region.[46] Spatial homogeneity assumes that people behave identically in spreading disease.[47] But if a group of people lives in a particular area, and its members spread disease differently from the rest of society, then this violates the assumption of interchangeability.[48] For the simple analysis of herd immunity to hold true, both compositional and spatial homogeneity must exist.[49]

As a practical matter, however, compositional homogeneity *never* holds. Social stratification by age, ethnicity, class, gender, race, and sexual orientation, among other factors, results in differing individual risks.[50] For example, the Centers for Disease Control and Prevention (CDC) noted that more than fifty percent of all new cases of HIV infection between 2006 and 2009 were among men who have sex

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42 *See generally* DIETRICH STOYAN ET AL., STOCHASTIC GEOMETRY AND ITS APPLICATIONS (2d ed. 1995) (discussing spatial homogeneity in the context of stochastic point processes); *see also* Fine, *Rough Guide*, *supra* note 2, at 913 (discussing models of heterogeneous populations).

43 *Id.*

44 *Id.*

45 *Id.*

46 *See generally* STOYAN ET AL., *supra* note 42.

47 Spatial homogeneity is mathematically defined by the property of translation-invariance for all probabilistic descriptors governing the spatial correlations among groups of individuals within a population, implying that the choice of origin for a Euclidean coordinate system adopted to describe the spatial region does not affect measured statistical properties.

48 Fine, *Rough Guide*, *supra* note 2, at 913.

49 *Id.* (listing heterogeneous populations as a complex problem disrupting herd immunity's core assumptions).

50 *See generally CDC Fact Sheet: Estimates of New HIV Infections in the United States, 2006–2009,* CTRS. FOR DISEASE CONTROL & PREVENTION 1, 3 (Aug. 2011), http://www.cdc.gov/nchhstp/newsroom/docs/Hiv-infections-2006-2009.pdf (providing statistics showing disparities in HIV outbreaks among differing populations).

with men.[51] Additionally, African Americans accounted for forty-four percent of new HIV infections in 2009.[52] These types of differences are compositional, relating to characteristics that distinguish population subgroups. Compositional heterogeneity increases the herd immunity threshold for the population, meaning that the minimum number of people vaccinated must be higher, because vaccination of low-risk individuals provides little marginal herd effect.

Spatial homogeneity, another bedrock assumption of herd immunity, similarly does not hold true in practice.[53] Scientists have studied the effects of clustering using network models, showing individuals as nodes on a graph with intersections indicating transmissible contacts.[54] Limiting the types and numbers of transmissible contacts can substantially change the rate at which a disease spreads through the population.[55] The existence of isolated, highly clustered groups of susceptible individuals can increase the required herd immunity threshold for the population as a whole because vaccinating people outside the clustered group provides little benefit.

Diseases spread more slowly when there is more distance between people.[56] This spatial effect can result in rapid disease spread within clustered areas, such as cities, even when disease spread is decreasing overall.[57] As travel technology continues to develop, diseases can spread quickly, both domestically and internationally. However, spatial dissemination coupled with transmission dynamics may lead to

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51 *Id.*

52 *Id.* at 4.

53 *See* Martial L. Ndeffo Mbah et al., *The Impact of Imitation on Vaccination Behavior in Social Contact Networks*, 8 PLOS COMPUTATIONAL BIOLOGY 1, 7 (2012) (noting that spatial homogeneity fails to take into account the fact that "individuals frequently imitate others").

54 *See generally* Chris T. Bauch & Alison P. Galvani, *Using Network Models to Approximate Spatial Point-Process Models*, 184 MATHEMATICAL BIOSCIENCES 101 (2003) (using network models to evaluate spatial effects on ecological and epidemiological systems); Matt J. Keeling & Ken T.D. Eames, *Networks and Epidemic Models*, 2 J. ROYAL SOC'Y INTERFACE 295 (2005) (providing an overview of the process of approximating a network); Martial L. Ndeffo Mbah et al., *supra* note 53 (using network-based models to examine the correlation between the spread of disease and social contacts).

55 Keeling & Eames, *supra* note 54, at 300–01 (contrasting networking models that account for clustering with random networks, which assume that connections are formed at random).

56 *See* Bauch & Galvani, *supra* note 54, at 102.

57 *Id.*

stationary patterns of infectious regions.[58] In sum, neither compositional nor spatial homogeneity assumptions hold true in the real world.

2. The Assumption of a Well-Mixed Population

The well-mixing assumption refers to the notion that all susceptible individuals are equally likely to become sick from an infectious individual.[59] Network models can test the well-mixing assumption and, in a well-mixed population, each node in a network model will have an intersection with every other node in that same model.[60] To understand how well-mixing affects the dynamics, consider the simple case of a population of nine individuals, three of whom are susceptible and six of whom are infected. If each infected individual contacts only one susceptible person, and if each susceptible person contacts two infected people, it follows that there are only six possible transmissible contacts in the population.

By contrast, the well-mixing assumption implies that there are eighteen transmissible contacts, overestimating the disease propagation rate by a factor of three. Isolated groups of highly connected, susceptible people may face particularly rapid disease transmission that might otherwise have spread relatively slowly through the population as a whole.[61] Clustering of susceptible individuals is again the key to understanding how to control disease dynamics. Indeed, all statewide mandates are for children and young adults, representing clusterings of susceptible individuals. No states mandate vaccination for the entire population today. The result of this

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58 This pattern-forming phenomenon arises from an identical mechanism for the formation of so-called Turing patterns in reaction-diffusion chemical systems. Such patterns, which are stationary in time but heterogeneous in space, develop when an "inhibiting" species diffuses faster in space than a competing "growth" species, resulting in local activation of dynamic transmission that is inhibited on a global scale. *See* A.M. Turing, *The Chemical Basis of Morphogenesis*, 237 PHIL. TRANSACTIONS ROYAL SOC'Y LONDON 37, 57–58 (1952).

59 James Holland Jones, *Notes on R_0*, DEP'T ANTHROPOLOGICAL SCI. STANFORD U. 1, 2 (2007), http://www.stanford.edu/~jhj1/teachingdocs/Jones-on-R0.pdf.

60 Alun L. Lloyd et al., *Infection Dynamics on Small-World Networks*, *in* MATHEMATICAL STUDIES ON HUMAN DISEASE DYNAMICS: EMERGING PARADIGMS AND CHALLENGES 209, 220–21 (Contemporary Mathematics Ser. Vol. 412, Abba B. Gumel et al. eds., 2006).

61 *See* Fine, *Rough Guide*, *supra* note 2, at 913–14.

type of clustering is that the herd immunity threshold may be higher than estimated from the well-mixing assumption.[62]

U.S. policies for hepatitis B disease prevention provide a good example of how the well-mixing assumption applies in practice.[63] Although only a small portion of the U.S. population was at risk of contracting hepatitis B, namely intravenous drug users, those who had unprotected sex with multiple partners, and infants of hepatitis B positive mothers, it proved difficult for public health authorities to gain compliance among these target groups in the 1980s.[64] As a result, even though the herd immunity threshold would be much lower for the general population than the target group, U.S. public health authorities recommended universal vaccination of infants against hepatitis B to achieve herd immunity, and forty-seven states now mandate the vaccine.[65]

3. The Assumption of Random Vaccination of Individuals

In a heterogeneous population, different subgroups may face unique risks to certain infections and vaccine injuries.[66] A vaccination program that randomly immunizes people will generally require an especially high vaccination coverage ratio to achieve herd immunity because the disease will be able to propagate efficiently among high-risk individuals.[67] One solution is therefore to target the vaccination

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62 *See id.* at 913.

63 *See* Mary Holland, *Compulsory Vaccination, the Constitution, and the Hepatitis B Mandate for Infants and Young Children*, 12 YALE J. HEALTH POL'Y L. & ETHICS 39, 41 (2012); Rui Xu & Zhien Ma, *An HBV Model with Diffusion and Time Delay*, 257 J. THEORETICAL BIOLOGY 499, 499 (noting that "it is implicitly assumed that cells and viruses are well mixed").

64 Holland, *supra* note 63, at 68–69 (citing Ctrs. for Disease Control & Prevention, *Recommendation of the Immunization Practices Advisory Committee (ACIP) Inactivated Hepatitis B Virus Vaccine*, 31 MORBIDITY & MORTALITY WKLY. REP. 317 (1982), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/00001116.htm) (outlining recommendations of U.S. public health authorities that "higher-risk groups" receive hepatitis B vaccinations).

65 *See Hepatitis B Prevention Mandates for Daycare and K-12,* IMMUNIZATION ACTION COALITION, http://www.immunize.org/laws/hepb.asp (last updated May 26, 2011).

66 *See People at High Risk of Developing Flu-Related Complications,* CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/flu/about/disease/high_risk.htm (last updated Nov. 7, 2013) (listing specific subgroups that are particularly susceptible to flu-related complications).

67 *See* Fine, *Rough Guide*, *supra* note 2, at 914.

program only to those individuals who are at a highest risk of infection.[68]

Fine provides a simple example of this type of targeted vaccination program by considering a sample population composed of two equal-sized subgroups: high-risk and low-risk.[69] Following Fine's analysis, assume that each individual in the high-risk group, if infected, would infect five other high-risk members, and each low-risk individual, if infected, would infect one other low-risk member.[70] Under this idealized scheme, the high-risk and low-risk dynamics are separable because there are no transmissible contacts between groups.[71] The disease among the low-risk group is controllable without vaccination because the reproduction rate, $R_0^{(\mathrm{LR})}$, for the low-risk group is one, meaning that each person in this group would infect one other person on average.[72] This implies that the herd immunity threshold within the low-risk group is zero, and the disease will not spread, or $\theta_H^{(\mathrm{LR})} = 0$.[73]

By contrast, the disease will exhibit epidemic dynamics among the high-risk group because each high-risk individual will on average infect five others, so $R_0^{(\mathrm{HR})} = 5$ and $\theta_H^{(\mathrm{HR})} = 0.8$.[74] If vaccination is only for the high-risk group, only 80% of that group needs to receive the vaccine to induce herd immunity in the population as a whole.[75] Surprisingly, such a program targeted only at high-risk individuals would require vaccinating only 40% of the total population, representing a substantial increase in the health of society at lower financial cost and risk of vaccine injury.[76] But a vaccination program that randomly vaccinated 80% of the total population from the high-risk and low-risk groups would *not* provide herd immunity at all

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68 *See* Holland, *supra* note 63, at 68 (targeting hepatitis B vaccinations to high-risk groups).

69 Fine, *Rough Guide*, *supra* note 2, at 914.

70 *Id.*

71 *See id.*

72 *See id.*

73 Some care is required here. If $R_0 = 1$ exactly, then the disease will exist in an endemic steady state in which the number of infected individuals neither increases nor decreases on average. We therefore assume without loss of generality that the basic reproduction number is actually infinitesimally smaller than one to ensure that the disease is unable to sustain itself.

74 Fine, *Rough Guide*, *supra* note 2, at 914.

75 *Id.*

76 *See id.*

because the fractional vaccination coverage for the high-risk population would be less than its required herd immunity threshold.[77]

Although society can achieve the greatest benefits by targeting high-risk groups, such a policy imposes the full costs of vaccination on one identifiable group while the benefits diffuse to the greater population.[78] One could characterize this program as imposing a tax on specific individuals based on inherent characteristics,[79] precluding an equitable distribution of the costs and benefits to society. This policy becomes particularly troubling when its targets are children, who are low-risk subjects, selected for convenience, as in the case with mandatory vaccination of schoolchildren against hepatitis B, a sexually transmitted disease.[80] Random vaccination fails to maximize herd immunity or herd effect; only targeted or universal vaccination can achieve that result.

4. The Assumption of Perfect Vaccine Efficacy

Vaccines do not induce immunity perfectly; they usually fail in a certain fraction of people for a variety of reasons.[81] Furthermore, as a practical matter, vaccine "efficacy" is highly uncertain.[82] Scientists refer to efficacy as the relative fractional decrease in the rate of disease transmission between unvaccinated and vaccinated individuals in double-blind, randomized, clinically-controlled studies.[83] By contrast, the concept of vaccine "effectiveness" refers to the performance of the vaccine in the "real world," outside of clinical trials.[84] This distinction is not necessarily clear because the goal of

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77 *See id.*

78 *See id.* (discussing potential equal rights violations in mandating that all young children receive the hepatitis B vaccine).

79 Indeed, the Supreme Court's recent extension of the taxation power in the Court's ruling on the Affordable Care Act suggests that such a tax may be constitutional. *See* Nat'l Fed'n of Indep. Bus. v. Sebelius, 132 S. Ct. 2566, 2599 (2012) (holding that the Constitution does not protect individuals from "taxation through inactivity").

80 *See* Holland, *supra* note 63, at 41.

81 *See Flu Vaccine Effectiveness: Questions and Answers for Health Professionals*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm (last updated Nov. 27, 2013) (finding, for example, that influenza vaccines are less effective in people with chronic, high-risk medical conditions).

82 John Clemens et al., *Evaluating New Vaccines for Developing Countries: Efficacy or Effectiveness?*, 275 J. AM. MED. ASS'N 390, 392 (1996).

83 *See* Geoffrey A. Weinberg & Peter G. Szilagyi, *Vaccine Epidemiology: Efficacy, Effectiveness, and the Translational Research Roadmap*, 201 J. INFECTIOUS DISEASES 1607 (2010); Fine, *Rough Guide*, *supra* note 2, at 913 tbl.1; *Flu Vaccine Effectiveness: Questions and Answers for Health Professionals*, *supra* note 81.

84 Weinberg & Szilagyi, *supra* note 83, at 1608.

any vaccination policy is to control the rate of disease transmission. Nevertheless, either definition is sufficient for our discussion of herd immunity.

If a fraction, ϕ, of the vaccinated population fails to develop immunity and thus remains susceptible to infection, then the fraction of the total population that must receive the vaccine to ensure herd immunity is $\theta_H' = (1\text{-}1/R_0)/\phi = \theta_H/\phi$.[85] If the fraction of the population that fails to develop immunity is greater than the herd immunity threshold, or $\phi < \theta_H$, then herd immunity is theoretically impossible, even if the entire population is vaccinated.[86] A herd immunity threshold, θ_H, is generally high, ranging from 80%–99%.[87] For example, Fine estimates that the threshold for measles is 83%–94% and pertussis is 92%–94%.[88] As an illustration of the problem, measles vaccine has an estimated vaccine efficacy rate of 85%–95% for the first dose given to babies between 12 and 15 months.[89] This leaves unclear whether herd immunity is even theoretically achievable for measles. Thus, the assumption of perfect vaccine efficacy has limited bearing in real-world conditions.

5. The Assumption of Age Uniformity

Modern immunization programs target infants and young children for both scientific and practical reasons. Experience and science suggest that children are more vulnerable to infectious disease, but the practical reasons are also compelling.[90] Linking recommended and compulsory vaccination to "well-baby" and school check-ups provides a relatively low-cost method to oversee vaccination compliance. Adults, by contrast, lead more diverse lives and are more

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85 *See generally* Fine, *History*, *supra* note 2.

86 *Id.*

87 *See* Fine, *History*, *supra* note 2, at 268 (providing estimates of the herd immunity thresholds for the following diseases: diphtheria (85%); malaria (80%–99%); measles (83%–94%); mumps (75%–86%); pertussis (92%–94%); polio (80%–86%); rubella (83%–85%); smallpox (80%–85%)); *see also* Fine, *Rough Guide*, *supra* note 2, at 913. It should be noted that there is scientific uncertainty regarding the precise values of the herd immunity thresholds for various diseases.

88 Fine, *History*, *supra* note 2, at 268.

89 *Canadian Immunization Guide: Measles Vaccine*, PUB. HEALTH AGENCY CAN., http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-meas-roug-eng.php (last modified Oct. 9, 2013); Fine, *History*, *supra* note 2, at 268 tbl.1.

90 *See* Gaston De Serres & Bernard Duval, *Pertussis Vaccination Beyond Childhood*, 365 LANCET 1015, 1015 (2005).

likely to assert autonomy rights in the courts and through political participation than young children or their parents.[91]

Children face particular problems from waning vaccine-induced immunity.[92] Immunity from vaccines generally requires several boosters to extend the period of protection. Adults, who may be less likely to receive boosters, have a greater fraction of susceptible individuals as a group than children.[93] Furthermore, unlike in prior decades, younger adults today do not have naturally acquired immunity because they never had infectious childhood diseases. Why then does the disease not produce an epidemic among adults? Are adults free riding on the vaccination programs of children?

We gain some insight into this question by comparing the differing vaccination policies for pertussis in European countries and the United States in the 1980s.[94] European countries had little or no pertussis immunization in childhood, resulting in widespread pertussis transmission among infants and children, but few adolescent or adult cases due to long-lasting natural immunity.[95] By contrast, the United States consistently administered pertussis vaccines to infants and children in the 1980s, causing an increase in pertussis cases among adults and adolescents because temporary vaccine-induced immunity had waned.[96] Therefore, while the adult population is not completely free riding on the vaccination of children, vaccinating children may have the unintended effect of increasing the average age when people become infected. For example, while chickenpox is a relatively mild disease among children, it can have extremely serious consequences in high-risk populations, including pregnant women, the elderly, and those who have compromised immunity.[97] Society may be disadvantaged by vaccinating children early, thus creating conditions

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91 *See generally* Peter A. Briss et al., *Reviews of Evidence Regarding Interventions to Improve Vaccination Coverage in Children, Adolescents, and Adults*, 18 AM. J. PREVENTATIVE MED. 97 (2000).

92 *Id.*

93 *See generally* Ctrs. for Disease Control & Prevention, *Noninfluenza Vaccination Coverage Among Adults—United States, 2011*, 62 MORBIDITY & MORTALITY WKLY. REP. 66 (2013), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6204a2.htm?s_cid=mm6204a2_w.

94 De Serres & Duval, *supra* note 90, at 1015–16.

95 *Id.*

96 *Id.*

97 *Chickenpox (Varicella): People at High Risk for Complications*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/chickenpox/hcp/high-risk.html (last updated Nov. 16, 2011).

where older adults acquire the illness with greater risk of complications.[98]

While herd immunity assumes age uniformity, in practice this is virtually never present in real-world vaccination programs.[99] Overwhelmingly, children are the targets of mandatory vaccination programs, and this lack of age uniformity poses significant challenges given the temporary nature of vaccine protection.[100]

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In sum, the five underlying assumptions at the foundation of herd immunity—population homogeneity, well-mixing, random vaccination, perfect vaccine efficacy, and age uniformity—are of exceedingly limited practical relevance. The following cases highlight these limitations in practice.

E. Herd Immunity Theory in Practice

Recent experience shows infectious disease outbreaks in highly vaccinated populations. Such outbreaks seeming to violate the herd immunity theory have caused many researchers to reject the theory altogether. For instance, the International Medical Council on Vaccination states in its "Principles and Findings," that "[w]e find the premise of herd immunity to be a faulty theory."[101] Dr. Russell Blaylock argues that "[h]erd immunity is mostly a myth and applies only to natural immunity—that is, contracting the infection itself."[102] Dr. Suzanne Humphries argues that "[s]ince the beginning of vaccination, there is little proof that vaccines are responsible for eradicating disease even when herd immunity vaccination levels have

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98 *See* Timothy C. Reluga et al., *Optimal Timing of Disease Transmission in an Age-Structured Population*, 69 BULL. MATHEMATICAL BIOLOGY 2711, 2719 (2007) (suggesting that foregoing vaccination at a young age may provide greater aggregate social health benefits).

99 *See* Briss et al., *supra* note 91.

100 *Id.*

101 *Principles and Findings*, INT'L MED. COUNCIL ON VACCINATION, http://www.vaccinationcouncil.org/about/ (last visited Mar. 9, 2014).

102 Russell Blaylock, *The Deadly Impossibility of Herd Immunity Through Vaccination*, INT'L MED. COUNCIL ON VACCINATION (Feb. 18, 2012), http://www.vaccinationcouncil.org/2012/02/18/the-deadly-impossibility-of-herd-immunity-through-vaccination-by-dr-russell-blaylock/.

been reached."[103] Dr. Tetyana Obukhanych explains that "[t]he absence of viral epidemics in the [United States] is due to the absence of endemic viral exposure, not due to . . . herd immunity, and sporadic outbreaks . . . occur due to . . . viral exposure brought from abroad."[104]

While these researchers acknowledge that vaccinations can create short-term immunity, and that vaccines can cause herd effect, they argue that vaccination's long-term effects are often harmful to individuals and society. Despite nearly three hundred years of vaccination, scientists have not rigorously compared the long-term health outcomes of vaccinated versus unvaccinated subjects.[105] Without such critical information, some scientists are profoundly skeptical of current vaccine policies, including the goal of vaccine-induced herd immunity.[106]

Below, we consider empirical examples illustrating a range of problems with herd immunity in practice. They include: (1) primary vaccine failure—when a vaccine initially fails to induce immunity; (2) secondary vaccine failure—when the immunity the vaccine induced has waned over time and no longer offers protection; (3) mutation of the infectious virus—suggesting that the vaccine itself may have contributed to the viral shift; (4) importation of viral infections "just a plane ride away"; and (5) disease transmission, or "viral shedding," by vaccinated people who show no symptoms of disease. In addition, there have been disease outbreaks in vaccinated populations that scientists simply cannot explain. While there are many examples, we will focus on the measles and varicella vaccination programs.

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103 Suzanne Humphries, *"Herd Immunity." The Flawed Science and Failures of Mass Vaccination*, INT'L MED. COUNCIL ON VACCINATION (July 5, 2012), http://www.vaccinationcouncil.org/2012/07/05/herd-immunity-the-flawed-science-and-failures-of-mass-vaccination-suzanne-humphries-md-3/#sthash.aRBEJNVz.dpuf.

104 TETYANA OBUKHANYCH, VACCINE ILLUSION: HOW VACCINATION COMPROMISES OUR NATURAL IMMUNITY AND WHAT WE CAN DO TO REGAIN OUR HEALTH 90 (2012).

105 However, a bipartisan bill introduced in the U.S. House of Representatives on April 25, 2013, cited as the "Vaccine Safety Study Act," seeks to "conduct or support a comprehensive study comparing total health outcomes, including risk of autism, in vaccinated populations in the United States with such outcomes in unvaccinated populations in the United States." H.R. 1757, 113th Cong. (2013), *available at* https://www.govtrack.us/congress/bills/113/hr1757/text. Although this bill only has a one percent chance of being enacted according to *GovTrack.us*, its purpose is to fund science that needs to be done to compare vaccinated versus unvaccinated health outcomes. *H.R. 1757: Vaccine Safety Study Act*, GOVTRACK.US, https://www.govtrack.us/congress/bills/113/hr1757 (last visited Mar. 14, 2014).

106 *See, e.g.*, *Principles and Findings*, *supra* note 101.

1. The Case of Measles Vaccination and Immunity

Before the United States embarked on state mandates for measles vaccination, one of the leading proponents of the vaccine, Alexander Langmuir, characterized the disease as a "self-limiting infection of short duration, moderate severity, and low fatality."[107] In the same article, he noted that the disease had maintained a "remarkably stable biological balance over the centuries," and that "[t]he decline in mortality demonstrates the degree to which we have adapted to this balance and have learned to live with this parasite."[108] He explained that measles vaccination was by no means an urgent public health necessity, but rather he sought measles eradication because "it can be done."[109] In the 1960s, Langmuir seemed to believe that vaccination policies could eradicate measles in the near term.

a. Measles Outbreaks in Highly Vaccinated Populations

At that time, scientists believed the herd immunity threshold to be 70% and that one dose of the vaccine would confer long-lasting immunity.[110] Over time, however, scientists pushed the herd immunity threshold up to 95%[111] and started requiring two doses of the vaccine.[112] Evidence suggests, however, that even these policies have not been enough to create herd immunity. During a 1985 measles outbreak in a Texas high school, more than 99% of the 1806 students in the school had been vaccinated against measles.[113] Upon testing, only 4.1% of the students, or 74 of them, lacked detectable antibodies due to either primary or secondary vaccine failure.[114] The authors concluded, "outbreaks of measles can occur in secondary

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107 Alexander D. Langmuir et al., *The Importance of Measles as a Health Problem*, 52 AM. J. PUB. HEALTH 1, 1 (1962).

108 *Id.*

109 *Id.* at 3 (citation omitted) (internal quotation marks omitted).

110 Fine, *History*, *supra* note 2, at 285 (showing that as late as 1982, the World Health Organization estimated the herd immunity threshold for measles to be 70%).

111 *Id.*

112 *See Immunization Schedules: Recommended Immunization Schedule for Persons Aged 0 Through 18 Years*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html (last updated Jan. 31, 2014) (stating that children should receive two doses of the measles-mumps-rubella vaccine by six years of age).

113 Tracy L. Gustafson et al., *Measles Outbreak in a Fully Immunized Secondary-School Population*, 316 NEW ENGL. J. MED. 771, 771 (1987).

114 *Id.* at 772.

schools, even when more than 99[%] of the students have been vaccinated and more than 95[%] are immune," that is, they have measles antibodies.[115] They acknowledged that such an outbreak should have been virtually impossible but rationalized that the "[r]ates of primary vaccine failure in this range [*eds.*: 4.1%] are expected."[116]

Another measles outbreak occurred in a 100% vaccinated school population in Illinois in 1984:

> The affected high school had 276 students and was in the same building as a junior high school with 135 students. A review of health records in the high school showed that all 411 students had documentation of measles vaccination on or after their first birthday, in accordance with Illinois law.[117]

Not all students became ill, but scientists noted that those students who had received vaccines within the previous ten years were less likely to become sick than those who had been vaccinated more than ten years earlier.[118] Notably, officials could not explain how the seventeen-year-old index patient came down with the measles.[119]

The Centers for Disease Control and Prevention's editors noted several possible reasons for the outbreak, including vaccine failure due to improper storage, vaccination of infants younger than one who might be less likely to acquire protection, and other factors.[120] Still, they concluded that "these risk factors did not adequately explain the occurrence of this outbreak."[121] They further noted, "this outbreak suggests that measles transmission can occur within the 2%–10% of expected vaccine failures."[122] In other words, they acknowledged that even with 100% vaccination, they could not ensure herd immunity with existing vaccine technology and stated explicitly that "[t]his outbreak demonstrates that transmission of measles can occur within

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115 *Id.* at 771.

116 *Id.* at 773.

117 Ctrs. for Disease Control & Prevention, *Measles Outbreak Among Vaccinated High School Students–Illinois*, 33 MORBIDITY & MORTALITY WKLY. REP. 349 (1984), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/00000359.htm [hereinafter *Measles Outbreak*]; *see generally* Benjamin M. Nkowane et al., *Measles Outbreak in a Vaccinated School Population: Epidemiology, Chains of Transmission and the Role of Vaccine Failures*, 77 AM. J. PUB. HEALTH 434 (1987) (describing a 1984 outbreak in a Massachusetts high school with a 98% immunization level, providing evidence that outbreaks may occur in highly immunized populations).

118 *Measles Outbreak*, *supra* note 117, at 350.

119 *Id.* at 349.

120 *Id.* at 350.

121 *Id.*

122 *Id.* (citations omitted).

a school population with a documented immunization level of 100%."[123]

b. Actual and Perceived Outbreaks in Unvaccinated Populations

Measles outbreaks have also occurred among the unvaccinated. A recent example happened in 2013 in a largely intentionally unvaccinated Hasidic community in Brooklyn, New York, when a teenager returned from abroad with subclinical measles.[124] Fifty-eight members of the Orthodox Jewish community became infected, the largest outbreak in the United States since 1996.[125] No one died, and no one outside the religious community became infected, but many of those who became ill had in fact been vaccinated.[126]

Sometimes, public health officials and others have blamed disease outbreaks on vaccine critics. Some have blamed Dr. Andrew Wakefield for measles outbreaks; in February 1998, he suggested that there might be a causal link between the MMR vaccine, gastrointestinal disease, and autism.[127] Having observed a new syndrome of gastrointestinal disease and autism in some children after vaccination with the MMR, he publicly recommended that parents consider using the single measles vaccine rather than the combination vaccine.[128] At the time he made the recommendation, a single measles vaccine was available. A few months later, the United Kingdom government took the single measles vaccine off the market.

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123 *Id.*

124 Ctrs. for Disease Control & Prevention, *Notes from the Field: Measles Outbreak Among Members of a Religious Community – Brooklyn, New York, March–June 2013*, 62 MORBIDITY & MORTALITY WKLY. REP. 752, 752 (2013) http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6236a5.htm; *see also* Renee Ghert-Zand, *Measles Vaccine Developer Warns Jewish Anti-Vaxxers*, TIMES OF ISRAEL (Dec. 11, 2013), http://www.timesofisrael.com/measles-vaccine-developer-warns-jewish-anti-vaxxers/.

125 *Id.*

126 *Id.*

127 A.J. Wakefield et al., *Ileal-Lymphoid-Nodular Hyperplasia, Non-Specific Colitis, and Pervasive Developmental Disorder in Children*, 351 LANCET 637 (1998), *retracted*, Feb. 2, 2010, for reasons related to patient referrals and ethics committee approvals, not scientific fraud, *available at* http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(97)11096-0/abstract (last visited Mar. 9, 2014). For a discussion of the article and subsequent retraction, see Mary Holland, *Who is Dr. Andrew Wakefield*, *in* VACCINE EPIDEMIC, *supra* note 13, at 311–19; David Lewis, *The Exoneration of Professor Walker-Smith*, *in* VACCINE EPIDEMIC, *supra* note 13, at 320–38.

128 F. Edward Yazbak, *Measles in the United Kingdom: The "Wakefield Factor,"* VACCINATION NEWS, http://www.vaccinationnews.com/measles-united-kingdom-wake field-factor (last visited Mar. 9, 2014).

Many in the media have argued vociferously that Dr. Wakefield's public statement caused measles outbreaks in the United Kingdom.[129]

There is little data to support such assertions. In a careful review of United Kingdom data on measles in the ten years preceding Dr. Wakefield's statement and the ten years after, Dr. Yazbak notes that there were 188,483 reported measles cases in the ten years before 1998, compared to 28,289 cases in the ten years after, an 85% decrease.[130] Comparing the five years before and after 1998 also showed a 67% decline, suggesting that there was little or no "Wakefield Factor" for reported measles cases.[131]

Dr. Yazbak notes that measles outbreaks were occurring at about the same time in other countries. He points out that in Saudi Arabia, where vaccination rates were between 95% and 98%, there were 4648 cases of measles in 2007 compared to 373 in 2005.[132] The rate of infection was considerably higher in Saudi Arabia than the United Kingdom, and despite media sensationalism, rates of measles infection in the United Kingdom have declined steadily overall.[133]

c. Potential Explanations for Outbreaks in Highly Vaccinated Populations

Some argue that outbreaks in highly vaccinated populations are possible because mass vaccination creates "quasi-sterile environment[s]."[134] "[C]onstant re-infection cycles have an essential role in building a stable herd immunity. In a population that is not constantly exposed to the infection . . . a serious risk of re-emerging infections may arise."[135] In other words, young children's infections play a critical role in continually boosting the entire population's immunity. On measles, Dr. Humphries observes:

> Susceptible age groups have essentially traded places since vaccinating. What used to happen with measles is that infants were protected by maternal antibodies, adults were protected by continued exposure, and infected children handled the disease normally and became immune for long periods of time. So, while

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129 *Id.*; *see also* Holland, *supra* note 127; Lewis, *supra* note 127.

130 Yazbak, *supra* note 128.

131 *Id.*

132 *Id.*

133 *Id.*

134 Humphries, *supra* note 103.

135 *Id.* (citing A.A. Navarini et al., *Long-Lasting Immunity by Early Infection of Maternal-Antibody-Protected Infants,* 40 EUR. J. IMMUNOLOGY 113 (2010)).

> measles vaccines have decreased the expression of measles infections, it has not necessarily improved the bigger picture.[136]

In sum, two doses of measles vaccine, even to one hundred percent of school populations, does not ensure societal protection from measles outbreaks. While there may be strong rationales for individuals to choose to vaccinate, there would appear to be a weak rationale to compel all children to take the vaccine if one hundred percent vaccination cannot reliably induce herd immunity.

2. The Case of Varicella Vaccination and Immunity

The U.S. varicella vaccination program provides perhaps an even more troubling example of imperfect vaccines and herd immunity. Drs. Goldman and King have surveyed this program since its inception in 1995.[137] They concluded, based on extensive data and analysis, that "rather than eliminating varicella in children as promised, routine vaccination against varicella has proven extremely costly and has created continual cycles of treatment and disease."[138]

a. The Rollout of the U.S. Varicella Program

The varicella-zoster virus (VZV) causes chickenpox or varicella as a primary infection.[139] A latency period follows the initial infection, after which the lifelong VZV can subsequently reactivate as herpes zoster (HZ), commonly known as shingles, a secondary infection. After only short-term safety and efficacy clinical trials, pharmaceutical company Merck licensed its varicella vaccine for children one year of age and older.[140] By 1996, the CDC's Advisory Committee on Immunization Practices had recommended it for universal use in children twelve to eighteen months.[141] As of

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136 *Id.*

137 G.S. Goldman & P.G. King, *Review of the United States Universal Varicella Vaccination Program: Herpes Zoster Incidence Rates, Cost-Effectiveness, and Vaccine Efficacy Based Primarily on the Antelope Valley Varicella Active Surveillance Project Data*, 31 VACCINE 1680 (2013).

138 *Id.* at 1691 (citations omitted).

139 *Id.* at 1680.

140 *Id.*

141 Ctrs. for Disease Control & Prevention, *Prevention of Varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, 45 MORBIDITY & MORTALITY WKLY. REP. 1 (1996).

November 2012, all fifty states compelled varicella vaccination for preschool or schoolchildren.[142]

In cost-benefit analyses done before the start of the program, public health officials focused on chickenpox, largely disregarding possible effects on HZ epidemiology.[143] Lieu et al. modeled the cost-effectiveness of a routine varicella vaccination program, finding that vaccination was not cost effective.[144] Vaccine proponents could only justify the program by taking into account the cost of parents' absence from work due to sick children.[145]

Goldman worked as an analyst in one of the three CDC varicella surveillance sites from 1995 to 2005, so he closely observed the early rollout of the program.[146] He argues that the cost-effectiveness analysis from the beginning was based on four key but incorrect assumptions: (1) the vaccine's total cost of $40 per dose; (2) a single dose confers lifelong immunity; (3) vaccine effectiveness is between 85%–95% with negligible adverse effects; and (4) a universal varicella program has no negative impact on the incidence of HZ.[147] There were many at the prelicensure phase who questioned these optimistic assumptions, but the licensure process moved forward nonetheless.[148] After licensure, the cost of the vaccine doubled, and one dose failed to protect against disease breakthroughs.[149] An accurate preliminary cost-benefit analysis would have scratched the program.

In addition, though, the assumptions about adverse events and the influence on HZ were way off the mark. People have reported a wide range of adverse events from the varicella vaccine, which proponents had characterized as negligible. These have included problems with vision, the central nervous system, rashes, strokes, secondary transmission to others, pneumonia, breakthrough varicella, Stevens-Johnson syndrome, autoimmune disorders, and death.[150] A 2005

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142 *Varicella Prevention Mandates*, IMMUNIZATION ACTION COALITION, http://www.immunize.org/laws/varicel.asp (last updated Nov. 1, 2012).

143 Goldman & King, *supra* note 137, at 1680.

144 *Id.* at 1689.

145 *Id.*

146 *Id.* at 1681.

147 *Id.* at 1685.

148 *Id.*

149 *Id.*

150 *Id.* at 1690.

study found adverse events in one-sixth of the subjects within forty-two days following vaccination.[151]

b. Herpes Zoster and Varicella Zoster Virus

Goldman observed herd effect when varicella case reports dropped precipitously after introduction of the vaccine, but saw that the surveillance sites were not capturing data on HZ prevalence. Starting in 2000, at Goldman's recommendation, his surveillance site started to track HZ incidences. After two years, HZ reports remained the same or increased in every adult category except those for adults older than seventy.[152] HZ had also increased among children who previously had chickenpox.[153] When Goldman sought to publish data about trends in HZ, his supervisor arranged for the Los Angeles County Legal Department to send him a "cease and desist" letter[154] to censor publication of the studies.[155] With a response from Goldman's lawyer, the Los Angeles Legal Department dropped its demand, and he published three articles on VZV and HZ.[156]

After widespread introduction of the vaccine in 2002, its effectiveness rate declined significantly, in large part because the boosting effects of naturally circulating varicella virus were gone.[157] Vaccine effectiveness declined rapidly and steeply, such that in several disease outbreaks, the reported vaccine effectiveness rates were between 44% and 56%.[158]

The costs and complications of varicella and HZ in adults are a different magnitude than those of chickenpox in children. Because the

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151 Gary S. Goldman, *The Case Against Universal Varicella Vaccination*, 25 INT'L J. TOXICOLOGY 313, 315–16 (2006).

152 Goldman & King, *supra* note 137, at 1681.

153 *Id.* at 1682.

154 *See Brief Summary of Chickenpox: A New Epidemic of Disease and Corruption*, DR. GOLDMAN ONLINE, http://www.drgoldmanonline.com/SummaryofChickenpoxVaccine.pdf (last visited Mar. 9, 2014) (discussing the "cease and desist" letter).

155 Goldman & King, *supra* note 137, at 1682.

156 G.S. Goldman, *Incidence of Herpes Zoster Among Children and Adolescents in a Community with Moderate Varicella Vaccination Coverage,* 21 VACCINE 4243 (2003); G.S. Goldman, *Using Capture-Recapture Methods to Assess Varicella Incidence in a Community Under Active Surveillance*, 21 VACCINE 4250 (2003); Gary S. Goldman, *Varicella Susceptibility and Incidence of Herpes Zoster Among Children and Adolescents in a Community Under Active Surveillance,* 21 VACCINE 4238 (2003).

157 Goldman, *The Case Against Universal Varicella Vaccination*, *supra* note 151, at 314.

158 Goldman & King*, supra* note 137, at 1689.

varicella vaccine's protection is short-lived, it shifted chickenpox to a more vulnerable adult population. Chickenpox in adults carries 20 times more risk of death and 10-15 times more risk of hospitalization compared to chickenpox in children.[159] A 2005 article reported that the universal varicella vaccination program caused an additional 14.6 million HZ cases, or a 42% increase among adults younger than fifty during a fifty-year period at a significant medical cost burden.[160]

The rationales for the varicella vaccination program were weak from the outset and weakened further with time. Rather than acknowledge problems and debate solutions when its weaknesses became clear, public health officials apparently made serious attempts to censor problematic information. Neither medical rationales (such as herd immunity) nor cost rationales (based on true cost-benefit analysis) seem to justify the vaccination program. Here, pursuing the objective of herd immunity created a far more costly public health problem than an elective program pursuing herd effect would have created. The varicella vaccine's apparent vaccine effectiveness rate was higher when the virus was in circulation. The marginal gains from the program have not outweighed their marginal costs. This recent example of a compulsory program to achieve herd immunity backfired; instead of herd immunity, the program created herd effect and a series of new, serious public health problems.

To be clear, vaccines have an important role in modern public health policy. Herd immunity as a theory, however, provides an irrational basis for guiding policy, leading to inefficiencies in the marketplace. Furthermore, policies based on herd immunity constrain the significant positive role that individual choice can play in furthering the public health.[161] Indeed, many of the failures noted above are a result of the modern insistence on compulsory vaccination as the only solution to the problem of infectious disease. Mandatory programs rely on unattainable herd immunity, which improperly balances the costs to individuals and the healthcare system with the marginal benefits from compulsory policies.

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159 *Id.* at 1691.

160 *Id.* at 1689.

161 In the language of administrative law, reliance on the herd immunity theory as the basis for vaccination policy must not be "arbitrary, capricious, [or] an abuse of discretion." 5 U.S.C. § 706(2)(A) (2012).

F. Eradication Versus Elimination: What Can Vaccination Policy Achieve?

Herd immunity theory rationalizes elimination of infection within a specific population, driving transmission of a disease to zero.[162] Eradication requires global coordination of disease-control programs to ensure that a pathogen is not able to reintroduce itself anywhere in the world.[163] As a result, achieving disease eradication or extinction involves huge investments of healthcare resources toward the goals of developing safe and effective vaccines, ensuring sufficient vaccination coverage to ensure herd immunity in all geographic regions, and efficiently tracking and isolating infections as they arise.[164]

Hinman and others have developed specific terminology to describe the possible objectives of vaccination policy, reproduced below[165]:

1. *Control*: Reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction;
2. *Elimination of disease*: Reduction to zero of the incidence of a specified disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required;
3. *Elimination of infection*: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required;
4. *Eradication*: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed;
5. *Extinction*: The specific infectious agent no longer exists in nature or the laboratory.

This hierarchy highlights the inherent geographic limitations of vaccination policy. Extinction and eradication involve *global* removal

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162 A. Hinman, *Eradication of Vaccine-Preventable Diseases*, 20 ANN. REV. PUB. HEALTH 211, 213 (1999).

163 *Id.*

164 *See generally* Fine, *History*, *supra* note 2 (detailing the efforts made throughout history toward global eradication of various diseases, including smallpox, influenza, polio, and pertussis).

165 Hinman, *supra* note 162.

of a specific pathogen from nature, whereas control and elimination, both of disease and of infection, primarily concern *local* efforts to mitigate disease.[166] Few diseases have ever been eradicated; extinction has never been achieved for any modern pathogen.[167]

Hinman identified the following factors favoring eradicability[168]:

1. A highly effective, safe, cheap, and stable vaccine;
2. Lifelong immunity after natural infection or immunization;
3. A short period of communicability;
4. A highly characteristic clinical disease syndrome;
5. An easy and reliable means of diagnosis;
6. The absence of a nonhuman or environmental reservoir of disease;
7. A genetically stable causative agent; and
8. Seasonality of occurrence.

These factors for effective disease eradication raise several issues for a "just" vaccination policy that we address in Part II below.

1. Limitations on U.S. Vaccination Policy

Can U.S. vaccination programs achieve control, elimination, or eradication of disease? Vaccine technology influences the theoretical capability to achieve any of these goals.[169] If the rate of vaccine failure exceeds the herd immunity threshold, society can *never* achieve elimination or eradication.[170] Therefore, disease control is likely the only feasible objective of vaccination programs when society possesses imperfect and potentially harmful vaccination tools.

If the harms of vaccination are high, increasing vaccination coverage imposes higher costs on society through adverse health effects.[171] When herd immunity is lacking, the marginal costs of mandates exceed their marginal benefits.[172] In the "just" vaccination framework, the results misallocate healthcare resources and fail to properly account for the individual's autonomy interest.[173]

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166 *Id.* at 213–14.

167 David H. Molyneux et al., *Disease Eradication, Elimination and Control: The Need for Accurate and Consistent Usage*, 20 TRENDS PARASITOLOGY 347, 347 (2004).

168 Hinman, *supra* note 162, at 214.

169 *See infra* Part II.D.4.

170 *See id.*

171 Steve P. Calandrillo, *Vanishing Vaccinations: Why Are So Many Americans Opting Out of Vaccinating Their Children?*, 37 U. MICH. J.L. REFORM 353, 388–93 (2004).

172 *See infra* Part II.

173 *See supra* Part I.

2. Communicability, Diagnosis, and the Problems of Contact Tracing

The capacity to control, eliminate, or eradicate a disease depends on the ability to identify cases of infection and proceed rapidly to isolate and treat them.[174] For a population lacking herd immunity, disease transmission among susceptible people is inevitable.[175] Control of infectious outbreaks then involves the process of contact tracing.[176] Contact tracing is the "backward" mapping of disease spread. Starting from any infected person or group of infected people, the problem is tracing the line of infectious contacts back to the first known "index" case, treating individuals along the chain to prevent further transmission.[177] Contact tracing is an iterative process that attempts to identify all contacts for each infected index case.[178]

If the rate of disease spread exceeds the rate at which scientists can trace cases, then the disease will spread faster than it is possible to control it, and contact tracing will fail.[179] The resulting "race to trace" involves a competition between infectious dynamics and the ability to identify and trace infectious individuals.[180] A short period of disease communicability facilitates elimination of a disease.[181] Conversely, a long period of communicability makes eradication or elimination virtually impossible.[182]

3. Disease Adaptability

To successfully eradicate infectious disease, the pathogen must be stable, and there must be no animal or other reservoir for the disease.[183] If a particular pathogen is not genetically stable, then

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174 *See* Ken T.D. Eames & Matt J. Keeling, *Contact Tracing and Disease Control*, 270 PROC. ROYAL SOC'Y LONDON 2565, 2569 (2003) (describing contact tracing as efficient means of identifying cases of infection).

175 *See* Fine, *Rough Guide*, *supra* note 2, at 913.

176 *See* Ken T.D. Eames, *Contact Tracing Strategies in Heterogeneous Populations*, 135 EPIDEMIOLOGY & INFECTION 443, 443 (2006) (discussing models of contact tracing); Eames & Keeling, *supra* note 174, at 2565 (discussing how contact tracing can efficiently be used to identify individuals with sexually transmitted diseases).

177 *See* Eames, *supra* note 176, at 444.

178 *See id.* at 446.

179 *See id.* at 448.

180 *See id.* at 450.

181 *See id.* at 448.

182 *See id.*

183 *See* David M. Morens & Anthony S. Fauci, *Emerging Infectious Diseases: Threats to Human Health and Global Stability*, 9 PLOS PATHOGENS 1, 2–3 (2013) (discussing

vaccines may not afford any protection against related strains.[184] A prime example is *Bordetella parapertussis*, which causes symptoms similar to *Bordetella pertussis*, the bacterium responsible for whooping cough.[185] Immunity to *B. pertussis* does not confer immunity against *B. parapertussis*, suggesting that the current *B. parapertussis* virus may have evolved in response to vaccination against *B. pertussis*.[186]

Diseases can also spread through animal and insect vectors.[187] For example, malaria infects humans through mosquitoes, so efforts to control malaria require insect-control programs.[188] More generally, when a pathogen can survive in nonhuman reservoirs, it can continue to infect the human population.[189] In many cases it may be impossible to identify which nonhuman repositories exist, making eradication unachievable.[190]

Disease eradication seems unattainable in the near future for all infectious childhood diseases, including measles and chickenpox.[191] Disease control seems to be the most viable goal. We consider next a framework within which to evaluate vaccination program objectives.

II
"JUST" VACCINATION POLICY AND PUBLIC HEALTH

Because herd immunity is not an appropriate objective of contemporary vaccination policy, the normative question arises as to what *should* be the correct goal. To address this issue, we adopt the Feudtner-Marcuse model of "just" vaccination policy, which identifies seven factors that must be appropriately weighted and balanced in designing vaccination programs.

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common reemergence of diseases with nonhuman reservoirs and pathogens that undergo rapid changes).

184 *See* Daniel N. Wolfe et al., *The O Antigen Enables* Bordetella Parapertussis *to Avoid* Bordetella Pertussis*-Induced Immunity*, 75 INFECTION & IMMUNITY 4972, 4978 (2007).

185 *See id.* at 4972.

186 *See* SUZANNE HUMPHRIES & ROMAN BYSTRIANYK, DISSOLVING ILLUSIONS: DISEASE, VACCINES, AND THE FORGOTTEN HISTORY 324–30 (2013) (discussing "original antigenic sin committed by vaccination"); *see also id.*

187 *See* Molyneux et al., *supra* note 167, at 351 (contemplating that insect vectors, such as mosquitoes, can infect humans with diseases).

188 *See id.* at 350 tbl.2.

189 *See id.* at 349.

190 *See id.*

191 *See infra* Part III.

Drs. Feudtner and Marcuse, who have worked extensively on U.S. vaccination programs, introduced the "just" vaccination policy framework more than a decade ago.[192] Overall, we agree with the elements of their framework; however, we draw substantially different conclusions concerning current U.S. vaccination policy.

A. Framework for "Just" Vaccination Policy

Feudtner and Marcuse's framework provides seven objectives for modern vaccination policy[193]:

1. Minimization of the deleterious effects of disease;
2. Minimization of the deleterious effects of vaccination;
3. Optimization of personal liberty to choose or to refuse vaccination;[194]
4. Maximization of an equitable distribution of benefits and burdens across members of society;
5. Promotion of the duty of families to protect children;
6. Promotion of the duty of society to protect current and future children; and
7. Prudent utilization of healthcare resources.[195]

The framework provides a reasonably comprehensive approach, although the model entirely discounts the possible benefits of contracting and overcoming disease naturally, thereby achieving long-lasting immunity. Below, we explore open questions about how to weigh the factors in "just" vaccination policy.[196]

Feudtner and Marcuse propose three types of programs: elective, recommended, and mandatory. An elective program uses public education to inform individuals about the availability, benefits, and risks of vaccination, but leaves the choice to immunize at the sole

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192 *See* Chris Feudtner & Edgar K. Marcuse, *Ethics and Immunization Policy: Promoting Dialogue to Sustain Consensus*, 107 PEDIATRICS 1158 (2001).

193 *Id.* at 1163 tbl.2.

194 Although Feudtner and Marcuse refer to the personal liberty objective in terms of "optimization," it is somewhat ambiguous whether this term is equivalent to *maximization* in the same sense as used in the other objectives or whether Feudtner and Marcuse intend this factor to carry less weight in the balancing analysis. This distinction in turn depends on the questions of how and whether to weigh these factors.

195 Feudtner & Marcuse, *supra* note 192, at 1163 tbl.2.

196 Indeed, Feudtner and Marcuse analyze their model with what amounts essentially to a tabulation of the various factors. Such an approach avoids the difficult question of weighing the policy considerations, but we also disagree with many of their conclusions concerning whether mandatory vaccination programs best achieve certain objectives.

discretion of parents in the case of childhood vaccination.[197] A recommended program, by contrast, uses public education and expert advice to induce uptake.[198] Whereas the elective program provides information to the vaccine consumer but offers no opinion, recommended programs aim to raise immunization rates.[199] Finally, mandatory programs leave almost no discretion to individuals on whether to vaccinate, with significant penalties for non-compliance.[200]

Feudtner and Marcuse argue that mandatory programs best minimize disease harms, maximize the equitable distribution of benefits and burdens within society, promote the societal duty to protect children, and use healthcare resources most prudently.[201] They acknowledge, though, that elective programs best minimize vaccine harms and optimize personal liberty.[202] Furthermore, they assert that recommended programs best promote a familial duty to protect children.[203] In the model, a simple tabulation of the seven factors suggests that mandatory programs are the most "just."[204] But to what extent does this conclusion follow? Agreeing with the model's objectives in principle, we consider each of their factors in turn.

1. Minimization of Disease Harm

A vaccination program in theory can reduce the risk of harm from infectious disease to zero if it completely eliminates the disease from circulation. The conclusion that a mandatory program best achieves this objective assumes that mandates ensure the highest level of uptake, thus reducing the rate at which disease can spread. Based on this theory, policymakers believe that minimizing individual choice necessarily reduces disease harms.[205] Imposing penalties for failure to vaccinate requires each individual to take on the burden of the collective, conceivably increasing the number of individuals willing to vaccinate.

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197 Feudtner & Marcuse, *supra* note 192, at 1161.

198 *Id.*

199 *Id.*

200 *Id.*

201 *Id.* at 1163 tbl.2.

202 *Id.* at 1163.

203 *Id.*

204 *Id.*

205 *Id.* at 1161.

This analysis fails, however, when it is possible to eliminate or sufficiently mitigate the spread of infection without requiring all individuals to vaccinate. If herd immunity is possible, then society can obtain the same benefits without imposing *unnecessary* vaccination costs. The herd immunity theory applies precisely to this situation because it predicts a unique threshold beyond which a disease can no longer sustain infection throughout the population. If enough people in society have immunity, and if either a recommended or an elective program is sufficient to achieve the herd immunity threshold, then *mandatory programs impose excessive costs with no marginal gains*. These costs include manufacturing, healthcare providers, administration, and the costs of potential injury and treatment.

2. Minimization of Vaccine Harm

Vaccine harm is zero when people do not vaccinate, making this objective the opposite of factor one's minimization of disease harms. Some balance between disease prevention and protection against vaccine harms is necessary. Mandatory programs do not necessarily reconcile these competing objectives, given the temporary protection of vaccine-induced immunity and the uncertainty about potential vaccine harms. Conversely, choosing a purely elective program may or may not reach the herd immunity threshold and sufficiently prevent disease in the broader society. Nevertheless, as Feudtner and Marcuse acknowledge, an elective program best minimizes vaccine-related harms.[206]

3. Maximization of an Equitable Distribution of Benefits and Harms

In the absence of vaccines, all people share the expected risks of disease, but they do not share them equally.[207] People of different ages and health statuses have differing levels of natural immunity.[208] Natural immunity implies that, with age, more and more people have acquired the disease, recovered from it, and subsequently become immune.[209] This is because: (1) a longer lifetime implies a greater chance of having already encountered the disease, and (2) naturally-

206 *Id.* at 1163 tbl.2.

207 *See, e.g.*, Reluga et al., *supra* note 98, at 2711–19.

208 *Id.* at 2718.

209 *See id.* at 2718–19.

acquired immunity among older individuals makes it more difficult for the disease to sustain itself among that group.[210] Thus, the result is that children are ordinarily at greater risk of infection than healthy adults.[211]

Vaccines create competing risks between infection and injury. On the one hand, requiring all children to vaccinate ensures that all children face the risks of both vaccination and disease. But such a program may not be preferable, however, if only a small portion of the population is particularly susceptible. Requiring vaccination of non-susceptible individuals forces them to accept risks without benefits, a scenario that raises the specter of constitutional equal protection violations under the Fourteenth Amendment.[212]

4. Optimization of Personal Liberty

Elective vaccination programs maximize individual choice, protecting the autonomy interest in bodily integrity.[213] How much weight should we give to this? Feudtner and Marcuse give individual liberty little or no deference, nor do other proponents of mandatory vaccination.[214]

Several commentators have recently proposed tort-based negligence liability for individuals who choose not to vaccinate and transmit disease.[215] They argue that the tort system would then force unvaccinated individuals to accept responsibility for their choice.[216] Such a proposal is another form of a mandatory program with enforcement through civil liability. Individuals then would discount the possible risks of their actions by the "detection" probability of

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210 *See id.* at 2712.

211 However, this observation is not universally true. One prominent example is rubella, which can have severe health complications on unborn children when acquired by a pregnant mother. In this case, the most severe health costs may be associated with the older subpopulation of pregnant women, which may alter the choice of a vaccination program. *See generally id.* at 2711–21.

212 *See* Holland, *supra* note 63, at 42–59, 85.

213 Feudtner & Marcuse, *supra* note 192, at 1163 tbl.2.

214 *See generally* Gregory A. Poland & Robert M. Jacobson, *The Clinician's Guide to the Anti-Vaccinationists' Galaxy*, 73 HUMAN IMMUNOLOGY 859 (2012); Susanne Sheehy & Joel Meyer, *Should Participation in Vaccine Clinical Trials be Mandated?*, 14 VIRTUAL MENTOR 35 (2012) (suggesting that the government should enforce a duty for all citizens to participate in clinical trials).

215 *See generally* Rebecca Rodal & Kumanan Wilson, *Could Parents Be Held Liable for Not Immunizing Their Children?*, 4 MCGILL J.L. & HEALTH 39 (2010); Diekema, *supra* note 7.

216 *See* Diekema, *supra* note 7, at 94.

facing a lawsuit.[217] Despite valuation problems, Feudtner and Marcuse acknowledge that elective vaccination programs best maximize liberty for parents to choose on their children's behalf.[218]

5. Promotion of a Familial Duty to Protect Children

Feudtner and Marcuse identify the familial duty to protect children as the sole objective that a recommended program best fulfills, arguing that medical professionals can best help families protect children.[219] Parents concerned about the potential harms of vaccines are often in direct conflict with their physicians, some of whom refuse to accept and retain children in their practices who fail to comply with vaccination recommendations.[220] Unfortunately, physicians who refuse to see noncompliant families may leave them without healthcare.[221] A recommended program may serve the interests of protecting children while preserving the right to informed consent for the parent, but both physician and patient are on uncertain ground.[222]

By contrast, a mandatory program gives parents no discretion to act in their own children's best interests, a situation that drives a wedge between parents and physicians.[223] This could result in a "black market" of vaccination records, providing false information, and inhibiting the capacity of state, local, and federal agencies to track and contain the spread of disease in the event of an epidemic. Just as in the cases of abortion, medical use of marijuana, and other medical prohibitions, some families simply will not comply with state public health laws as a matter of conscience.

6. Promotion of a Societal Duty to Protect Children

Feudtner and Marcuse conclude that mandatory vaccination programs, rather than recommended ones, best promote society's duty to protect children.[224] Some view mandatory programs as the best

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217 *See* Rodal & Wilson, *supra* note 215, at 63.

218 Feudtner & Marcuse, *supra* note 192, at 1162.

219 *Id.* at 1163.

220 *See* Douglas S. Diekema, *Improving Childhood Vaccination Rates*, 366 NEW ENG. J. MED. 391, 393 (2012) (noting that asking patients to seek other healthcare options is counterproductive).

221 *See id.*

222 Feudtner & Marcuse, *supra* note 192, at 1163.

223 *Id.* at 1161.

224 Feudtner & Marcuse, *supra* note 192, at 1163.

way for the state to exercise appropriate paternalism and prevent children from contracting disease. The reason for the discrepancy between society's duty and the familial one is the recognition of an *implied duty of care* between all members of society and children, not just a recognition of the state's duty to the child.[225] The legal foundation for this implied duty is suspect, because there is no clear analog in common law criminal or tort systems for a duty to rescue, even when a person can do so at small or no cost to herself.[226] If the common law is unwilling to impose liability on individuals toward strangers, Feudtner and Marcuse may be wrong as a matter of law to suggest that a mandatory program may impose a duty on all members of society to protect children.

There is a distinction between a duty to rescue and an implied duty to vaccinate. Children have a higher risk of infection than healthy adults because of their age. If vaccine-induced harm carries a relatively small risk, then there may be a basis to impose such a duty on society as a whole. However, it still does not follow that mandatory vaccination is the optimal mechanism. Under the theory of herd immunity, society need not achieve complete vaccination coverage to mitigate the spread of infection.[227] If a recommended or elective program can contain disease, then it is likely superior to a mandatory one.

7. Prudent Utilization of Healthcare Resources

Thoughtful use of resources, unlike the six factors above, refers to *implementing* a particular program rather than to theoretical tensions between liberty and collective security.[228] At first, resource allocation may appear only incidental to a "just" vaccination program; on further examination, however, it is of primary importance in balancing society's healthcare interests.[229] This factor is foremost in the discussion of vaccination choice in Part III. Society should be willing to invest healthcare resources, including funding, infrastructure, and research, in those endeavors that are likely to achieve the greatest aggregate benefit at the lowest aggregate cost.[230] Although Feudtner

225 *See id.* at 1160.

226 *See generally* Ernest J. Weinrib, *The Case for a Duty to Rescue*, 90 YALE L.J. 247 (1980) (evaluating the case for imposing a duty to rescue).

227 *See* Poland & Jacobson, *supra* note 214, at 862.

228 *See* Feudtner & Marcuse, *supra* note 192, at 1163.

229 *See id.* at 1160–61.

230 *See id.* at 1161.

and Marcuse suggest that a mandatory program best achieves the prudent use of resources,[231] this conclusion is doubtful. If the marginal benefit of a mandatory program does not exceed the marginal cost of implementation, then society can better invest its healthcare resources elsewhere.[232] This observation is particularly true for most childhood infectious diseases where herd immunity is per se unachievable because the vaccine failure rate exceeds the herd immunity threshold.[233] Undervaluing pragmatism risks exposing individuals to unnecessary harms for which there are no commensurate gains.[234] This factor is absolutely critical to ensuring efficiency in the vaccination market and therefore must play a central role in designing vaccination programs.

B. Weighing the Feudtner-Marcuse Factors

Feudtner and Marcuse's attempt to analyze the justice of vaccination policies is insightful.[235] While we do not reach the same conclusions they do, we find their measurements relevant and worthy of further examination. We may agree that a *uniform* "just" vaccination policy is impossible.[236] "Just" policies depend upon the specifics of the individual, the population, the disease, and the potential vaccine efficacy, injuries, and costs. There is no "one-size-fits-all" solution, although that seems to be the goal of most mandatory programs.

We argue that the original model undervalues considerations of individual autonomy, misapplies the notion of a social duty to vaccinate, and critically fails to provide a pragmatic use of healthcare resources for infectious disease. We claim that the proper focus of programs cannot be eradication of disease "at all costs"; indeed, Feudtner and Marcuse acknowledge this limitation by advocating prudent allocation of healthcare resources.[237] Efficiency requires taking account not only of the costs of infection, but also of the costs

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231 *Id.* at 1163.

232 *See id.* at 1161.

233 *See supra* Part I.E.1.i. (discussing measles as an example for which herd immunity is likely unattainable given the rapid rate at which the disease spreads through a population and the relatively low vaccine efficacy).

234 *See* Feudtner & Marcuse, *supra* note 192, at 1161.

235 *See id.* at 1160.

236 *See id.* at 1162.

237 *Id.* at 1160.

of the "cure."[238] In striving for unattainable herd immunity, society pays a heavy price.[239]

We conclude that the appropriate and rational objective of modern vaccination programs should be to maximize herd effect to the extent that marginal gains in vaccination coverage are not outweighed by the marginal costs to the individual, the healthcare system, and society. This objective is fully consistent with contemporary regulatory policy[240] and properly balances individual choice, direct and indirect costs to healthcare, and the real benefit that vaccines provide in protecting individuals from infectious diseases.

III
A GAME THEORY ANALYSIS OF VACCINATION DECISIONS

Proponents of mandatory policies argue that failure to vaccinate breaches an implied duty to other members of society to protect the herd.[241] Under free rider assumptions, herd immunity cannot exist without government compulsion.[242] Game theory, however, provides a useful alternative framework for examining the severity of the free rider problem. The aim of game theory is to identify optimal strategies for people in which their gains depend on others' choices.[243] Using game theory, Chris Bauch and David Earn have attempted to quantify the effect of risk perception on a person's willingness to vaccinate with perfectly efficacious vaccines.[244] Their analysis lays the foundation for market-based solutions to vaccination policy. In order to facilitate discussion, however, we will only generally review game theory and readers should refer to the original Bauch-Earn analysis for technical details.[245]

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238 *See id.* at 1163.

239 *See id.* at 1161.

240 *See* Exec. Order No. 12,866 § 1(b)(6) ("Each agency shall . . . adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs."); *id.* at § 1(b)(11) ("Each agency shall tailor its regulations to impose the least burden on society, including individuals, businesses of differing sizes, and other entities . . . consistent with obtaining the regulatory objectives . . . .").

241 *See* Diekema, *supra* note 7, at 93 (suggesting that parents who do not vaccinate their children should be subject to civil negligence liability).

242 *See id.* at 91.

243 *See generally* KEN BINMORE, GAME THEORY: A VERY SHORT INTRODUCTION (2007) (discussing game theory and the way humans interact in certain cooperative scenarios).

244 *See generally* Chris T. Bauch & David J.D. Earn, *Vaccination and the Theory of Games*, 101 PROCS. NAT'L ACAD. SCI. 13391 (2004).

245 *See id.*

A. Game Theory of Vaccination Choice

The following scenario provides the framework for the Bauch-Earn "vaccination game."[246] Alice is a rational "player" in a large, homogeneous population trying to decide whether to vaccinate or to take her chances and get sick. To help her with the decision, she has in front of her a box of coins. Each coin is labeled according to the probability *P* that on any given toss it will come up heads; the coins are therefore biased, or rigged, to come up heads a specific fraction of the time. Alice can choose any coin in the box, and she will choose to vaccinate if, upon tossing the coin, it comes up heads; otherwise, she will not vaccinate. The "vaccination game" is therefore as follows: which coin should Alice choose in order to maximize her expected net health benefits, given that everyone else in the population is also playing this same game? In other words, how does Alice maximize her *individual* health benefits given the *collective* choices of others?

The "vaccination game" is a form of cost-benefit analysis, based on the information she gathers from others' "successes" in the game. Furthermore, Alice is not an automaton; her goal is not merely to decide *whether* to vaccinate but, more importantly, to pick *the best* coin, that is, the coin that will minimize her risks of both vaccination and infection. Specifically, if her coin comes up heads, then Alice will face the risks of potential vaccine injury and future booster shots to preserve immunity.[247] Conversely, if the coin lands tails, then she faces the potential but uncertain risk of infection. Alice will discount the risks of infection by the probability that she may get sick, which decreases as a function of increasing vaccination coverage.[248] At the herd immunity threshold, Alice's risks of not vaccinating are zero because she can "free ride" on herd immunity. With her biased coin

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246 *Id.* at 13394 (describing how game theory can be used to develop schemes regarding disease eradication; the coin toss game set forth here serves as an illustration of the vaccination game described by Bauch and Earn).

247 Note that this cost is an average cost over all possible "adverse" events of the vaccine, including the chance that nothing will happen. This average cost is always negative because the net benefit of the vaccine is prevention of the disease, which is not a *net* gain to the player if she does not have the disease when she starts the game.

248 Beyond the herd immunity threshold, by definition the disease cannot support itself in the population, and no individual will attain the disease regardless of vaccination status. However, the rate at which a disease is transmitted through a population will increase as the fraction of people choosing to vaccinate falls below the herd immunity threshold, meaning that the probability of any individual acquiring the disease must also increase as the vaccine coverage level decreases.

and a perceived estimate of these risks, Alice can then figure out her best strategy.

To understand how other players will affect Alice's strategy in the "vaccination game," assume that Bob is also playing the game with a biased coin that comes up heads with probability *Q*. If Alice and Bob have equal information about the risks of vaccination and infection,[249] then they will both obtain gains. However, they will discount the risks differently because they are playing with different coins.[250] Who then is doing *better* in the game by drawing a greater payoff, where the payoff is maximization of all benefits and minimization of all harms? If Bob is obtaining a greater payoff with coin *Q*, then there is no reason for Alice to play with coin *P*; the converse will be true if Alice obtains a better payoff. Furthermore, if Cindy can beat both Alice and Bob by using coin *O*, then both Alice and Bob will switch to Cindy's coin. It is through this type of information exchange based on the performance of other players that we can identify the *optimal strategy* for the vaccination game, a coin P^* with an expected payoff greater than with any other coin.[251]

B. Theoretical Optimum Vaccination Choice Strategy

There are two possible variants to the "vaccination game": (1) the vaccine is perfectly efficacious, as in the scenario considered by Bauch and Earn,[252] and (2) the vaccine is imperfect, as in the "real-world" case. The analysis of this latter scenario is original to this Article.

1. Using a Perfect Vaccine

Bauch and Earn prove that there are two possible optimal strategies for the vaccination game with the perfectly efficacious vaccine.[253] If

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249 Alice and Bob represent "average" members of the population in the sense that their estimates rely on the same information available to the public. The Bauch-Earn framework therefore faces several of the same limitations of the herd immunity theory discussed in Part II, but the results provide a useful systematic framework for evaluating the scope and direction of U.S. vaccination policy.

250 Note that all players in the vaccination game will discount the costs of vaccination by the probability that the coin comes up heads and will similarly discount the costs of infection by the probability that the coin lands tails.

251 *See* Bauch & Earn, *supra* note 244, at 13394 (Bauch and Earn prove that P^* is a stable Nash equilibrium for the vaccination game, meaning roughly that it is indeed better than any other coin that Alice could choose from her box.).

252 *Id.*

253 *Id.*

the perceived risks of vaccination are greater than the perceived risks of infection when *no one* is vaccinating,[254] then the optimal strategy is in fact never to vaccinate.[255] Indeed, this "tragedy of the commons" occurs *only* when the costs to the individual from vaccine uptake are extraordinarily high.

In the alternative case where the perceived vaccination risks are less than the worst-case infectious disease scenario, there is a *stable equilibrium point* P^* between zero and one that Bauch and Earn show is equal to the vaccination coverage θ^* necessary to exactly balance the risks of vaccination and infection.[256] To understand why this result is true, note that when the perceived vaccination risks are less than the worst-case infectious disease scenario, then there must exist a vaccination coverage level θ^* at which the expected risks of vaccination balance the risks of infection.[257] If society vaccinates below this level, then risks of infection will be greater than the risks of vaccination, and unvaccinated individuals will have an incentive to vaccinate.[258] Conversely, when society vaccinates above this level, the aggregate risks of vaccination exceed the aggregate harms of infection, and the incentive is to forego vaccination.[259] Therefore, deviations in either direction from the equilibrium coverage θ^* should return over time to this equilibrium point.[260] The question is then whether θ^* is at least equal to the herd immunity threshold θ_H, the answer to which is no in practically all cases. Indeed, herd immunity is only obtainable as an equilibrium point when there are no further risks of vaccination or infection.[261] Bauch and Earn verify this

254 If no one in the population is vaccinating, then the vaccine coverage is zero, and the expected costs of infection are maximal for the individual.

255 Bauch & Earn, *supra* note 244, at 13393.

256 *Id.* at 13394.

257 Recall that the probability of acquiring an infection decreases with increasing vaccine coverage from the "worst-case scenario" at zero coverage until it vanishes at the herd immunity threshold. Therefore, if the costs of vaccinating are below the "worst-case" level, these vaccination costs must meet with the expected infection costs at some vaccination level between zero and one.

258 Bauch & Earn, *supra* note 244, at 13393–94.

259 *Id.*

260 *Id.* at 13394.

261 The only point where the costs of infection are zero is at the herd immunity threshold, meaning that if the herd immunity threshold is an equilibrium point, the costs of vaccination must also vanish.

conclusion through simulations on model populations of susceptible, infectious, and recovered individuals.[262]

2. Using an Imperfect Vaccine

As in the real world, what if a vaccine provides imperfect immunity with an efficacy of probability η? The new setup for the vaccination game then has several important changes:

- If Alice's biased coin comes up heads, she faces the expected risks of the vaccine itself *and also* the expected risks of infection if the vaccine fails.
- The expected risks of infection exist even at the herd immunity threshold because the vaccine is imperfect, meaning that society must invest additional resources to eliminate the disease. If the vaccine efficacy η is less than the herd immunity threshold, then herd immunity is impossible to achieve.

If the perceived risks of vaccination are greater than the "worst-case scenario" when no one vaccinates, then the optimal strategy is not to vaccinate.[263] However, the vaccination risks need not be this high. Alice would still choose not to vaccinate even if the expected vaccination risks are below the "worst-case" infection risks, because she also expects to face some infection risks when she vaccinates with an imperfect vaccine. In fact, this analysis predicts this "do not vaccinate" result in all cases where the expected vaccination risks exceed the "worst-case" infection risks *discounted* by the probability of vaccine efficacy η.

C. Vaccination Choice Strategy in the "Real World"

How does the equilibrium vaccination coverage with the imperfect vaccine compare to the result for the game with the perfect vaccine? Intuitively, one might think that the equilibrium vaccination coverage with the imperfect vaccine should be less than the corresponding equilibrium coverage for the perfect vaccine. However, it turns out that this result is only true when the expected vaccination risks are high. When the expected vaccination risks are relatively low,[264] there

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262 Bauch & Earn, *supra* note 244, at 13392.

263 *Id.* at 13393.

264 The notion of "relatively low" can be made quantitative by comparing the infectious cost curves for the perfect and imperfect vaccines and by noting that there exists a "cross-over" point at a certain level of vaccine coverage due to the longer tail on the cost distribution for the imperfect vaccine.

is a greater risk of infection than risk of vaccine harm.[265] When a vaccine provides even incomplete protection to infection, the marginal benefit of using it may be perceived to be relatively large.[266]

So what are the results of elective vaccination programs? A follow-up article by Perisic and Bauch in 2009 suggests that they work.[267] As with the herd immunity analysis in Part I, the game theory model assumes population homogeneity.[268] Utilizing a network population model, in which individuals in the population only interact with neighbors with whom they share a connection, Perisic and Bauch show that altruism develops within tightly connected "neighborhoods" of individuals, decreasing the total spread of disease.[269] Within small neighborhoods, people will voluntarily vaccinate with a relatively safe vaccine.[270] As the neighborhood size increases, however, the infection is more likely to escape to infect the larger population, thereby approaching the disease dynamics in a homogeneous population.[271]

Reluga, Medlock, Poolman, and Galvani have also shown that age stratification can affect optimal strategy.[272] They show that because vaccination at a young age increases the average age of initial infection, it may be better for people to acquire natural immunity through infection at a young age rather than to risk greater harm from waning vaccine-induced immunity at a later age.[273] Game theory suggests that a market will best balance vaccine and infection risks and benefits.

Although not the conventional wisdom, evidence suggests that individual choice is not at odds with public health benefits from vaccines. To the extent that individuals contribute to herd effect both through vaccine-induced and natural immunity, "soft" regulation of the market can create the same or higher levels of public health more efficiently than compulsion. Indeed, Drs. Yang and Debold have recently demonstrated that for several diseases, there is no statistically

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265 Bauch & Earn, *supra* note 244, at 13393–94.

266 *Id.*

267 Ana Perisic & Chris T. Bauch, *Social Contact Networks and Disease Eradicability Under Voluntary Vaccination*, 5 PLOS COMPUTATIONAL BIOLOGY 1, 2 (2009).

268 *Id.*

269 *Id.*

270 *Id.*

271 *Id.*

272 Reluga et al., *supra* note 98.

273 *Id.* at 2718–19.

significant relationship, at the ninety-five percent confidence level, between measures of non-medical childhood disease exemptions and disease incidence rates in the fifty states.[274] Although several open issues of their study remain for the scientific literature to consider,[275] their empirically-based study results strongly reinforce the view that herd immunity should not be the *de facto* objective of vaccination policy.

A voluntary approach to maximizing herd effect ensures efficiency of the vaccination marketplace and preserves individual choice. Policymakers should reconsider the appropriate level of regulation of the vaccination market, explicitly balancing the costs of vaccination coverage with the expected benefits from a particular vaccination program.[276]

CONCLUSION AND RECOMMENDATIONS

Herd immunity is generally unattainable in the real world because key assumptions, like population homogeneity, do not exist and because current vaccine technology is imperfect. Vaccination programs should therefore aim to achieve herd effect, not herd immunity and concomitantly, disease control rather than eradication.

The free rider problem is a red herring. The Bauch-Earn game theory analysis and experience suggest that it does not drive individual decision making in the real world.[277] If safe and effective vaccines are available, most people will voluntarily accept the risks of vaccination rather than the potential risks of serious infectious disease.

Market forces will naturally lead to an equilibrium point for vaccination; mandates to increase coverage above the equilibrium point yield little or no marginal gains in the absence of obtainable herd immunity. Vaccination programs should therefore focus on "soft" regulation by investing in safer and more efficacious vaccine

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274 Yang & Debold, *supra* note 14, at 374–76.

275 *Id.* at 375.

276 *See* OFFICE OF MGMT. & BUDGET, *supra* note 8, at 9–10 (noting that an agency "should also perform a [benefit-cost analysis] for major health and safety rulemakings to the extent that valid monetary values can be assigned to the primary expected health and safety outcomes[,]" and that even "[i]f the non-quantified benefits and costs are likely to be important, [the agency] should recommend which of the non-quantified factors are of sufficient importance to justify consideration in the regulatory decision").

277 Bauch & Earn, *supra* note 244, at 13393–94.

technology, ensuring informed consent and opening lines of communication between parents, physicians, and policymakers.

These conclusions lead to the following specific recommendations for U.S. federal and state vaccine policy makers. First, federal and state vaccination programs should acknowledge that the goal of vaccine policy is to control disease, not eradicate it. Effective programs should focus on creating herd effect, not herd immunity, and take into account all the economic costs and health risks of vaccination.

Second, states should experiment with market-based approaches to vaccination, freeing resources otherwise devoted to compliance to other healthcare needs. States can change mandates to recommended or elective programs with relative ease and observe what consequences follow. States can start by removing those vaccination mandates that have inadequate public health rationales, such as the mandate for tetanus, which is non-contagious, and for hepatitis B, which is primarily sexually transmitted and a disease for which children are at low risk.

Third, states should ensure that vaccine consumers receive complete information to make rational choices. States can impose higher informational requirements than current federal law. Under federal law, parents are required to receive only minimal information on vaccination benefits and risks.[278] States should require that parents or guardians receive all the information they would otherwise obtain with any prescription drug.

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Parents can and should be able to determine their own children's best interests and voluntarily choose vaccines based on complete and accurate information. Prior, free, and informed consent is the hallmark of modern ethical medicine.[279] The "choice" between fulfilling a child's vaccination mandates or foregoing her education is

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[278] 42 U.S.C. § 300aa—26 (2012) (describing the Vaccine Information Statements that the CDC now produces); *see Vaccine Information Statements*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/vaccines/hcp/vis/index.html?s_cid=cs_000 (last updated June 11, 2014).

[279] *Universal Declaration on Bioethics and Human Rights*, UNITED NATIONS EDUC., SCIENTIFIC, AND CULTURAL ORG. (UNESCO), at art. 6 (2005), unesdoc.unesco.org /images/0014/001461/146180e.pdf ("Any preventive, diagnostic and therapeutic medical intervention is only to be carried out with the prior, free and informed consent of the person concerned, based on adequate information.").

scarcely a voluntary choice; it is a coerced choice at best. Because public health policies have not attained herd immunity for any childhood disease despite sixty years of compulsory policies and intensive effort, it seems both logical and wise to recalculate our policies. It is time to abandon the illusion of herd immunity through compulsion and to adopt realistic and respectful policies to achieve herd effect based on parents' informed choices.

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DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—K. K. Appaji, G. Gaire, D. H. Melville-Swarries, Hnin Yee.

DIPLOMA IN CHILD HEALTH.—T. P. Linham, K. Tharmaraiah.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College held on September 29, 1958, Major-General G. T. L. Archer was admitted to the Fellowship of the College.

On November 7, 1958, T. E. Lear, S. Lourdenadin, J. S. McCormick, and G. B. Plunkett were admitted to the Membership.

At a meeting of the College held on December 5, 1958, with the President, Dr. P. T. O'Farrell, in the chair, Dr. J. J. Cockburn was admitted to the Licence and Membership of the College.

The following were admitted to the Licence in Medicine and Midwifery:

Y. M. Ali, R. G. R. Bobart, R. J. Christmas, Margaret M. Day, K. A. Docrat, Noreen M. Duffy, Mearl A. Fenwick, M. N. Fitzgibbon, H. Holmes, S. N. Jeawon, O. C. Parry-Jones, H. A. Marcelin, Louisa E. Moran, M. A. Q. Muhairez, J. McAleer, J. P. McCusker, R. H. Narozny, J. C. Okoye, P. R. Panniker, Janina Pisko-Dubienski, D. L. Scawn, M. E. Seedat, Y. Z. Shah, A. L. Tawiah.

Vital Statistics

MEASLES

REPORTS FROM GENERAL PRACTITIONERS

We are much indebted to the general practitioners whose names appear below for the following notes on the present outbreak of measles.

Dr. G. F. WATSON (Peaslake, Surrey) writes: Measles was introduced just before Christmas by a child from Petworth. He went to school, coughing, on December 15–17, 1958, and to the school party that afternoon, after which he developed his rash. In school and at the party he was in contact with 52 children, 25 of whom were said to be susceptible. Of these, 21 (84%) developed measles, 2 on December 27, 2 on the 28th, 6 on the 29th, 9 on the 30th, 3 on the 31st, 3 on January 1, 1959, and 2 on the 2nd. The shortest incubation was thus 12 days and the longest 16 until the rash appeared. Out of 27 other children who were said to have had measles or were doubtful, 6 (22%) developed it. One child's mother said he was 3 months old when previously affected, which suggests confusion wtih roseola infantum.

Treatment of Attack.—No drugs are given for either the fever or the cough; if pressed, I dispense mist. salin. *B.N.F.* as a placebo. Glutethimide 125 mg. may be given in the afternoon if the child is restless when the rash develops; 250 mg. in single or divided doses at bedtime ensures a good night's sleep in spite of coughing. I encourage a warm humid atmosphere in the room by various methods: some electric fires and most electric toasters allow an open pan of water to rest on top; an electric kettle blows off too much steam to be kept on for more than short periods. Parents, conscious of the need to darken the room and to forbid reading, may carry this to an unnecessary extreme, starting even before the rash appears. To save a mother some demands, the wireless is a boon to children in darkened rooms. They are allowed up when the rash fades from the abdomen—usually the fourth or fifth day—and may go outside on the next fine day. Apart from fruit to eat, solid food is avoided on the day the rash is appearing; fruit drinks or soups are all they appear to want.

Complications.—So far few complications have arisen. Four cases of otitis media occurred in the first 25 children, but only one had pain. No case of pneumonia has occurred, but one child had grossly abnormal signs in the chest for a few days after the fever subsided, uninfluenced by oral penicillin. One girl had a tear-duct infection and another an undue blepharitis. Of three adult males with the disease, two have been more severely affected than any of the children.

Treatment of Complications.—For otitis media with or without pain oral penicillin in therapeutic doses is given four times a day. Dacryocystitis was treated with an oral mixture of penicillin and sulphonamide.

Interesting Features.—The invasion phase of measles this year seems to be more drawn out than previously. Several children have been febrile for a week, one for nine days before the rash appeared. In two boys measles was tentatively excluded: the first developed no catarrhal signs in spite of his fever, and then mumps appeared; the second, who was coughing, had an evening temperature of 102° F. (38.9° C.) for three nights running, before signs of primary atypical pneumonia appeared in the right lung. Two children have had transient rashes on the trunk before the typical rash appeared on the face. One girl, who was given gamma globulin as an infant when her elder brother had measles, was on this occasion a house contact of a younger brother with a typical attack; in due course she developed a low fever and transient catarrh but no rash, at the same time that her younger sister developed a typical attack of measles. In a neighbouring practice a baby of 9 months developed fever and catarrh, but no rash, at the same time as two older children in the house developed typical attacks of measles. A girl of 2 years who has not had measles in the past failed to develop it from house contact with her father, although her younger sister had a typical attack. A girl of 8 was not infected at the school party, though she nursed the ailing victim on her knee, but later took the disease from her sisters, who were infected at the party.

LATE START

Dr. F. H. STAINES (Callington, Cornwall) writes: This practice had a large epidemic of measles from July to October, 1957 (overlapping with the Asian influenza), and a small epidemic in April, 1958, occurring in a village that was bypassed by the 1957 infection. The current epidemic has not yet reached here, and in this practice only one of the last five epidemics has started early in the New Year, the others all starting in spring or summer.

BED REST

Dr. R. E. HOPE SIMPSON (Cirencester, Glos) writes: We make no attempt to prevent the spread of measles, and would only use gamma globulin to mitigate the severity of the disease in the case of the exposure of a susceptible adult or child who is already severely debilitated. Bed rest, for seven days for moderate and severe cases and of five to six days in mild cases, seems to cut down the incidence of such complications as secondary bacterial otitis media and bronchopneumonia. We have not been impressed by the prophylactic or therapeutic use of antibiotics and

sulphonamides in the first week of the disease. As soon as the patient is out of bed we allow him out of doors almost regardless of the weather.

Otitis Media and Bronchopneumonia.—These conditions often appear so early, sometimes even before the rash, that in such cases one can only conclude that the responsible agent is the virus itself. Despite their initial alarming severity, they tend to resolve spontaneously, and treatment apart from first principles seems useless. When, on the other hand, otitis media or bronchopneumonia comes on after the subsidence of the initial symptoms of measles, it is probably due to a secondary bacterial invader, and we find antibiotics or sulphonamides useful if the severity of the complication demands them.

Staphylococcal Infections.—Styes and blepharitis commonly develop within six weeks of measles and can be dramatically severe. They often persist as a recurrent nuisance for months or even years. In the long view local applications are conspicuously unsuccessful, as are courses of antibiotics. Prolonged use of sulphonamides, on the other hand, often seems to stop the cycle of recurrences, and heartening results are achieved by the old-fashioned iron tonics or their vitamin-and-iron successors.

Experience bears out the expectation that children under 2 years old usually have mild attacks, and under 6 months often escape the disease altogether. These mild attacks in infancy do not appear to give a solid immunity, and such children are often subject to a second attack when they reach school age. One wonders if the same principle applies to attacks modified by gamma globulin.

Less Severe.—The present outbreak in this area is not distinguished by any peculiar characteristics except that it seems less severe than usual.

MILD AILMENT

DR. JOHN FRY (Beckenham, Kent) writes: The expected biennial epidemic of measles appeared in this region in early December, 1958, just in time to put many youngsters to bed over Christmas. To date there have been close on 150 cases in the practice, and the numbers are now steadily decreasing. Like previous epidemics, the primary cases have been chiefly in the 5- and 6-year-olds, with secondary cases in their younger siblings. No special features have been noted in this relatively mild epidemic. It has been mild because complications have occurred in only four children. One little girl aged 2 suffered from a lobular pneumonia, and three others developed acute otitis media following their measles. In the majority of children the whole episode has been well and truly over in a week, from the prodromal phase to the disappearance of the rash, and many mothers have remarked "how much good the attack has done their children," as they seem so much better after the measles.

A family doctor's approach to the management of measles is essentially a personal and individual matter, based on the personal experiences of the doctor and the individual character and background of the child and the family. In this practice measles is considered as a relatively mild and inevitable childhood ailment that is best encountered any time from 3 to 7 years of age. Over the past 10 years there have been few serious complications at any age, and all children have made complete recoveries. As a result of this reasoning no special attempts have been made at prevention even in young infants in whom the disease has not been found to be especially serious.

Treatment.—In the acute phase non-specific symptomatic measures such as aspirin and linctus have been the basis of treatment, and without the routine use of antibiotics or sulphonamides the rate of complications has not exceeded 3%. Even in the possibly susceptible "catarrhal children" with previous histories of recurrent ear and chest infections antibiotics have not been used in attempting to prevent complications; if and when these did occur they were treated on their merits. The few complications that did arise—namely, otitis media and chest infections—were either allowed to settle naturally on non-specific treatment, or, when severe enough, were treated with intramuscular injections of penicillin. In the present epidemic the one child with pneumonia and two of the children with acute otitis media were the only ones who required specific antibiotics. In all the others the disease followed a relatively uneventful course with complete and spontaneous resolution.

I would like to express my thanks to Dr. G. E. H. Callebaut, who has worked with me during this time.

NO PERMANENT DISABILITIES

DR. R. M. MCGREGOR (Hawick, Roxburghshire) writes: In Scotland measles is not a notifiable disease except in the case of certain ports. Information concerning incidence, therefore, is known only to the family doctor and to a lesser extent the school authorities. In this area since 1948 serious outbreaks have occurred in the autumn of 1950, in March and April of 1953, and in June and July of 1955. In the intervening periods, and since the last serious outbreak, sporadic cases have occurred without causing an epidemic. At present we enjoy a complete freedom from this disease, and it is hoped that the act of writing on the subject will not incur the penalty of a visitation.

Scanning the notes of the previous epidemics, it is evident that the 1955 episode was one of low virulence. Indeed, many of the cases were sufficiently mild as to make diagnosis difficult. The follow-up of all the epidemics reveals that the patients have not suffered any permanent disabilities. This could be due to the treatment given being satisfactory or to the excellent recuperative powers of a sturdy population.

It is conspicuous that the 5–15-years age group contained the vast majority of the cases. No effort was made to prevent the spread of the disease, except the ordinary precaution of not permitting juvenile visitors. Gamma globulin to thwart the onset of the disease was never used, since the few cases seen affecting the adults have always been severe. It is felt advisable to get the infection over in childhood and thus avoid this hazard in later life.

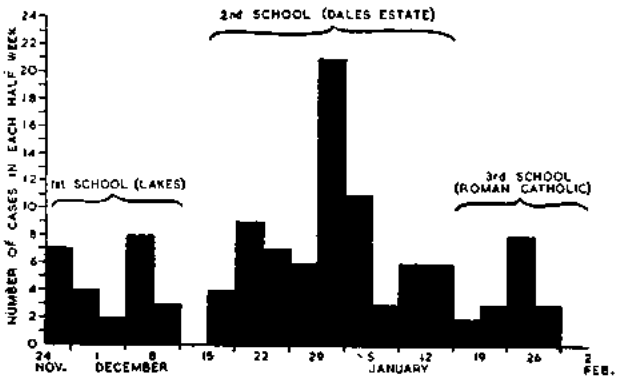
In these epidemics no serious complications were encountered. A troublesome cough for a few weeks after the infection was fairly frequent. In the 1955 episode only two cases of concomitant otitis media were seen, and in both cases it was a recrudescence of a previous attack. Contrariwise three of the cases had otitis media a few months before, and did not have a flare-up during the measles infection. In one case, as the rash of measles was fading, typical spots of chicken-pox were seen to develop. This superimposed infection did not prolong the convalescence.

The treatment given in all cases was sulphadimidine. In the older children it was dispensed in the form of tablets. In the younger children and in those that complained of difficulty in swallowing, the suspension was used. When the sulphadimidine was stopped, a sedative mixture was given to those who complained of a troublesome cough.

IMPORTANCE OF VISITS

DR. KEITH HODGKIN (Redcar, Yorks) writes: If the present measles epidemic of nearly 100 cases is compared with the two previous epidemics (250 cases), no obvious differences are observed. Several clinical observations were made which influence early diagnosis and treatment: (1) In *all* cases the classic triad of cough, Koplik's spots, and rash was found. (2) The cough began 1–5 (usually 3) days before the rash in over 80% of cases. (3) Koplik's spots were never observed more than 2 days before the onset of rash. Extensive Koplik infiltration appearing as a diffuse red granularity over the inside of the cheeks indicated the likelihood of a severe illness. (4) A stage of pulmonary catarrh as judged by moist adventitious sounds was observed in 54% of cases. This stage always appeared 1–3 days after the appearance of rash—i.e., just as the clinical condition was improving. These catarrhal sounds had disappeared in most cases four days later.

Complications.—Only three complications were observed: (1) In 6% of cases the illness followed its normal course but was unusually severe. These cases developed severe prostration and rapid respiration while the rash was at its



height. Extensive Koplik infiltration usually proceeded these developments. (2) In 3% of cases the stage of pulmonary catarrh progressed to a pneumonitis, or bronchopneumonia, with persistent fever and localizing pulmonary adventitious sounds. (3) In 6% of cases there was acute otitis media which appeared to be related to the cough.

Prophylaxis.—Isolation is a practical impossibility. Gamma globulin was used successfully to protect weakly susceptibles on three occasions.

Treatment and Prevention of Complications.—Adequate bed rest, fluids, soluble aspirin, and a cough linctus were the routine treatment in all cases. Penicillin V was used in 12% of cases when there was clinical evidence of one of the three complications mentioned above. In a further 12% penicillin was used as an "umbrella" to protect chesty children.

In the three epidemics there were no deaths and no admissions to hospital, and in no case did pulmonary complications persist long enough to show on an *x*-ray when the child was well. Pneumonia is most likely to supervene during the stage of pulmonary catarrh when the child is improving clinically. At this stage parents, especially those in overcrowded homes, are apt to allow children to get up or even to go out. The most important measure is to insist on absolute bed rest until fever and chest signs have disappeared. *Visiting on alternate days to ensure that parents carry this out is essential.*

It is suggested that the many good results claimed for different forms of therapy in measles may be artificial, and that it is the frequent visiting by the interested clinician and not the therapy which produces the good results.

Week Ending January 24

Infectious diseases were more prevalent in England and Wales during the week ending January 24. The rises in the numbers of notifications included 1,038 for measles, from 12,671 to 13,709, 355 for dysentery, from 839 to 1,194, 325 for scarlet fever, from 1,103 to 1,428, 150 for whooping-cough, from 508 to 658, 93 for food-poisoning, from 107 to 200, and 84 for acute pneumonia, from 527 to 611.

The largest rises in the incidence of measles were 201 in Middlesex, from 640 to 841 (Harrow M.B. 102, Ealing M.B. 88, Wembley M.B. 80), 153 in Bedfordshire, from 272 to 425 (Luton M.B. 180), 152 in Hampshire, from 178 to 330, 122 in Yorkshire West Riding, from 1,223 to 1,345 (Sheffield C.B. 214, Leeds C.B. 197, York C.B. 106), 116 in Essex, from 1,047 to 1,163 (Ilford M.B. 195, West Ham C.B. 148), and 104 in Warwickshire, from 402 to 506 (Birmingham C.B. 188, Coventry C.B. 140); the largest exceptions to an increased incidence were falls of 133 in Lincolnshire, from 452 to 319, and 77 in Staffordshire, from 441 to 364. No large fluctuations were recorded in the local returns of whooping-cough. The largest increases in the number of notifications of scarlet fever were 45 in Yorkshire West Riding, from 137 to 182, and 36 in Hertfordshire, from 47 to 83. 4 cases of diphtheria were notified, being 1 more than in the preceding week.

The notifications of acute poliomyelitis numbered 18 and were 7 fewer for paralytic and 1 fewer for non-paralytic cases than in the preceding week. The largest returns were 3 cases in Essex and in Cheshire.

Another 40 cases were notified from the outbreak of *Salmonella limete* paratyphoid fever in Nottingham C.B., where 28 cases were notified in the preceding week.

The largest rise in dysentery was 72 cases in Glamorganshire. The chief centres of infection were Glamorganshire 201 (Cardiff C.B. 84, Barry M.B. 62, Rhondda M.B. 37), Yorkshire West Riding 175 (Leeds C.B. 107, Bradford C.B. 24), Lancashire 109 (Liverpool C.B. 36, Eccles M.B. 16, Manchester C.B. 12), Lincolnshire 87 (Grimsby C.B. 38, Boston M.B. 15, Scunthorpe M.B. 10), London 79 (Wandsworth 18, Bermondsey 15), Essex 76 (Walthamstow M.B. 48), Warwickshire 66 (Coventry C.B. 55, Birmingham C.B. 10), Nottinghamshire 60 (Carlton U.D. 46), Yorkshire East Riding 43 (Kingston upon Hull C.B. 30), Hampshire 35 (Southampton C.B. 21), Staffordshire 35 (Litchfield R.D. 11, Stoke on Trent C.B. 10), Durham 25 (South Shields C.B. 12), Middlesex 24, and Northumberland 21 (Newcastle upon Tyne C.B. 21).

Venereal Diseases

In England and Wales during the quarter ending September 30, 1958, 1,032 new cases of syphilis were reported as attending the clinics, as compared with 1,240 the previous year. Of these, 170 were classified as primary, secondary, or latent in the first year of infection. 7 cases of congenital syphilis in children aged under 1 year were reported, and 96 cases in persons over that age. New cases of gonorrhoea (with corresponding 1957 figures in parentheses) numbered 7,986 (7,155), of chancroid 65 (66), and of non-gonococcal urethritis (males only) 5,197 (4,408).—*Monthly Bulletin of the Ministry of Health*, January, 1959.

Influenza

In the week ending January 24, 55 deaths from influenza were reported in England and Wales. This total was 22 more than in the previous week, but it is only a quarter of the total in the corresponding week last year, when Asian influenza was epidemic. Pneumonia notifications remain low for the time of year (see graph). In the week ending January 24 there were 875 deaths from pneumonia, compared with 992 in the corresponding week last year. Influenza-like illness has been reported in a few scattered districts, and serological evidence of the Asian strain has been obtained in some cases. In Birmingham for about three weeks there has been a sustained demand for hospital beds for infants with acute respiratory disease.

Industrial Accidents and Diseases

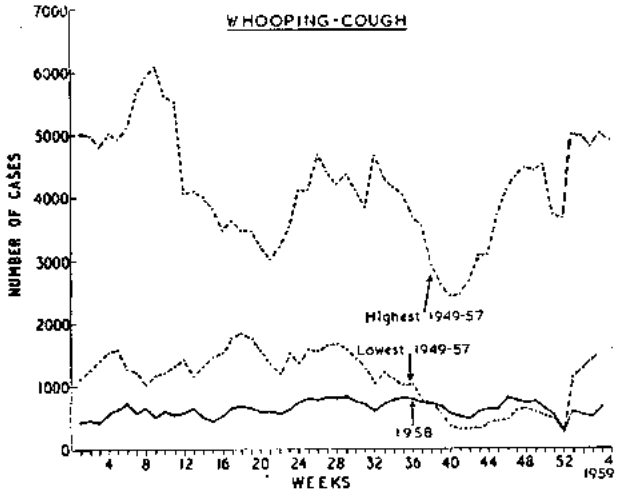
A total of 1,183 workpeople died from notifiable accidents in the course of their employment in Great Britain during 1958, compared with 1,272 in 1957. The number of cases of industrial diseases reported was 469, of which 17 were fatal; the numbers for 1957 were 518 and 15. The 1958 deaths were as follows: epitheliomatous ulceration due to mineral oil 11 and due to pitch and tar 5; toxic jaundice 1.

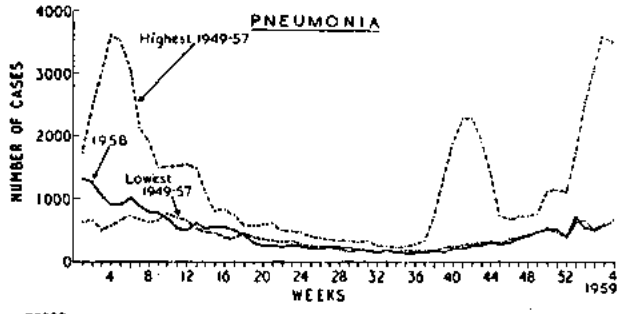
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in December, 1958, was 101, compared with 118 in the previous month and 119 in December, 1957.

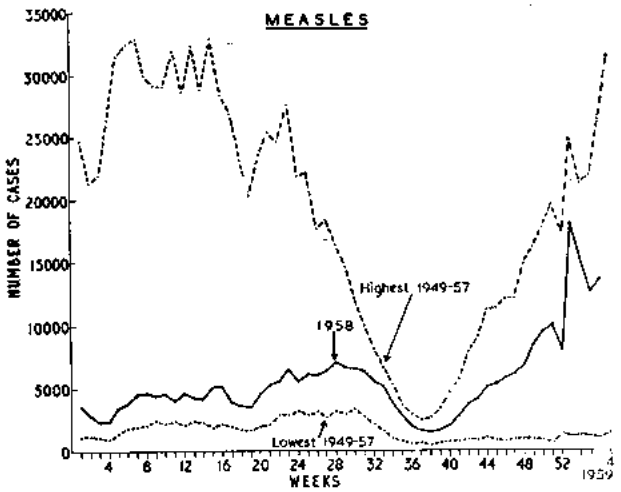
The numbers of cases of industrial diseases in the United Kingdom reported during December, 1958, were as follows: Lead poisoning 12, mercurial poisoning 3, compressed air illness 1, anthrax 1, epitheliomatous ulceration 30, chrome ulceration 20; total 67. There were eight deaths from epitheliomatous ulceration, 3 due to pitch and tar and 5 due to mineral oil.—*Ministry of Labour Gazette*, January, 1959.

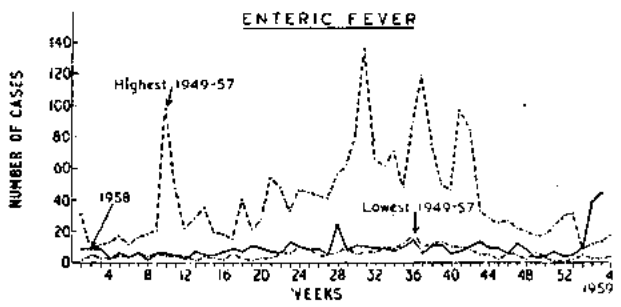
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - - -, the figures for 1958–9 thus ————. Except for the curves showing notifications in 1958–9, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 17** (No. 2) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	5	2	2	0	4	7	1	6	0	4
Dysentery	839	69	177	12	1	574	119	114	7	4
Encephalitis, acute	3	0		0		3	0		0	
Enteric fever:										
Typhoid	1	1	1	0		2	0	0	0	1
Paratyphoid	37	2	0	0		7	0	1 (B)	0	
Food-poisoning	107	14	12	0		139	14	26	0	
Infective enteritis or diarrhoea under 2 years				7	15				11	11
Measles*	12,671	1001	536	89	615	2,888	39	90	83	13
Meningococcal infection	24	0	13	1	2	34	3	15	0	
Ophthalmia neonatorum	17	5	4	0		22	1	12	0	
Pneumonia†	527	39	350	13	2	1,292	123	568	6	21
Poliomyelitis, acute:										
Paralytic	21	1	1	1		28	1	2	0	6
Non-paralytic	5	0				8	0			
Puerperal fever§	172	24	11	0	1	235	64	22	1	
Scarlet fever	1,103	63	88	22	22	501	34	69	12	6
Tuberculosis:										
Respiratory	481	61	75	20		566	68	82	30	
Non-respiratory	48	6	5	2		50	6	8	8	
Whooping-cough	508	18	48	52	101	460	17	38	4	6

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	1	No comparable figures available.	0	0	0	0
Dysentery	2	0		0			0		0	
Encephalitis, acute		0			0		0			
Enteric fever	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	0	0	2		0	0	0	1
Influenza	33	1	4	1	1		21	2	0	4
Measles		0	1	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia	800	77	41	19	12		117	61	12	11
Poliomyelitis, acute	4	0		0	0		1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	113	11	14	3	5		10	9	1	3
Non-respiratory		1	0	0	1		2	1	0	0
Whooping-cough	1	0	0	1	0		0	0	0	0
Deaths 0–1 year	352	34	42	4	23		43	58	8	11
Deaths (excluding stillbirths)	13,259	1098	872	164	215		1254	839	134	202
LIVE BIRTHS	14,554	1241	1048	254	362		1313	1142	238	353
STILLBIRTHS	324	25	29				26	28		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

The Questionable Contribution of Medical Measures to the Decline of Mortality in the United States in the Twentieth Century

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". . . by the time laboratory medicine came effectively into the picture the job had been carried far toward completion by the humanitarians and social reformers of the nineteenth century. Their doctrine that nature is holy and healthful was scientifically naive but proved highly effective in dealing with the most important health problems of their age. When the tide is receding from the beach it is easy to have the illusion that one can empty the ocean by removing water with a pail."

R. Dubos, Mirage of Health,
New York: Perennial Library, 1959, p. 23

Introducing a Medical Heresy

The modern "heresy" that medical care (as it is traditionally conceived) is generally unrelated to improvements in the health of populations (as distinct from individuals) is still dismissed as unthinkable in much the same way as the so-called heresies of former times. And this is despite a long history of support in popular and scientific writings as well as from able minds in a variety of disciplines. History is replete with examples of how, understandably enough, self-interested individuals and groups denounced popular customs and beliefs which appeared to threaten their own domains of practice, thereby rendering them heresies (for example, physicians' denunciation of midwives as witches, during the Middle Ages). We also know that vast institutional resources have often been deployed to neutralize challenges to the assumptions upon which everyday organizational activities were founded and legitimated (for example, the Spanish Inquisition). And since it is usually difficult for organizations themselves to directly combat threatening

"heresies," we often find otherwise credible practitioners, perhaps unwittingly, serving the interests or organizations in this capacity. These historical responses may find a modern parallel in the way the everyday practitioners of medicine, on their own altruistic or "scientific" grounds and still perhaps unwittingly, serve present-day institutions (hospital complexes, university medical centers, pharmaceutical houses, and insurance companies) by spearheading an assault on a most fundamental challenging heresy of our time: *that the introduction of specific medical measures and/or the expansion of medical services are generally not responsible for most of the modern decline in mortality.*

In different historical epochs and cultures, there appear to be characteristic ways of explaining the arrival and departure of natural viscissitudes. For salvation from some plague, it may be that the gods were appeased, good works rewarded, or some imbalance in nature corrected. And there always seems to be some person or group (witch doctors, priests, medicine men) able to persuade others, sometimes on the basis of acceptable evidence for most people at that time, that they have *the* explanation for the phenomenon in question and may even claim responsibility for it. They also seem to benefit most from common acceptance of the explanations they offer. It is not uncommon today for biotechnological knowledge and specific medical interventions to be invoked as *the major reason* for most of the modern (twentieth century) decline in mortality.[1] Responsibility for this decline is often claimed by, or ascribed to, the present-day major beneficiaries of this prevailing explanation. But both in terms of the history of knowledge and on the basis of data presented in this paper, one can reasonably wonder whether the supposedly more sophisticated explanations proffered in our own time (while seemingly distinguishable from those accepted in the past) are really all that different from those of other cultures and earlier times, or any more reliable. Is medicine, the

[1]It is obviously important to distinguish between (a) advances in knowledge of the cause and natural course of some condition and (b) improvements in our ability to effectively treat some condition (that is, to alter its natural course). In many instances these two areas are disjoint and appear at different stages of development. There are, on the one hand, disease processes about which considerable knowledge has been accrued, yet this has not resulted (nor necessarily will) in the development of effective treatments. On the other hand, there are conditions for which demonstrably effective treatments have been devised in the absence of knowledge of the disease process and/or its causes.

physician, or the medical professsion any more entitled to claim responsibility for the decline in mortality that obviously has occurred in this century than, say, some folk hero or aristocracy of priests sometime in the past?

Aims

Our general intention in this paper is to sustain the ongoing debate on the questionable contribution of specific medical measures and/or the expansion of medical services to the observable decline in mortality in the twentieth century. More specifically, the following three tasks are addressed: (a) selected studies are reviewed which illustrate that, far from being idiosyncratic and/or heretical, the issue addressed in this paper has a long history, is the subject of considerable attention elsewhere, attracts able minds from a variety of disciplines, and remains a timely issue for concern and research; (b)age- and sex-adjusted mortality rates (standardized to the population of 1900) for the United States, 1900–1973, are presented and then considered in relation to a number of specific and supposedly effective medical interventions (both chemotherapeutic and prophylactic). So far as we know, this is the first time such data have been employed for this particular purpose in the United States, although reference will be made to a similar study for England and Wales; and (c) some policy implications are outlined.

Background to the Issue

The beginning of the serious debate on the questionable contribution of medical measures is commonly associated with the appearance, in Britain, of Talbot Griffith's (1967) *Population Problems in the Age of Malthus.* After examining certain medical activities associated with the eighteenth century—particularly the growth of hospital, dispensary, and midwifery services, additions to knowledge of physiology and anatomy, and the introduction of smallpox inoculation—Griffith concluded that they made important contributions to the observable decline in mortality at that time. Since then, in Britain and more recently in the United States, this debate has continued, regularly engaging scholars from economic history, demography, epidemiology, statistics, and other disciplines. Habakkuk

(1953), an economic historian, was probably the first to seriously challenge the prevailing view that the modern increase in population was due to a fall in the death rate attributable to medical interventions. His view was that this rise in population resulted from an increase in the birth rate, which, in turn, was associated with social, economic, and industrial changes in the eighteenth century.

McKeown, without doubt, has pursued the argument more consistently and with greater effect than any other researcher, and the reader is referred to his recent work for more detailed background information. Employing the data and techniques of historical demography, McKeown (a physician by training) has provided a detailed and convincing analysis of the major reasons for the decline of mortality in England and Wales during the eighteenth, nineteenth, and twentieth centuries (McKeown et al., 1955, 1962, 1975). For the eighteenth century, he concludes that the decline was largely attributable to improvements in the environment. His findings for the nineteenth century are summarized as follows:

> . . . the decline of mortality in the second half of the nineteenth century was due wholly to a reduction of deaths from infectious diseases; there was no evidence of a decline in other causes of death. Examination of the diseases which contributed to the decline suggested that the main influences were: (a) rising standards of living, of which the most significant feature was a better diet; (b) improvements in hygiene; and (c) a favorable trend in the relationship between some micro-organisms and the human host. *Therapy made no contributions, and the effect of immunization was restricted to smallpox which accounted for only about one-twentieth of the reduction of the death rate.* [Emphasis added. McKeown et al., 1975, p. 391]

While McKeown's interpretation is based on the experience of England and Wales, he has examined its credibility in the light of the very different circumstances which existed in four other European countries: Sweden, France, Ireland, and Hungary (McKeown et al., 1972). His interpretation appears to withstand this cross-examination. As for the twentieth century (1901–1971 is the period actually considered), McKeown argues that about three-quarters of the decline was associated with control of infectious diseases and the remainder with conditions not attributable to micro-organisms. He distinguishes the infections according to their modes of transmission (air- water- or food-borne) and isolates three types of influences which figure during the period considered: medical measures (specific therapies and immunization), reduced exposure to infection, and improved nutrition. His conclusion is that:

> the main influences on the decline in mortality were improved nutrition on air-borne infections, reduced exposure (from better hygiene) on water- and food-borne diseases and, less certainly, immunization and therapy on the large number of conditions included in the miscellaneous group. Since these three classes were responsible respectively for nearly half, one-sixth, and one-tenth of the fall in the death rate, it is probably that the advancement in nutrition was the major influence. [McKeown et al., 1975, p. 422]

More than twenty years of research by McKeown and his colleagues recently culminated in two books—*The Modern Rise of Population* (1976a) and *The Role of Medicine: Dream, Mirage or Nemesis* (1976b)—in which he draws together his many excellent contributions. That the thesis he advances remains highly newsworthy is evidenced by recent editorial reaction in *The Times* of London (1977).

No one in the United States has pursued this thesis with the rigor and consistency which characterize the work by McKeown and his colleagues in Britain. Around 1930, there were several limited discussions of the questionable effect of medical measures on selected infectious diseases like diptheria (Lee, 1931; Wilson and Miles, 1946; Bolduan, 1930) and pneumonia (Pfizer and Co., 1953). In a presidential address to the American Association of Immunologists in 1954 (frequently referred to by McKeown), Magill (1955) marshalled an assortment of data then available—some from England and Wales—to cast doubt on the plausibility of existing accounts of the decline in mortality for several conditions. Probably the most influential work in the United States is that of Dubos who, principally in *Mirage of Health* (1959), *Man Adapting* (1965), and *Man, Medicine and Environment* (1968), focused on the nonmedical reasons for changes in the health of overall populations. In another presidential address, this time to the Infectious Diseases Society of America, Kass (1971), again employing data from England and Wales, argued that most of the decline in mortality for most infectious conditions occurred prior to the discovery of either "the cause" of the disease or some purported "treatment" for it. Before the same society and largely on the basis of clinical experience with infectious diseases and data from a single state (Massachusetts), Weinstein (1974), while conceding there are some effective

treatments which seem to yield a favorable outcome (e.g., for poliomyelitis, tuberculosis, and possibly smallpox), argued that despite the presence of supposedly effective treatments some conditions may have increased (e.g., subacute bacterial endocarditis, streptococcal pharyngitis, pneumococcal pneumonia, gonorrhea, and syphilis) and also that mortality for yet other conditions shows improvement in the absence of any treatment (e.g., chickenpox). With the appearance of his book, *Who Shall Live?* (1974), Fuchs, a health economist, contributed to the resurgence of interest in the relative contribution of medical care to the modern decline in mortality in the United States. He believes there has been an unprecedented improvement in health in the United States since about the middle of the eighteenth century, associated primarily with a rise in real income. While agreeing with much of Fuchs' thesis, we will present evidence which seriously questions his belief that "beginning in the mid '30s, major therapeutic discoveries made significant contributions independently of the rise in real income."

Although neither representative nor exhaustive, this brief and selective background should serve to introduce the analysis which follows. Our intention is to highlight the following: (a) the debate over the questionable contribution of medical measures to the modern decline of mortality has a long history and remains topical; (b) although sometimes popularly associated with dilettantes such as Ivan Illich (1976), the debate continues to preoccupy able scholars from a variety of disciplines and remains a matter of concern to the most learned societies; (c) although of emerging interest in the United States, the issue is already a matter of concern and considerable research elsewhere; (d) to the extent that the subject has been pursued in the United States, there has been a restrictive tendency to focus on a few selected diseases, or to employ only statewide data, or to apply evidence from England and Wales directly to the United States situation.

How Reliable are Mortality Statistics?

We have argued elsewhere that mortality statistics are inadequate and can be misleading as indicators of a nation's overall health status (McKinlay and McKinlay, forthcoming). Unfortunately, these are the only types of data which are readily accessible for the examination of time trends, simply because comparable morbidity

and disability data have not been available. Apart from this overriding problem, several additional caveats in the use of mortality statistics are: (a) difficulties introduced by changes in the registration area in the United States in the early twentieth century; (b) that often no single disease, but a complex of conditions, may be responsible for death (Krueger, 1966); (c) that studies reveal considerable inaccuracies in recording the cause of death (Moriyama et al., 1958); (d) that there are changes over time in what it is fashionable to diagnose (for example, ischaemic heart disease and cerebrovascular disease); (e) that changes in disease classifications (Dunn and Shackley, 1945) make it difficult to compare some conditions over time and between countries (Reid and Rose, 1964); (f) that some conditions result in immediate death while others have an extended period of latency; and (g) that many conditions are severely debilitating and consume vast medical resources but are now generally non-fatal (e.g., arthritis and diabetes). Other obvious limitations could be added to this list.

However, it would be foolhardy indeed to dismiss all studies based on mortality measures simply because they are possibly beset *with known limitations.* Such data are preferable to those the limitations of which are either unknown or, if known, cannot be estimated. Because of an overawareness of potential inaccuracies, there is a timorous tendency to disregard or devalue studies based on mortality evidence, even though there are innumerable examples of their fruitful use as a basis for planning and informed social action (Alderson, 1976). Sir Austin Bradford Hill (1955) considers one of the most important features of Snow's work on cholera to be his adept use of mortality statistics. A more recent notable example is the study by Inman and Adelstein (1969) of the circumstantial link between the excessive absorption of bronchodilators from pressurized aerosols and the epidemic rise in asthma mortality in children aged ten to fourteen years. Moreover, there is evidence that some of the known inaccuracies of mortality data tend to cancel each other out.[2] Consequently, while mortality statistics may be unreliable for

[2]Barker and Rose cite one study which compared the ante-mortem and autopsy diagnoses in 9,501 deaths which occurred in 75 different hospitals. Despite lack of a concurrence on *individual* cases, the *overall* frequency was very similar in diagnoses obtained on either an ante-mortem or a post-mortem basis. As an example they note that clinical diagnoses of carcinoma of the rectum were confirmed at autopsy in only 67 percent of cases, but the incorrect clinical diagnoses were balanced by an almost identical number of lesions diagnosed for the first time at autopsy (Barker and Rose, 1976).

use in individual cases, when pooled for a country and employed in population studies, they can reveal important trends and generate fruitful hypotheses. They have already resulted in informed social action (for example, the use of geographical distributions of mortality in the field of environmental pollution).

Whatever limitations and risks may be associated with the use of mortality statistics, they obviously apply equally to all studies which employ them—both those which attribute the decline in mortality to medical measures and those which argue the converse, or something else entirely. And, if such data constitute acceptable evidence in support of the presence of medicine, then it is not unreasonable, or illogical, to employ them in support of some opposing position. One difficulty is that, depending on the nature of the results, double standards of rigor seem to operate in the evaluation of different studies. Not surprisingly, those which challenge prevailing myths or beliefs are subject to the most stringent methodological and statistical scrutiny, while supportive studies, which frequently employ the flimsiest impressionistic data and inappropriate techniques of analysis, receive general and uncritical acceptance. Even if all possible "ideal" data were available (which they never will be) and if, after appropriate analysis, they happened to support the viewpoint of this paper, we are doubtful that medicine's protagonists would find our thesis any more acceptable.

The Modern Decline in Mortality

Despite the fact that mortality rates for certain conditions, for selected age and sex categories, continue to fluctuate, or even increase (U.S. Dept. HEW, 1964; Moriyama and Gustavus, 1972; Lilienfeld, 1976), there can be little doubt that a marked decline in overall mortality for the United States has occurred since about 1900 (the earliest point for which reliable national data are available).

Just how dramatic this decline has been in the United States is illustrated in Fig. 1 which shows age-adjusted mortality rates for males and females separately.[3] Both sexes experienced a marked

[3]All age and sex adjustments were made by the "direct" method using the population of 1900 as the standard. For further information on this method of adjustment, see Hill (1971) and Shryock et al. (1971).

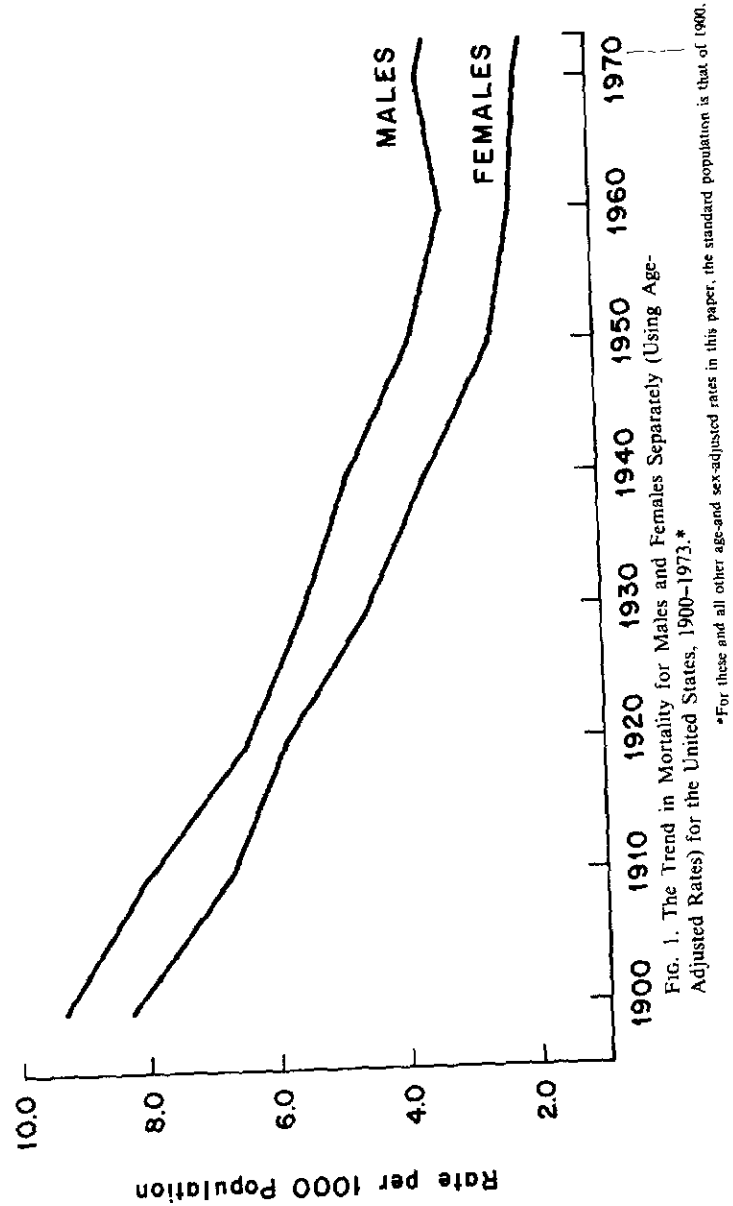

FIG. 1. The Trend in Mortality for Males and Females Separately (Using Age-Adjusted Rates) for the United States, 1900–1973.*

*For these and all other age-and sex-adjusted rates in this paper, the standard population is that of 1900.

decline in mortality since 1900. The female decline began to level off by about 1950, while 1960 witnessed the beginning of a slight increase for males. Figure 1 also reveals a slight but increasing divergence between male and female mortality since about 1920.

Figure 2 depicts the decline in the overall age- and sex-adjusted rate since the beginning of this century. Between 1900 and 1973, there was a 69.2 percent decrease in overall mortality. The average annual rate of decline from 1900 until 1950 was .22 per 1,000, after which it became an almost negligible decline of .04 per 1,000 annually. Of the total fall in the standardized death rate between 1900 and 1973, 92.3 percent occurred prior to 1950. Figure 2 also plots the decline in the standardized death rate *after* the total number of deaths in each age and sex category has been reduced by the number of deaths attributed to the eleven major infectious conditions (typhoid, smallpox, scarlet fever, measles, whooping cough, diphtheria, influenza, tuberculosis, pneumonia, diseases of the digestive system, and poliomyelitis). It should be noted that, although this latter rate also shows a decline (at least until 1960), its slope is much more shallow than that for the overall standardized death rate. A major part of the decline in deaths from these causes since about 1900 may be attributed to the virtual disappearance of these infectious diseases.

An absurdity is reflected in the third broken line in Fig. 2 which also plots the increase in the proportion of the Gross National Product expended annually for medical care. *It is evident that the beginning of the precipitate and still unrestrained rise in medical care expenditures began when nearly all (92 percent) of the modern decline in mortality this century had already occurred.*[4]

Figure 3 illustrates how the proportion of deaths contributed by infectious and chronic conditions has changed in the United States since the beginning of the twentieth century. In 1900, about 40 percent of all deaths were accounted for by eleven major infectious diseases, 16 percent by three chronic conditions, 4 percent by accidents, and the remainder (37 percent) by all other causes. By 1973, only 6 percent of all deaths were due to these eleven infectious

[4]Rutstein (1967), although fervently espousing the traditional view that medical advances have been largely responsible for the decline in mortality, discussed this disjunction and termed it "The Paradox of Modern Medicine." More recently, and from a perspective that is generally consistent with that advanced here, Powles (1973) noted the same phenomenon in England and Wales.

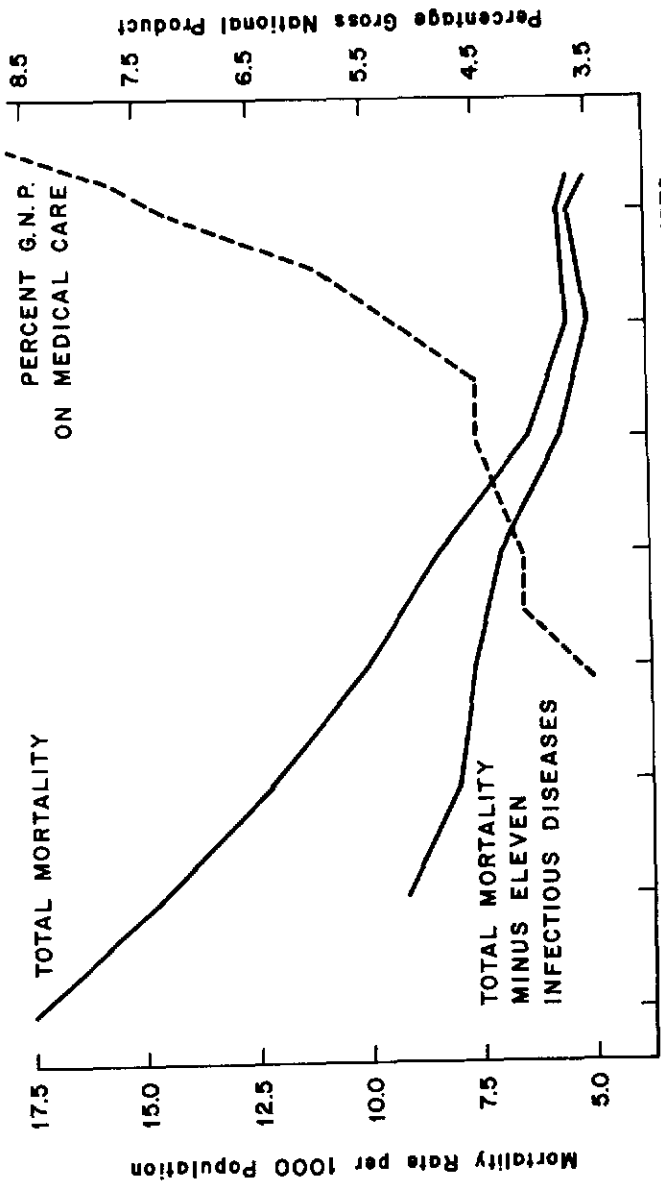

FIG. 2. Age-and Sex-Adjusted Mortality Rates for the United States 1900–1973, Including and Excluding Eleven Major Infectious Diseases, Contrasted with the Proportion of the Gross National Product Expended on Medical Care.

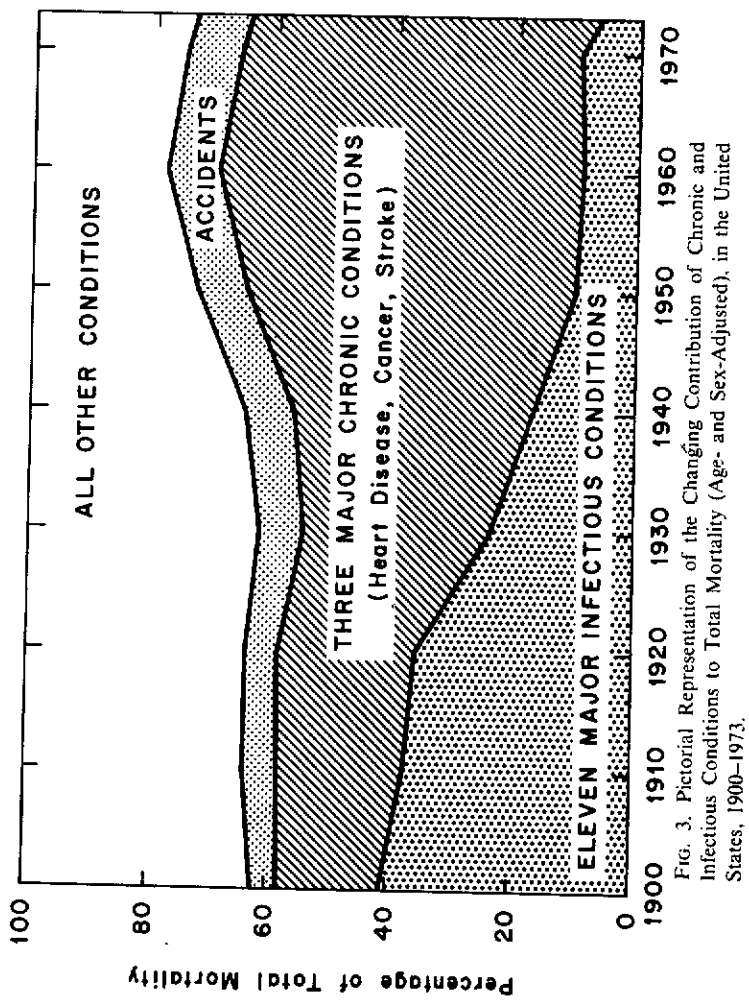

FIG. 3. Pictorial Representation of the Changing Contribution of Chronic and Infectious Conditions to Total Mortality (Age- and Sex-Adjusted), in the United States, 1900–1973.

diseases, 58 percent to the same three chronic conditions, 9 percent to accidents, and 27 percent were contributed by other causes.[5]

Now to what phenomenon, or combination of events, can we attribute this modern decline in overall mortality? Who (if anyone), or what group, can claim to have been instrumental in effecting this reduction? Can anything be gleaned from an analysis of mortality experience to date that will inform health care policy for the future?

It should be reiterated that a major concern of this paper is to determine the effect, if any, of specific medical measures (both chemotherapeutic and prophylactic) on the decline of mortality. It is clear from Figs. 2 and 3 that most of the observable decline is due to the rapid disappearance of some of the major infectious diseases. Since this is where most of the decline has occurred, it is logical to focus a study of the effect of medical measures on this category of conditions. Moreover, for these eleven conditions, there exist clearly identifiable medical interventions to which the decline in mortality has been popularly ascribed. No analogous interventions exist for the major chronic diseases such as heart disease, cancer, and stroke. Therefore, even where a decline in mortality from these chronic conditions may have occurred, this cannot be ascribed to any specific measure.

The Effect of Medical Measures on Ten Infectious Diseases Which Have Declined

Table 1 summarizes data on the effect of major medical interventions (both chemotherapeutic and prophylactic) on the decline in the age- and sex-adjusted death rates in the United States, 1900–1973, for ten of the eleven major infectious diseases listed above. Together, these diseases accounted for approximately 30 percent of all deaths at the turn of the century and nearly 40 percent of the total decline in the mortality rate since then. The ten diseases were selected on the following criteria: (a) some decline in the death rate had occurred in the period 1900–1973; (b) significant decline in the death rate is commonly attributed to some specific medical

[5]Deaths in the category of chronic respiratory diseases (chronic bronchitis, asthma, emphysema, and other chronic obstructive lung diseases) could not be included in the group of chronic conditions because of insurmountable difficulties inherent in the many changes in disease classification and in the tabulation of statistics.

TABLE 1

The Contribution of Medical Measures (Both Chemotherapeutic and Prophylactic) to the Fall in the Age and Sex-Adjusted Death Rates (S.D.R.) of Ten Common Infectious Diseases, and to the Overall Decline in the S.D.R., for the United States, 1900–1973

Disease	*Fall in S.D.R. per 1,000 Population, 1900–1973 (a)*	*Fall in S.D.R as % of the Total Fall in S.D.R. (b)=(a)/1214 x 100%*	*Year of Medical Intervention (Either Chemotherapy or Prophylaxis)*	*Fall in S.D.R per 1,000 Population After Year of Intervention (c)*	*Fall in S.D.R After Intervention as % of Total Fall for the Disease (d) = (c) ÷ (a)*	*Fall in S.D.R. After Intervention as % of Total Fall in S.D.R for All Causes (e)=(b)x(c)/(a)*
Tuberculosis	2.00	16.48	Izoniazid/ Streptomycin, 1950	0.17	8.36	1.38
Scarlet Fever	0.10	0.84	Penicillin, 1946	0.00	1.75	0.01
Influenza	0.22	1.78	Vaccine, 1943	0.05	25.33	0.45
Pneumonia	1.42	11.74	Sulphonamide, 1935	0.24	17.19	2.02
Diptheria	0.43	3.57	Toxoid, 1930	0.06	13.49	0.48
Whooping Cough	0.12	1.00	Vaccine, 1930	0.06	51.00	0.51
Measles	0.12	1.04	Vaccine, 1963	0.00	1.38	0.01
Smallpox	0.02	0.16	Vaccine, 1800	0.02	100.00	0.16
Typhoid	0.36	2.95	Chloramphenicol, 1948	0.00	0.29	0.01
Poliomyelitis	0.03	0.23	Vaccine, Salk/ Sabin, 1955	0.01	25.87	0.06

TABLE 2

Pair-Wise Correlation Matrix for 44 Countries, Between Four Measures of Health Status and Three Measures of Medical Care Input

	Variable	*Matrix of Coefficients*							
1.	Infant Mortality Rate (1972)								
2.	Crude Mortality Rate (1970–1972)	-0.14							
3.(a)	Life Expectancy (Males) at 25 Years	-0.14	-0.12						
3.(b)	Life Expectancy (Females) at 25 Years	-0.12	0.04	0.75					
4.(a)	Life Expectancy (Males) at 55 Years	-0.01	0.10	0.74	0.93				
4.(b)	Life Expectancy (Females) at 55 Years	-0.13	0.01	0.75	0.98	0.95			
5.	Population per Hospital Bed (1971–1973)	0.64	-0.30	0.05	-0.02	0.17	0.0		
6.	Population per Physician (1971–1973)	0.36	-0.30	0.11	0.04	0.16	0.07	0.70	
7.	Per Capita Gross National Product: In $U.S. Equivalent (1972)	-0.66	0.26	0.16	0.18	0.07	0.22	-0.56	-0.46
	Variable (by number)	1	2	3a	3b	4a	4b	5	6

Sources:

1. *United Nations Demographic Yearbook: 1974.* New York, United Nations Publications, 1975. (For the Crude and Infant Mortality Rates).
2. *World Health Statistics Annual:* 1972, Vol. I, Geneva, World Health Organization, 1975, pp. 780–783. (For the Life Expectancy Figures).
3. *United Nations Statistical Yearbook, 1973 and 1975.* New York, United Nations Publications, 25th and 27th issues, 1974 and 1976. (For the Population bed/physician ratios).
4. *The World Bank Atlas.* Washington, D.C., World Bank, 1975. (For the per capita Gross National Product).

measure for the disease; and (c) adequate data for the disease over the period 1900–1973 are available. The diseases of the digestive system were omitted primarily because of lack of clarity in diagnosis of specific diseases such as gastritis and enteritis.

Some additional points of explanation should be noted in relation to Table 1. First, the year of medical intervention coincides (as nearly as can be determined) with the first year of widespread or commercial use of the appropriate drug or vaccine.[6] This date does *not* necessarily coincide with the date the measure was either first discovered, or subject to clinical trial. Second, the decline in the death rate for smallpox was calculated using the death rate for 1902 as being the earliest year for which this statistic is readily available (U.S. Bureau of the Census, 1906). For the same reasons, the decline in the death rate from poliomyelitis was calculated from 1910. Third, the table shows the contribution of the decline in each disease to the total decline in mortality over the period 1900–1973 (column b). The overall decline during this period was 12.14 per 1,000 population (17.54 in 1900 to 5.39 in 1973). Fourth, in order to place the experience for each disease in some perspective, Table 1 also shows the contribution of the relative fall in mortality after the intervention to the overall fall in mortality since 1900 (column e). In other words, the figures in this last column represent the percentage of the total fall in mortality contributed by each disease after the date of medical intervention.

It is clear from column b that only reductions in mortality from tuberculosis and pneumonia contributed substantially to the decline in total mortality between 1900 and 1973 (16.5 percent and 11.7 percent, respectively). The remaining eight conditions *together* accounted for less than 12 percent of the total decline over this period. Disregarding smallpox (for which the only effective measure had been introduced about 1800), only influenza, whooping cough, and poliomyelitis show what could be considered substantial declines of 25 percent or more after the date of medical intervention. However, even under the somewhat unrealistic assumption of a constant (linear) rate of decline in the mortality rates, only whooping cough and poliomyelitis even approach the percentage which would have been expected. The remaining six conditions (tuberculosis, scarlet fever, pneumonia, diphtheria, measles, and typhoid) showed negligible declines in their mortality rates subsequent to the date of medical intervention. The seemingly quite large percentages for pneumonia and diphtheria (17.2 and 13.5, respectively) must of course be viewed in the context of relatively early interventions—1935 and 1930.

[6] In determining the dates of intervention we relied upon: (a) standard epidemiology and public health texts; (b) the recollections of authorities in the field of infectious diseases; and (c) recent publications on the same subject.

In order to examine more closely the relation of mortality trends for these diseases to the medical interventions, graphs are presented for each disease in Fig. 4. Clearly, for tuberculosis, typhoid, measles, and scarlet fever, the medical measures considered were introduced at the point when the death rate for each of these diseases was already negligible. Any change in the rates of decline which may have occurred subsequent to the interventions could only be minute. Of the remaining five diseases (excluding smallpox with its negligible contribution), it is only for poliomyelitis that the medical measure appears to have produced any noticeable change in the trends. Given peaks in the death rate for 1930, 1950 (and possibly for 1910), a comparable peak could have been expected in 1970. Instead, the death rate dropped to the point of disappearance after 1950 and has remained negligible. The four other diseases (pneumonia, influenza, whooping cough, and diphtheria) exhibit relatively smooth mortality trends which are unaffected by the medical measures, even though these were introduced relatively early, when the death rates were still notable.

It may be useful at this point to briefly consider the common but dubious practice of projecting estimated mortality trends (Witte and Axnick, 1975). In order to show the beneficial (or even detrimental) effect of some medical measure, a line, estimated on a set of points observed prior to the introduction of the measure, is projected over the period subsequent to the point of intervention. Any resulting discrepancy between the projected line and the observed trend is then used as some kind of "evidence" of an effective or beneficial intervention. According to statistical theory on least squares estimation, an estimated line can serve as a useful predictor, but the prediction is only valid, and its error calculable, within the range of the points used to estimate the line. Moreover, those predicted values which lie at the extremes of the range are subject to much larger errors than those nearer the center. It is, therefore, probable that, even if the projected line was a reasonable estimate of the trend after the intervention (which, of course, it is not), the

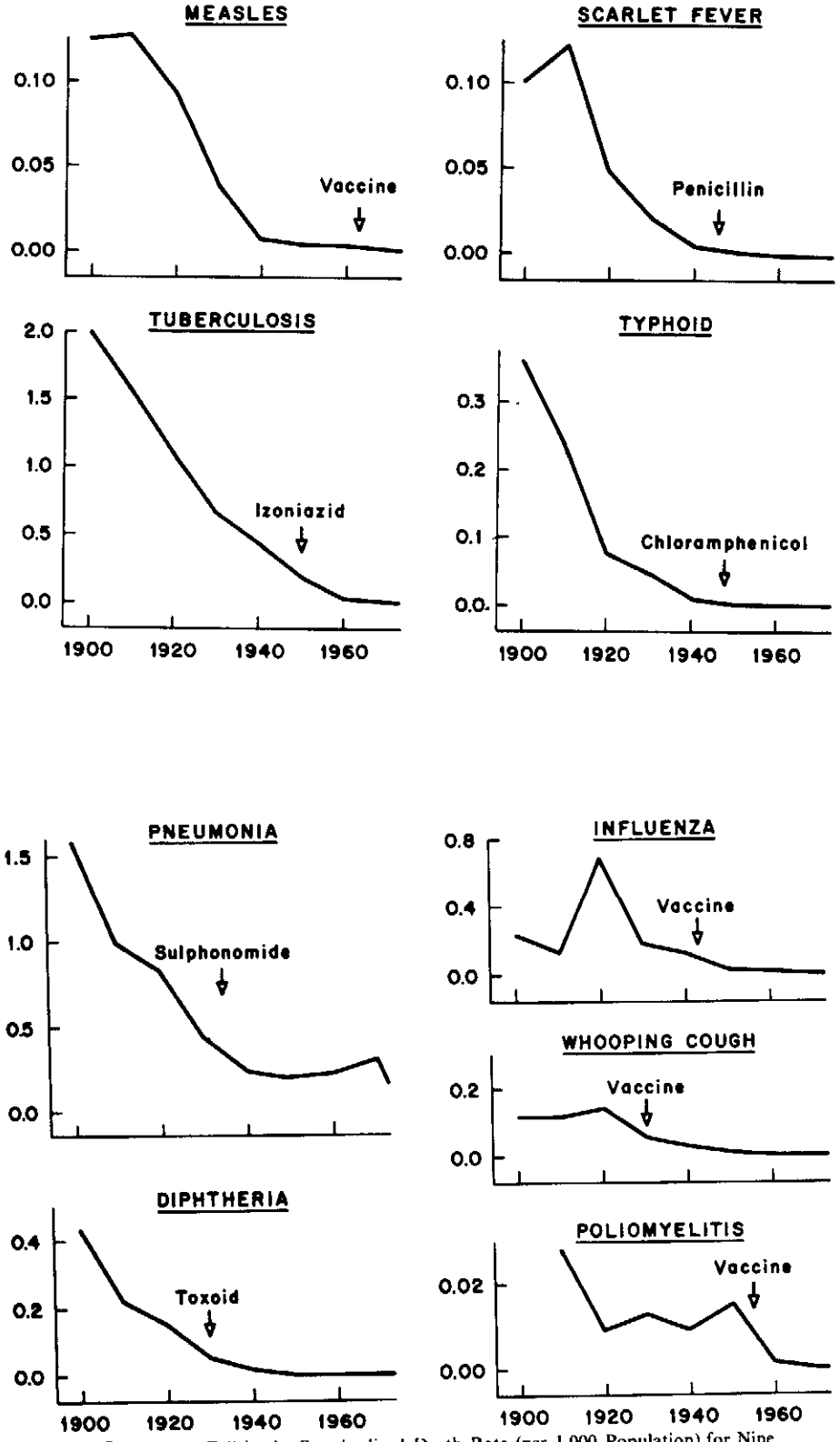

FIG. 4. The Fall in the Standardized Death Rate (per 1,000 Population) for Nine Common Infectious Diseases in Relation to Specific Medical Measures, for the United States, 1900–1973.

divergent observed trend is probably well within reasonable error limits of the estimated line (assuming the error could be calculated), as the error will be relatively large. In other words, this technique is of dubious value as no valid conclusions are possible from its application, and a relatively large prediction error cannot be estimated, which is required in order to objectively judge the extent of divergence of an observed trend.

With regard to the ten infectious diseases considered in this paper, when lines were fitted to the nine or ten points available over the entire period (1900–1973), four exhibited a reasonably good fit to a straight line (scarlet fever, measles, whooping cough, and poliomyelitis), while another four (typhoid, diphtheria, tuberculosis, and pneumonia) showed a very good quadratic fit (to a curved line). Of the remaining two diseases, smallpox showed a negligible decline, as it was already a minor cause of death in 1900 (only 0.1 percent), and influenza showed a poor fit because of the extremely high death rate in 1920. From Fig. 4 it is clear, however, that the rate of decline slowed in more recent years for most of the diseases considered—a trend which could be anticipated as rates approach zero.[7]

Now it is possible to argue that, given the few data points available, the fit is somewhat crude and may be insensitive to any changes subsequent to a point of intervention. However, this can be countered with the observation that, given the relatively low death rates for these diseases, any change would have to be extremely marked in order to be detected in the overall mortality experience. Certainly, from the evidence considered here, only poliomyelitis appears to have had a noticeably changed death rate subsequent to intervention. Even if it were assumed that this change was entirely due to the vaccines, then only about one percent of the decline following interventions for the diseases considered here (column d of Table 1) could be attributed to medical measures. Rather more conservatively, if we attribute some of the subsequent fall in the death rates for pneumonia, influenza, whooping cough, and diphtheria to medical measures, then perhaps 3.5 percent of the fall in the overall death rate can be explained through medical intervention in the major infectious diseases considered here. Indeed, given that it is precisely for these diseases that medicine claims most success in lowering mortality, 3.5 percent probably represents a reasonable upper-limit estimate of the total contribution of medical measures to the decline in mortality in the United States since 1900.

[7]For this reason, a negative exponential model is sometimes used to fit a curved line to such data. This was not presented here as the number of points available was small and the difference between a simple quadratic and negative exponential fit was not, upon investigation, able to be detected.

Conclusions

Without claiming they are definitive findings, and eschewing pretentions to an analysis as sophisticated as McKeown's for England and Wales, one can reasonably draw the following conclusions from the analysis presented in this paper:

In general, medical measures (both chemotherapeutic and prophylactic) appear to have contributed little to the overall decline in mortality in the United States since about 1900—having in many instances been introduced several decades after a marked decline had already set in and having no detectable influence in most instances. More specifically, with reference to those five conditions (influenza, pneumonia, diphtheria, whooping cough, and poliomyelitis) for which the decline in mortality appears substantial after the point of intervention—and on the unlikely assumption that all of this decline is attributable to the intervention—it is estimated that at most 3.5 percent of the total decline in mortality since 1900 could be ascribed to medical measures introduced for the diseases considered here.

These conclusions, in support of the thesis introduced earlier, suggest issues of the most strategic significance for researchers and health care legislators. Profound policy implications follow from either a confirmation or a rejection of the thesis. If one subscribes to the view that we are slowly but surely eliminating one disease after another because of medical interventions, then there may be little commitment to social change and even resistance to some reordering of priorities in medical expenditures. If a disease X is disappearing primarily because of the presence of a particular intervention or service Y, then clearly Y should be left intact, or, more preferably, be expanded. Its demonstrable contribution justifies its presence. But, if it can be shown convincingly, and on commonly accepted grounds, that the major part of the decline in mortality is unrelated to medical care activities, then some commitment to social change

and a reordering of priorities may ensue. For, if the disappearance of X is largely unrelated to the presence of Y, or even occurs in the absence of Y, then clearly the expansion and even the continuance of Y can be reasonably questioned. Its demonstrable ineffectiveness justifies some reappraisal of its significance and the wisdom of expanding it in its existing form.

In this paper we have attempted to dispel the myth that medical measures and the presence of medical services were primarily responsible for the modern decline in mortality. The question now remains: if they were not primarily responsible for it, then how is it to be explained? An adequate answer to this further question would require a more substantial research effort than that reported here, but is likely to be along the lines suggested by McKeown which were referred to early in this paper. Hopefully, this paper will serve as a catalyst for such research, incorporating adequate data and appropriate methods of analysis, in an effort to arrive at a more viable alternative explanation.

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Notes to Contributors

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... studies by Smith et al. (1972) show ...
... an earlier study (Smith, 1971) shows ...
... earlier reports (Smith, 1970; Jones and Brown, 1969) ...

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Smith, J. 1961. Title of the article. *Journal of Communication* 125: 965–72.
Jones, J. S. 1953. *Title of the book.* Boston: Timely Press.
Brown, P. 1959. Title of chapter. In *Title of volume,* ed. J. Smith, pp. 441–65. New York: Wiley.

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History of Drinking Water Treatment

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American drinking water supplies are among the safest in the world. The disinfection of water has played a critical role in improving drinking water quality in the United States. In 1908, Jersey City, New Jersey was the first city in the United States to begin routine disinfection of community drinking water. Over the next decade, thousands of cities and towns across the United States followed suit in routinely disinfecting their drinking water, contributing to a dramatic decrease in disease across the country (Fig 1).

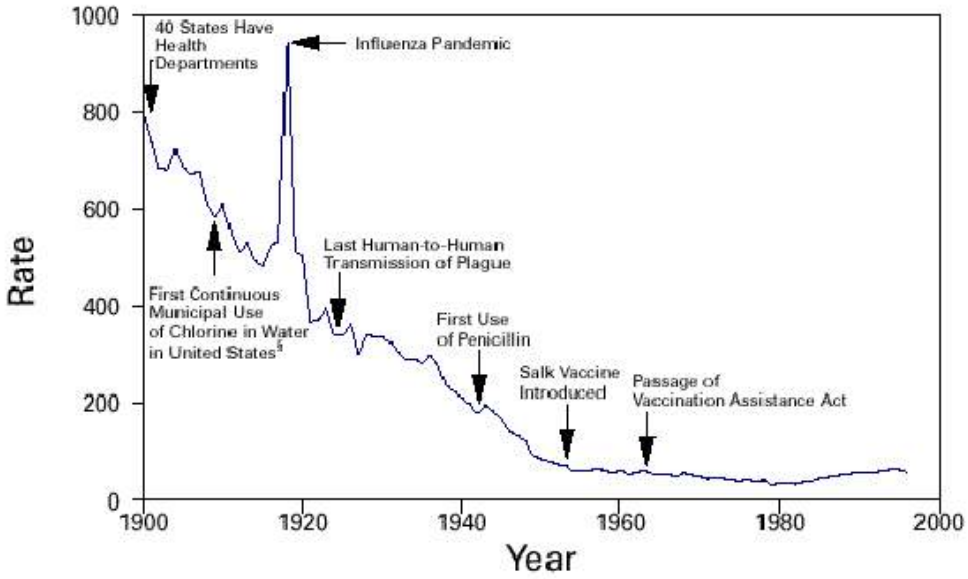


Figure 1. Crude death rate* for infectious diseases - United States, 1900-1996

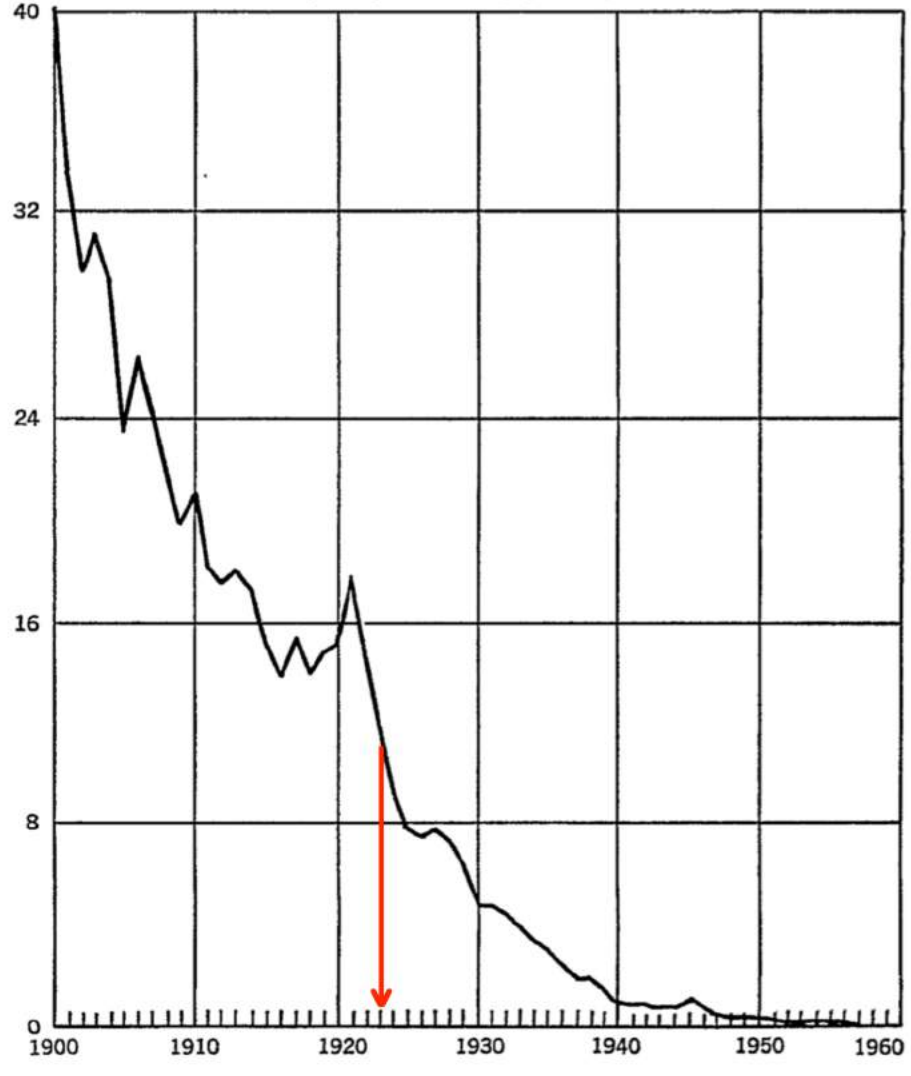
*Per 100,000 population per year.

The occurrence of diseases such as cholera and typhoid dropped dramatically. In 1900, the occurrence of typhoid fever in the United States was approximately 100 cases per 100,000 people. By 1920, it had decreased to 33.8 cases per 100,000 people. In 2006, it had decreased to 0.1 cases per 100,000 people (only 353 cases) with approximately 75% occurring among international travelers. Typhoid fever decreased rapidly in cities from Baltimore to Chicago as water disinfection and treatment was instituted. This decrease in illness is credited to the implementation of drinking water disinfection and treatment, improving the quality of source water, and improvements in sanitation and hygiene.

It is because of these successes that we can celebrate over a century of public drinking water disinfection and treatment – one of the greatest public health achievements of the 20th century.

Figure 18.—Death Rates for Diphtheria: Death-registration States, 1900–32, and United States, 1933–60

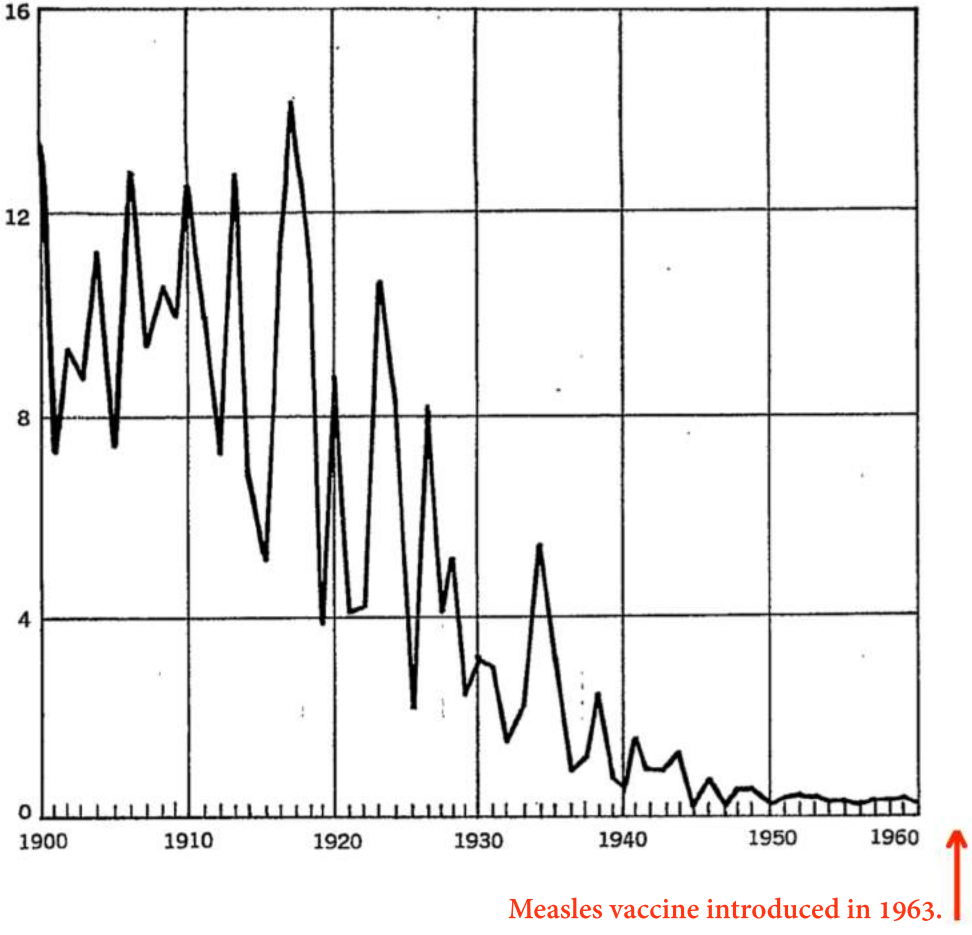
(Rates per 100,000 population)



Diphtheria vaccine introduced in 1923,
but not widely used until the 1930s.

Figure 19.—Death Rates for Measles: Death-registration States, 1900–32, and United States, 1933–60

(Rates per 100,000 population)



Measles vaccine introduced in 1963.

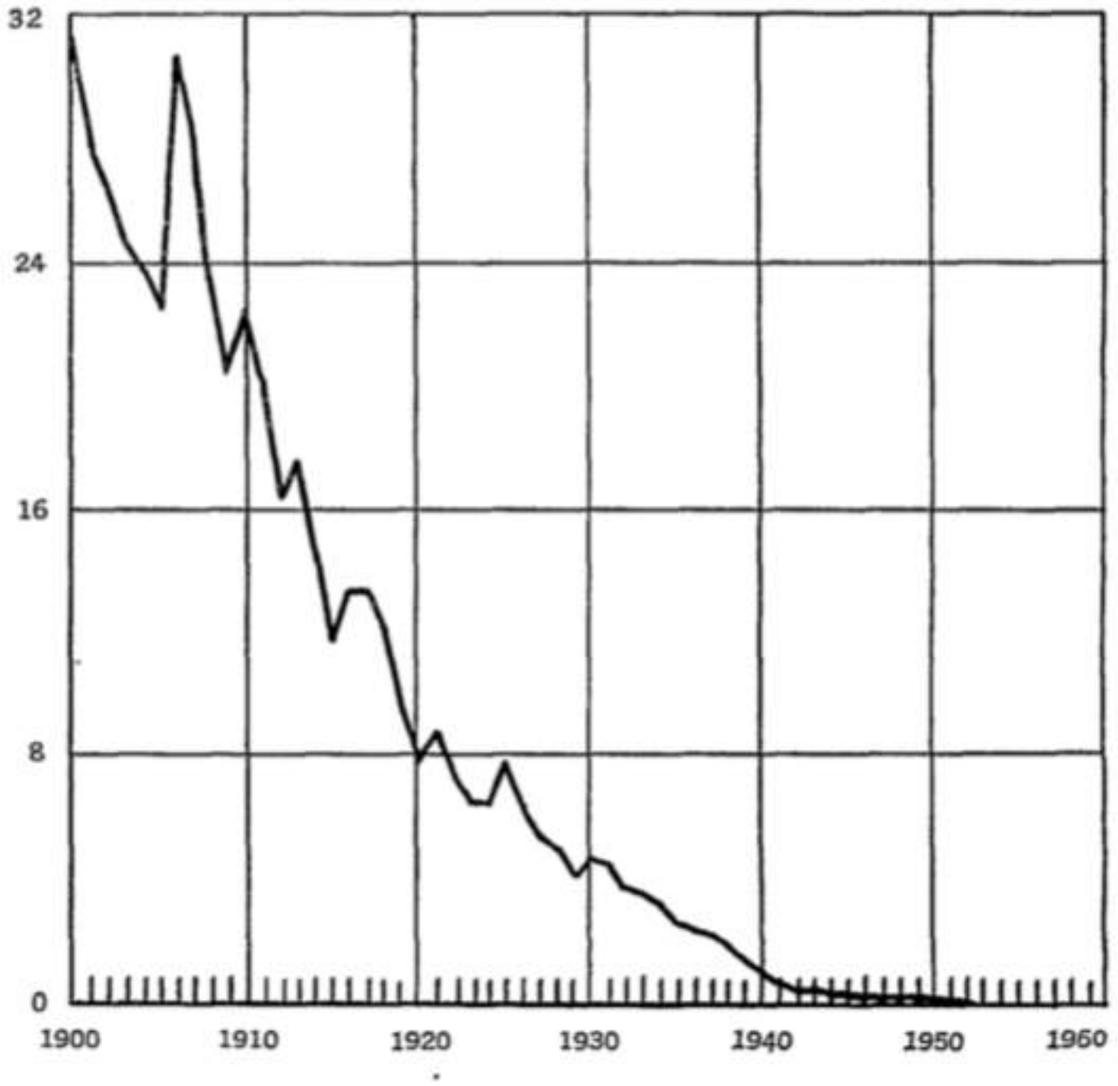
Source: https://www.cdc.gov/nchs/data/vsus/vsrates1940_60.pdf

Figure 14.—Death Rates for Tuberculosis, All Forms: Death-registration States, 1900–32, and United States, 1933–60

(Rates per 100,000 population)

Figure 16.—Death Rates for Typhoid Fever: Death-registration States, 1900–32, and United States, 1933–60

(Rates per 100,000 population)



No widespread vaccination, similar decline.

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In vitro inhibition of mumps virus by retinoids

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Abstract

Background: Mumps virus (MuV) is a highly infectious paramyxovirus closely related to measles virus (MeV). Despite the availability of a mumps vaccine, outbreaks continue to occur and no treatment options are available. Vitamin A and other naturally occurring retinoids inhibit the replication of MeV *in vitro*.

Methods: Anti-viral effects of retinoids were observed in cell culture using the myelomonocytic U937, NB4/R4, and Huh7/7.5 cells. Observations of anti-viral effect were quantified using TCID50 analysis. Molecular properties of the antiviral effect were analysed using quantitative RT-PCR and western blot.

Results: The current work demonstrates that retinoids inhibit MuV *in vitro* due to up-regulation of type I interferon (IFN) and IFN stimulated genes. This effect is mediated by nuclear retinoid receptor signalling and RIG-I is required. The antiviral retinoid-induced state makes cells less permissive to viral replication from subsequent challenge with either MuV or MeV for less than 12 hours.

Conclusions: These results demonstrate that retinoids inhibit MuV replication in uninfected bystander cells through a retinoid inducible gene I (RIG-I), retinoic acid receptor (RAR) and IFN dependent manner making them refractory to subsequent rounds of viral replication. These observations raise the possibility that pharmacological doses of retinoids might have clinical benefit in MuV infection.

Text

The *Paramyxoviridae* are single stranded, enveloped, negative sense RNA viruses. They are among the most important viral pathogens of humans and animals. Many of the *Paramyxoviridae* replicate only in the respiratory epithelium, but *Morbillivirus* and *Rubulavirus* members typically have wider tissue tropism and can cause severe, systemic disease [1]. *Paramyxovirdae* epidemics in virgin populations can be devastating [1]. Vaccines are available for only a small number of the *Paramyxoviridae* and antiviral drugs are not yet available for most of these agents.

Mumps virus (MuV) is a *Rubulavirus* in the *Paramyxoviridae* family. It is the causative agent of mumps [2]. MuV is a highly contagious infection of humans and was historically one of the most common childhood illnesses. The virus infects and replicates in the nasal mucosa and upper-respiratory tract [2]. A transient cell-associated viremia (of mononuclear cells) contributes to systemic viral spread [2]. In young children, MuV infection is typically a mild disease characterized by fever, headache and swelling of the salivary glands. Complications such as meningitis, encephalitis or orchitis may occur. Mumps is a leading cause of acquired sensorineural deafness among children. Rates of post-infectious meningoencephalitis can be 1-10% of clinical mumps cases. Although the fatality rate of mumps encephalitis is low (0.1-0.5% of clinical mumps cases), the risk of permanent neurologic sequelae in encephalitis cases is 25% [3]. Furthermore, MuV infection during the first trimester of pregnancy is associated with a 25% incidence of spontaneous abortion [3].

There is no current treatment for mumps other than supportive care [2]. Vaccination programs in developed countries have markedly increased the average age at which clinical mumps occurs and dramatically reduced the incidence of mumps infection [2]. Unfortunately, large outbreaks have recently occurred in Europe, North America, Australia and Israel [4–12].

In the last 2 decades, many studies have documented the beneficial effects of vitamin A supplements on general mortality and/or morbidity in young children in a wide

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range of developing countries. In 2000, a meta-analysis of eight studies demonstrated an overall 30% reduction in infant mortality attributable to vitamin A supplements [13–15]. A surprising spin-off from these vitamin A supplementation studies was the re-discovery that vitamin A 'treatment' can significantly decrease the morbidity and mortality associated with acute MeV infection [16–19]. The mechanism underlying the positive effects of vitamin A supplements and treatment in measles are not well understood [13]. Since the mid-1990s, the WHO and UNICEF have recommended vitamin A treatment for acute measles in regions of the developing world with high mortality rates [20].

Vitamin A (retinol) is a fat-soluble vitamin. Its natural and synthetic derivatives as well as metabolites are collectively referred to as retinoids [21,22]. Retinol is obtained from the diet as either retinyl esters or carotenoids. Retinoids are required for a wide-range of crucial biological processes including regulation of embryonic development, maintenance of the integrity of epithelial cell surfaces, vision and immunity [23]. The metabolite, all-*trans* retinoic acid (ATRA) is responsible for mediating many of the important biological functions of retinoids [22]. ATRA is the natural ligand for retinoic acid receptors (RAR), which form heterodimers with the retinoid X receptors (RXR) within the nucleus [24]. RAR-RXR heterodimers bind to retinoic acid response elements (RARE) on the promoters of target genes to activate transcription when bound by ligand [21,22,24]. The protein products of retinoid-responsive genes are responsible for exerting the effects of retinoids in the cell.

Retinoids have been shown to play a role in innate immune responses and to regulate the expression of a number of interferon stimulated genes [25–27]. Of particular interest among the retinoid-responsive genes is the type I interferon (IFN) pathway. A powerful trigger for type I IFN production is the recognition of virus-associated molecular patterns by pattern recognition receptors [28]. These cytokines trigger a rapid and strong innate defense against many viruses, leading to the transcription of several hundred ISGs controlled by the IFN-stimulated gene factor 3 (ISGF3) complex [29].

Of particular importance to the current work, retinoids have specifically been implicated in regulating expression of the ISG (Interferon Stimulated Gene) retinoid-inducible gene I (RIG-I) and IFN regulatory factor 1 (IRF-1) [30–39]. RIG-I is a pattern recognition receptor that was originally understood to detect 5'-triphosphorylated, single-stranded RNA [40–42] and is expressed at a basal level in many cell types. The current consensus is that the minimal requirement for RIG-I activation is a blunt-ended base paired RNA 10-20 bp long with a 5' triphosphate [43]. It can initiate the production of type I IFN and is itself an ISG [44]. IFN has been reported to induce RIG-I expression by causing the IRF-1 transcription factor to bind to the RIG-I promoter [45].

Anti-MeV effects of retinoids have been observed in a number of primary human cells and cell lines of diverse tissue origin [46–48], including the myelomonocytic U937 cells, which were an important model for our work with MuV presented herein. We hypothesize that ATRA treatment during other viral infections would also have an antiviral effect. We set out to test whether or not MuV replication could be inhibited by retinoids. Based on our previous studies, we hypothesize that retinoids would inhibit MuV replication *in vitro* and that this inhibition would depend upon RAR signalling, type I interferon and functional RIG-I.

Results

Mumps virus can be inhibited in vitro

U937 cells are neoplastic and histiocytic progenitors of monocytes that have been extensively used in immunological studies [49] including investigation of interferon pathways during MuV infection [50–52]. In these cells, increasing doses of retinol resulted in a significant inhibition of MuV replication as quantified by $TCID_{50}$ (Figure 1A). Significant inhibition was achieved at concentrations as low as 1 μM, a dose at which increased expression of the retinoid responsive gene RARβ is readily observed (Figure 1C) [53]. Treatment of U937 cells with increasing doses of ATRA was even more effective as an inhibitor of MuV output (Figure 1B) and in the induction of RARβ mRNA expression (Figure 1D) [53]. All subsequent investigations of the antiviral effect of retinoids on MuV were performed using ATRA at a dose of 1 μM.

Retinoid treatment enhances IFN signalling

The innate immune response is thought to be responsible for the initial control of infectious agents. It has long been known that up-regulation of the type I IFN response functions in an auto-response feedback loop that is critically important for antiviral responses. In the U937 model, MuV infection alone is able to induce the expression of IFNα1 mRNA (Figure 2A). However, ATRA treatment of MuV infected cells synergistically increases the expression of IFNα1 mRNA and supernatant protein levels (Figure 2A-B). IFNβ mRNA expression and protein levels are also synergistically increased by the combined treatment of ATRA and MuV infection (Figure 2C-D).

The increased type I IFN production leads to the expression of ISGs. In the U937 model, IRF-1 mRNA expression is significantly increased over control by ATRA treatment alone (Figure 2E), in agreement with our previous work [47] and the literature [30,38,39]. However, treatment of MuV infected cells with ATRA further increases the expression of IRF-1 mRNA (Figure 2E). This combined treatment (MuV + ATRA) resulted in a robust increase in RIG-I mRNA expression (Figure 2F). The mRNA levels of two other IFN-responsive

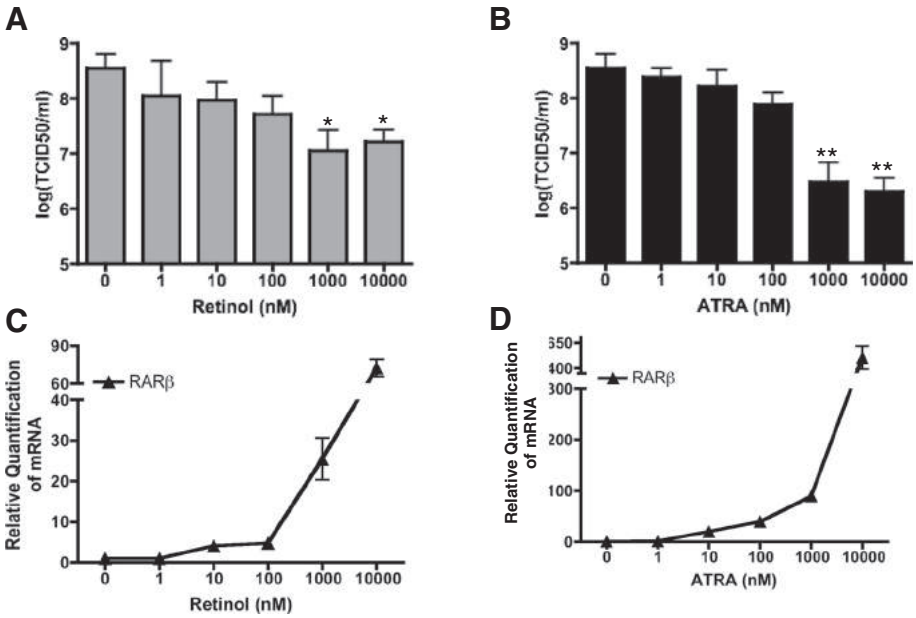

Figure 1 *In vitro* inhibition of mumps virus by retinoids. (A) (B) U937 cells were infected with MuV at an MOI of 0.01 and treated with increasing doses of retinol or all-*trans* retinoic acid (ATRA) as indicated. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. **(C) (D)** RNA was extracted from parallel U937 cultures treated with increasing doses of retinol or ATRA and analyzed for RAR-β expression by qPCR. Data presented reflect three experiments performed in triplicate (N = 3). *$p < 0.05$, **$p < 0.01$.

genes, IRF-7 and MDA-5, also showed similar patterns of increased expression in response to MuV + ATRA (data not shown). In addition to the regulation of ISG expression, treatment of MuV infected U937 cells with ATRA also increased STAT1 activation as indicated by phosphorylation of tyrosine 701 (Figure 2G).

The increased expression of these ISGs can be attributed to the increased activation of the type I IFN pathway. When a monoclonal antibody specific to IFNα/β receptor 1 was used to prevent IFN signalling during MuV + ATRA treatment, ISG mRNA expression was blocked, as demonstrated by RIG-I mRNA (Figure 2H). This observation demonstrates that IFN signalling is required for the retinoid-MuV antiviral response.

Functional nuclear retinoid receptors mediate antiviral activity of retinoids

To determine whether the antiviral activity of retinoids requires nuclear receptor signalling, we utilized the well-characterized NB4/R4 cell model (retinoid responsive versus retinoid unresponsive) [54]. NB4 cells respond to ATRA at pharmacologic concentrations, while the NB4 subclone R4 is completely resistant, regardless of the concentration [54,55]. Both NB4 and R4 cells were readily infected with MuV. In NB4 cells, 1 μM of ATRA was able to inhibit MuV output but had no effect in R4 cells (Figure 3A). At this concentration, the level of inhibition observed was unlikely due to retinoid-driven differentiation of the NB4 cells [46,48]. Like the U937 cells, expression of the ISG, IRF-1, was also increased in NB4 cells exposed to ATRA alone but was higher in cells exposed to MuV + ATRA infection (Figure 3B). IRF-1 mRNA expression was very low during MuV infection alone in this model. In the retinoid-unresponsive R4 cells, IRF-1 expression was not seen either with ATRA treatment alone or in response to MuV + ATRA (Figure 3B). Exogenous IFNβ treatment alone was not able to induce the expression of IRF-1 in either cell line, suggesting the requirement of ATRA for IRF-1 expression.

RIG-I mRNA expression was also significantly increased by the combined treatment of MuV + ATRA in NB4 cells (Figure 3C). Both MuV alone and ATRA alone increased the expression of RIG-I over mock treatment, but the expression was greatly enhanced by combined treatment. Neither ATRA, nor MuV + ATRA induced the expression of RIG-I mRNA in R4 cells (Figure 3C). When treated with exogenous IFNβ, both NB4 and R4 cells increased the expression of RIG-I mRNA suggesting that IFN signalling is functional in both cell lines (Figure 3C). Expression of other ISGs, including IRF-7 and MDA-5, showed a similar pattern of up-regulation in NB4 cells and no response in R4 cells (data not shown).

As a further confirmation of the role of RARα mediated signalling in the retinoid-MuV antiviral response, treatment of U937 cells with RO 41–5253, a specific RARα antagonist, reversed the impact of ATRA on MuV replication and reduced the expression of the ISGs in response to MuV + ATRA (data not shown).

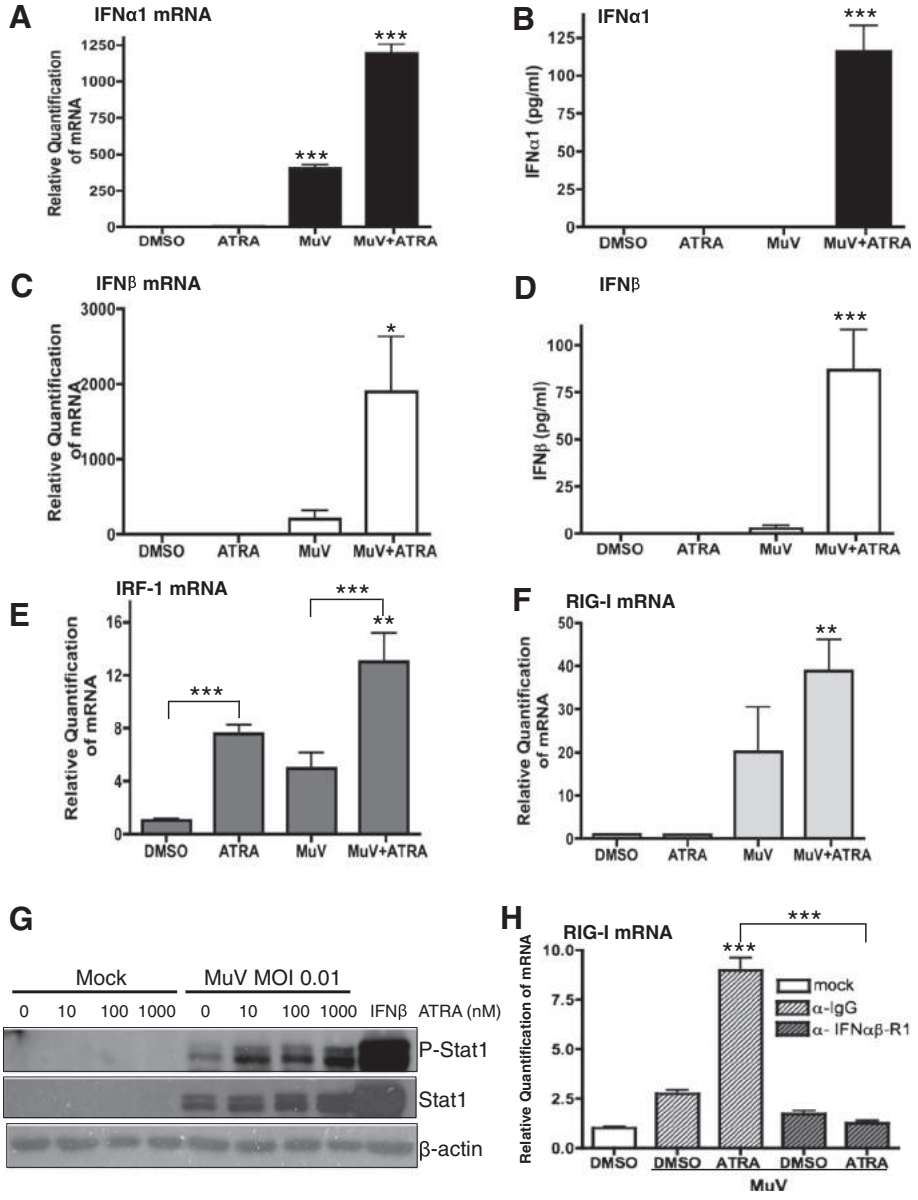

Figure 2 Type I interferon signaling is required for the induction of the retinoid anti-MuV response. U937 cells were infected with MuV at an MOI of 0.01 and treated with 1 μM ATRA or DMSO. 48 hr post-infection, RNA was extracted and analyzed for IFNα1 **(A)**, IFNβ (C), IRF-1 **(E)** and RIG-I **(F)** expression by qPCR. Supernatants were analyzed by ELISA for IFNα1 **(B)** or IFNβ **(D)** protein. **(G)** U937 cells were treated with increasing doses of ATRA (0-1000nM) and either mock infected or infected with MuV at an MOI 0.01. Protein was isolated from whole cell extracts and analyzed by western blot for phospho-STAT1 (Y701), total STAT1 or β-actin. **(H)** U937 cells were infected with MuV at an MOI of 0.01 and treated with 1 μM ATRA or DMSO and isotype control antibody or IFNAR2 antibody. 24 hr post-infection RNA was extracted and analyzed for RIG-I expression by qPCR. Data presented reflect three experiments performed in triplicate (N = 3). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

RIG-I is required for the retinoid-induced antiviral response

RIG-I is both retinoid responsive and IFN stimulated. It was clearly up regulated in our *in vitro* model systems in response to MuV + ATRA (Figures 2F, 3C). To investigate the requirement of RIG-I signalling in the cellular response to combined MuV + ATRA exposure, we used the Huh7 cell line, which is derived from a human hepatocellular carcinoma and has been used extensively in hepatitis C virus (HCV) research [56,57]. Of particular interest for our studies, an Huh7 subclone (Huh7.5) has a point mutation in the first CARD domain of RIG-I, rendering the protein non-functional [57,58].

We turned to the Huh7/7.5 model to demonstrate the importance of RIG-I rather than using RNA interference (RNAi) after initial experiments demonstrated that both

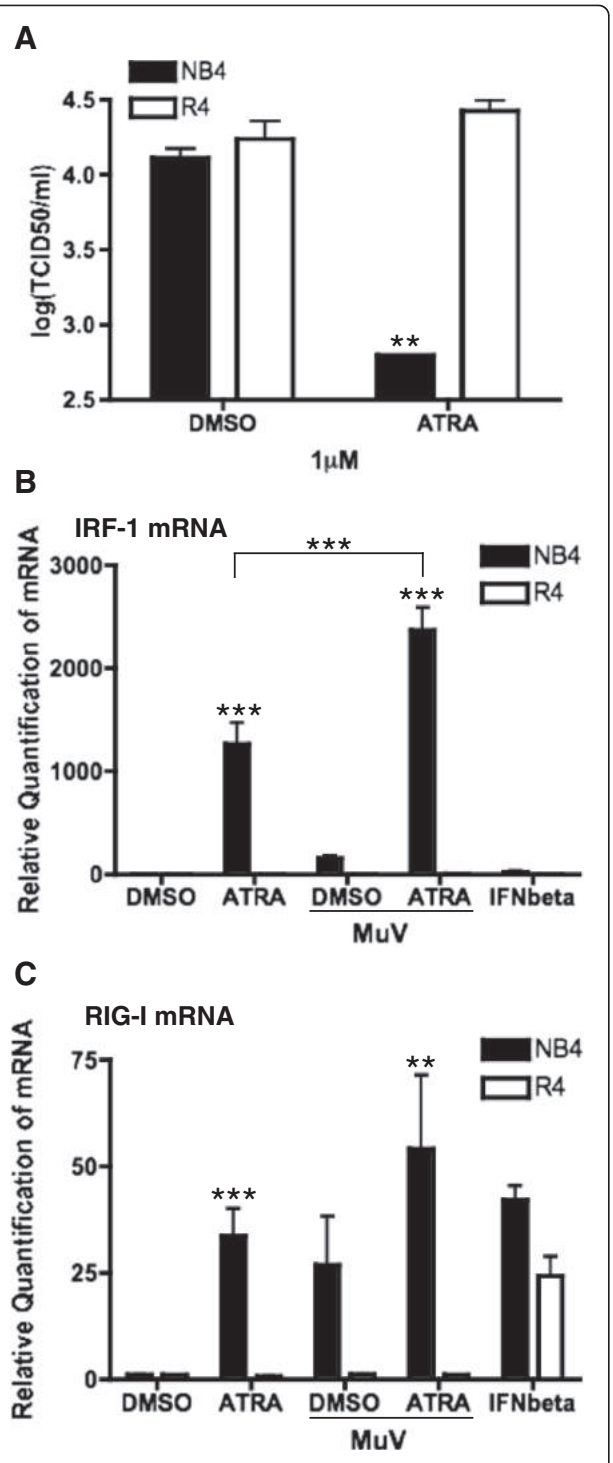

Figure 3 Retinoid signaling is required for the inhibition of MuV *in vitro*. NB4 and R4 cells were infected with MuV at an MOI of 0.01, treated with 1 μM ATRA or DMSO and/or treated with 1000 U/mL IFNβ (PBL Interferon Source, New Jersey) as indicated. **(A)** Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. RNA was extracted and analyzed for IRF-1 **(B)** and RIG-I **(C)** expression by qPCR. Data presented reflect three experiments performed in triplicate (N = 3). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

control and RIG-I specific siRNA were sufficient to induce the expression of RIG-I and other interferon stimulated genes (data not shown, also demonstrated in [59,60]). In MuV infected Huh7 cells treated with ATRA, virus output was significantly reduced (Figure 4A) but ATRA had no effect on MuV replication in the Huh7.5, RIG-I non-functional cells (Figure 4A).

It has recently been demonstrated that RIG-I complementation in Huh7.5 cells can restore the IRF3 pathway, making these cells less permissive to Sendai virus (SeV) infection [58]. This observation suggests that the non-functional RIG-I encoded in the Huh7.5 cells can be complemented by exogenous expression of the protein. When RIG-I was transfected into the Huh7.5 cells, inhibition of MuV replication was restored (Figure 4B). These data demonstrate the requirement of RIG-I in the retinoid-MuV antiviral response.

Antiviral response is created in uninfected bystander cells

To determine whether or not a bystander effect was induced following MuV infection, we repeated key experiments using 0.02 μm-pore membrane transwell tissue culture inserts (depicted in [48] and [47]). In these experiments, the inner-chamber U937 cells could be exposed to the products of infection in the outer-chamber cells without direct contact with either MuV itself or the MuV-infected cells. We confirmed that MuV was not able to cross the membrane by $TCID_{50}$ assay of the inner-chamber cells in each experiment.

ATRA-stimulated ISG expression was just as strong in the inner-chamber (uninfected) as the outer-chamber (infected) cells despite the absence of active infection. Specifically, we found strong up-regulation of mRNA expression for IRF-1 (Figure 5A) and RIG-I (Figure 5B), as well as MDA-5 and IRF-7 (data not shown), in the inner-chamber cells.

When the supernatant (or conditioned media) from the inner-chamber bystander U937 cells was applied to fresh cells, we observed a striking induction in the expression of these same ISGs as shown for RIG-I (Figure 5C).

Bystander cells are protected from infection

To determine whether or not the uninfected inner-chamber, bystander cells would have reduced susceptibility to future infection these cells were harvested and challenged with MuV at an MOI of 0.1 immediately following incubation in the transwell. Compared with control cells not treated with ATRA and exposed to the products of MuV infection, the inner-chamber cells were relatively resistant to MuV replication (one log reduction in MuV titres produced, Figure 6A). This relatively refractory state persisted for up to 6 hours but was lost at 12 hours (Figure 6B).

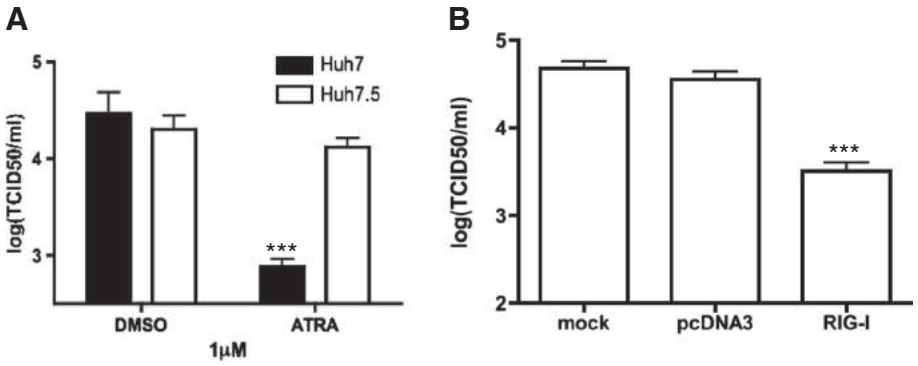

Figure 4 RIG-I is required for the inhibition of MuV by retinoids. (A) Huh7 and Huh7.5 cells were infected with MuV at an MOI of 0.01 and treated with 1 μM ATRA or DMSO. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. **(B)** Huh7.5 cells were transfected with mock, pcDNA3.1 or pRIG-I-myc and incubated overnight. Following transfection, the cells were infected with MuV at an MOI of 0.01 and treated with 1 μM ATRA. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. Western blotting was not performed since Huh7.5 cells produce a defective RIG-I protein that cannot be distinguished from the wild-type protein by commercially-available antibodies. Data presented reflect two experiments performed in triplicate (N = 2). ***$p < 0.001$.

These data suggest that the antiviral state created in the bystander U937 cells is short lived.

When inner-chamber bystander cells treated with ATRA and exposed to the products of MuV infection were challenged with MeV at an MOI 0.1 MeV replication was also reduced by at least 1 log compared to untreated controls or cells treated with only ATRA or exposed to the products of outer-chamber MuV infection (Figure 6C). The antiviral state induced in these cells was not virus-specific.

Discussion

The potential role of individual micronutrients in specific infectious diseases has been the subject of considerable interest for decades (reviewed in [61]). To our knowledge, retinol (Vitamin A) is currently the only micronutrient routinely used to 'treat' a viral disease. In fact, both vitamin A supplementation and therapy appear to have significant clinical benefit in natural MeV infection [16–19,21]. However, the effects of vitamin A on viral infections have been highly variable and at times, completely contradictory.

Although reduced mortality from diarrheal disease is associated with vitamin A supplements in children of the developing world this benefit appears to be due largely to milder bacterial infections [14,62,63]. In Mexican children receiving vitamin A supplements, the incidence of Norovirus diarrhea was reduced but gut viral titres and the period of virus shedding in these children were both significantly increased [64].

In human immunodeficiency virus (HIV) infection, pre-antiretroviral treatment (ART) studies suggested that low serum retinol levels were associated with rapid progression of acquired immunodeficiency syndrome (AIDS) but later studies showed little-to-no impact of supplements on disease progression or survival (reviewed in [65]). Perinatal vitamin A supplements in HIV-positive women can improve the survival of the seronegative children but can increase mother-to-child HIV transmission [65], possibly through increased viral loads in breast milk [66]. *In vitro*, retinoids have been found to both increase and decrease HIV replication in different model systems [67,68].

Patients infected with Hepatitis C virus (HCV) and treated with 9-*cis* retinoic acid or ATRA in combination with pegylated IFNα have lower viral loads [69,70]. In contrast, supplements do not increase viral clearance in human papilloma virus (HPV)-infected women [71].

Both vitamin A supplementation and treatment have either no or negative effects on respiratory tract infections including the common paramyxovirus, respiratory syncytial virus (RSV) [72–74]. Studies with another paramyxovirus have shown that vitamin A deficient chickens suffer increased morbidity from Newcastle disease virus (NDV) [75–77]. Using the paramyxovirus most closely related to measles, our group has demonstrated that canine distemper virus (CDV)-infected ferrets treated with vitamin A develop less severe disease [78]. In aggregate, these observations suggest that vitamin A and its derivatives may play an important role in antiviral responses but demonstrate clearly that mechanistic studies are essential to fully understand and exploit this potential.

Previously we have shown that retinoids can inhibit MeV replication *in vitro* via retinoid nuclear receptor activating type I IFN signalling [46,48]. We hypothesized that ATRA treatment during MuV infection may also inhibit MuV replication *in vitro*. We further sought to determine if the retinoid-MuV antiviral response would require type IFN signalling, RAR signalling and functional RIG-I. The current work demonstrates that ATRA similarly exerts anti-viral effects on MuV. We believe that

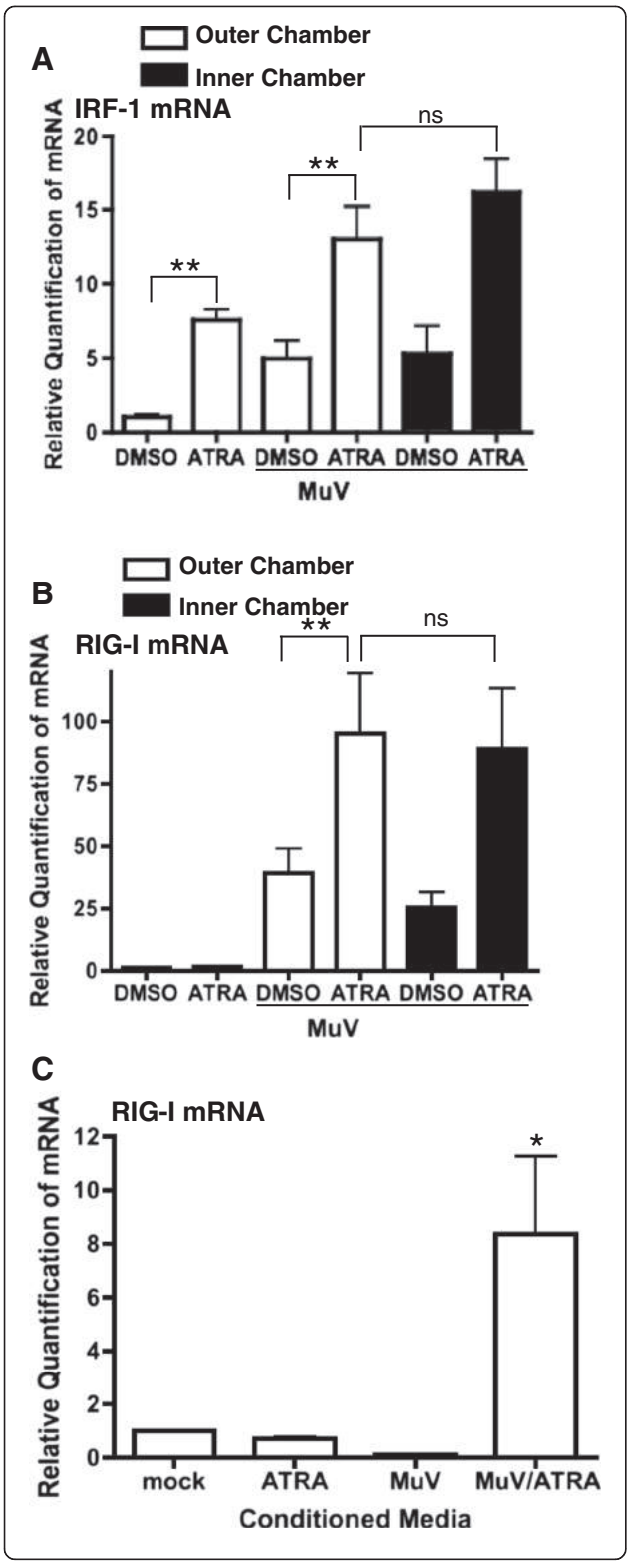

Figure 5 Retinoids induce an anti-MuV state in the uninfected, bystander cells. U937 cells were infected with MuV at an MOI of 0.01 in the presence of 1 μM ATRA or DMSO. Transwell membrane inserts with 0.02 μm pores were used to separate the infected cells in the outer chamber from the uninfected, bystander cells in the inner chamber [48]. Cells from control wells (no membrane insert), outer and inner chamber bystander cells were harvested after 48 hours and IRF-1 **(A)** and RIG-I **(B)** mRNA were measured by qPCR. As indicated on the Figure, outer chamber cells infected by MuV are represented by open bars and inner chamber (uninfected) cells are represented by the filled bars. **(C)** Conditioned media from the control and transwell inner chambers were applied to fresh U937 cells. After 24 hours of incubation with the conditioned media, RNA was extracted and RIG-I expression was analyzed. Data presented reflect three experiments performed in triplicate (N = 3). * $p < .02$,** $p < 0.01$.

these effects are not virus-specific, but rather extend to multiple members of the Paramyxovirus family or more broadly, to viruses that are detected by RIG-I. Figure 7 depicts our current understanding of retinoid action on Paramyxovirus infection. In Figure 7A, ATRA alone has no protective capacity on initially infected cells. These cells will produce the same amount of virus as untreated cells and ultimately, will die as a result of infection. However, the initially uninfected cells in the culture are primed for ISG expression by ATRA treatment through activation of the nuclear retinoid receptors. In Figure 7B, retinoid-primed cells effectively up-regulate ISG expression and type I IFN production upon viral infection. The combination of type I IFN and ATRA induces RIG-I expression in uninfected bystander cells, further improving the innate anti-viral response. ATRA is essential for initiating positive feedback through RIG-I activation and type I IFN pathways, which protects uninfected cells.

In the current work, we used a variety of *in vitro* models to extend our central observation of retinoid-induced anti-viral effects to MuV (Figures 1A, 1C, 3A, 4A). Although the cell lines used in this work varied in their overall sensitivity to retinoids (NB4 > U937 > Huh7>> R4), all supported the growth of MuV. Retinoid-induced suppression of MuV replication could be demonstrated in all but the R4 cells. Retinol (ROH) is the form of vitamin A found in the circulation at concentrations up to 2 μM [79]. The degree of inhibition of MuV replication was much greater using ATRA, a natural derivative of ROH and ligand that binds directly to nuclear receptors. ATRA is generally found in the intracellular space, but can be found in the serum in the 5–10 nM range [79]. As a result, we believe the mechanisms that we have documented *in vitro* to be potentially active *in vivo*. Indeed, the outcome of any infection is essentially a 'race' between pathogen replication and the developing immune response. In this context, it is plausible that the modest reduction in the rate of MuV replication that we observed with retinoid 'treatment'

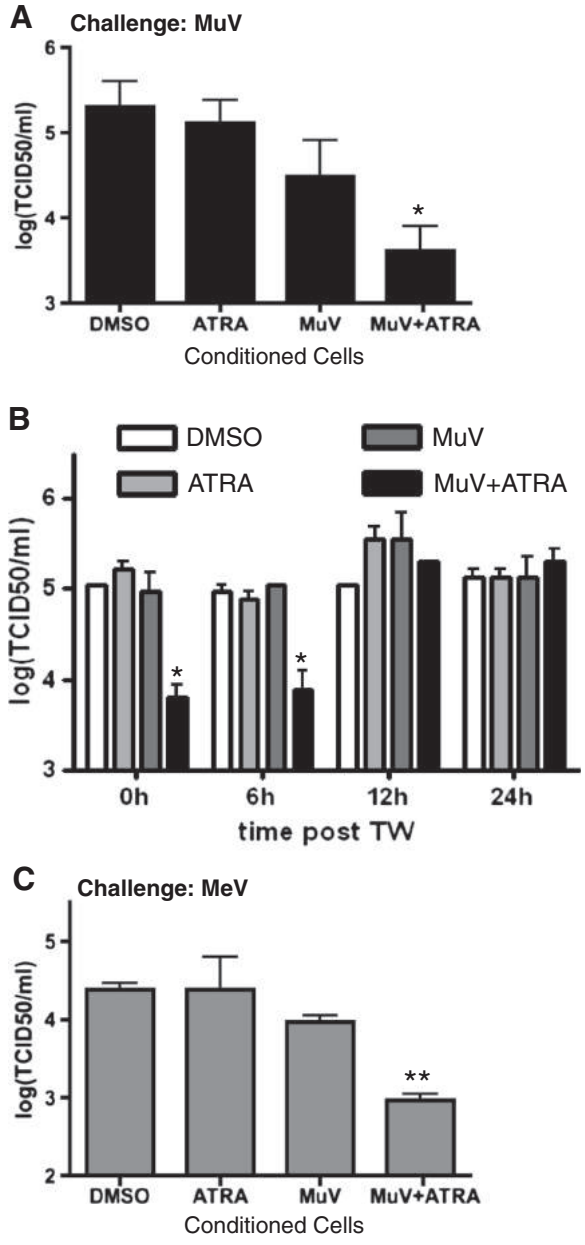

Figure 6 Antiviral state is short-lived and virus non-specific. (A) The inner chamber bystander cells were harvested and challenged with MuV at an MOI of 0.1. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. **(B)** To assess the duration of the anti-viral state, U937 cells were suspended in TW inner-chamber conditioned media and incubated for the indicated time at 37°C then challenged with MuV at an MOI of 0.1. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. **(C)** The inner chamber bystander cells were harvested and challenged with MuV at an MOI of 0.1. Whole cell lysates were harvested after 48 hours and viral titers were measured by $TCID_{50}$. Data presented are representative of two-three experiments performed in triplicate (N = 2-3). *$p < 0.05$, **$p < 0.01$.

in vitro could translate into clinical benefit during natural disease, as occurs with vitamin A treatment in natural MeV infection. To our knowledge, there has not yet been any attempt to use retinol (or other retinoids) to modulate the course of mumps infection. Unfortunately, there is no animal model for mumps in which this possibility can be directly tested.

The antiviral state created by the combination of MuV infection and ATRA treatment was ultimately generated by the expression of type I interferon. We have demonstrated that the combination of MuV + ATRA leads to transcription of IFN genes and at least additive increases in IFNα1 and IFNβ levels in culture supernatants, as well as enhanced transcription of ISGs (Figure 2A-F). Increasing doses of ATRA in the context of MuV infection led to marked increases in STAT1 activation (Figure 2G) and, when type I IFN signalling was blocked, the antiviral state is lost (Figure 2H). MuV normally escapes type I IFN control by targeting STAT1 for proteasomal degradation. Variations in the V protein sequence can decrease the efficiency of proteosomal targeting of STAT1, [80] resulting in differing sensitivity to type I IFNs and potentially the IFN dependent antiviral state produced by retinoid treatment. We are currently collecting wild-type MuV isolates to correlate retinoid sensitivity with V protein sequence to better understand this apparent paradox. At the current time, we also cannot fully explain differences in ATRA-induced up-regulation of RIG-I expression between the U937 and NB4 cells other that to postulate greater retinoid sensitivity in the RIG-I promoter of the former line. It is also possible that the timing of sample collection contributed to these results. Similarly, the timing of sampling may underlie the up-regulation of RIG-I mRNA in NB4 cells in response to IFNβ stimulation despite the apparent absence of IRF-1 induction (Figure 3B/C). Time course studies are currently underway to address these issues.

We further demonstrate that nuclear retinoid receptor signalling was also central to the antiviral effect of retinoids against MuV. Although it is possible that more than one nuclear receptor may be involved, our current data suggest that RARα plays an important role in mediating the antiviral effects against MuV. In our NB4/R4 model, RAR signalling was not only required for the antiviral effect (Figure 3A), it was essential for the expression of ISGs that contribute to the antiviral response (Figure 3B-C).

Finally, we demonstrate a similar retinoid signalling mechanism in response to MuV + ATRA (Figures 2E, 3C, Figure 4A). Most convincing, we have shown that overexpression of RIG-I in Huh7.5 cells with non-functional RIG-I signalling, can reinstate the retinoid-induced inhibition of MuV. The results in the Huh7.0/7.5 model are particularly interesting because MuV output does not differ greatly at 48 hours, suggesting that intact RIG-I

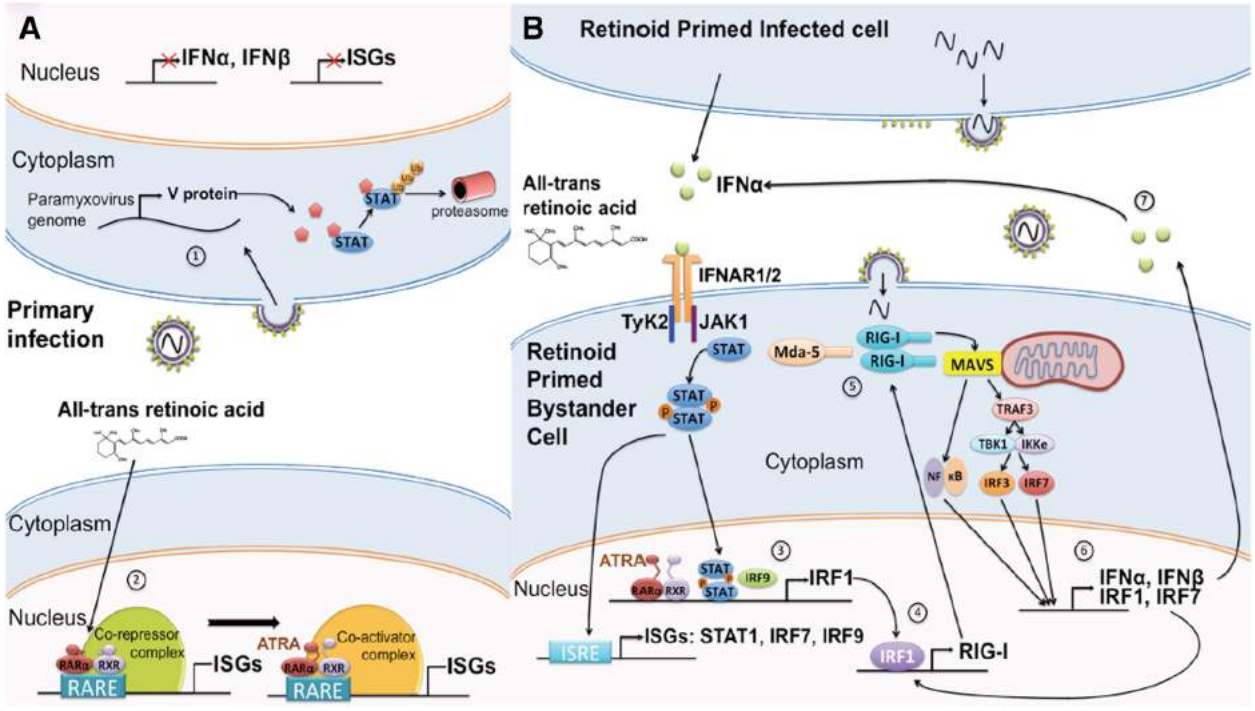

Figure 7 Retinoid action during paramyxovirus infection. (A) 1) Jak/STAT signaling is inhibited as a result of viral infection and ATRA treatment is unable to effectively promote unregulation of ISGs and type I IFN production. 2) Cells exposed to the products of the primary infection and primed with ATRA can more efficiently secrete type I IFN upon infection. **(B)** 3) Exposure to ATRA and type I IFN in the supernatant signals through the Jak/STAT pathway with the combination of nuclear localization of STAT1/2 heterodimer and activation of the RAR/RXR complex results in the transcription of multiple ISGs, importantly IRF1. For simplicity, only IFNα and its receptor IFNAR1/2 are shown to promote Jak/STAT signaling. 4) RIG-I expression is greatly up-regulated under these conditions, by IRF1 binding to the interferon response element (IRE) on its promoter. 5) Increased cytoplasmic quantities of RIG-I provide protection in the bystander cell upon virus infection. RIG-I detects viral RNA and associates with the adaptor protein MAVS, which initiates downstream activation of NFκB and IRF3/7. Nuclear translocation to their respective promoter elements induces transcription of antiviral genes, i.e., type I IFN and IRF1/7 production. It is not clear what role the second cytoplasmic RNA helicase (mda5) plays in this cascade although mda5 has been implicated in responses to several Paramyxoviridae. 6) These proteins feedback onto their respective pathways and promote RIG-I expression, further improving the antiviral state of the cell. 7) Increased production of type I IFN from the retinoid-primed bystander cell provides both an autocrine and paracrine signal to further protect the uninfected cells in culture.

signalling (by itself) does not play a major role in limiting viral replication. However. transfection of a functional RIG-I clearly restores retinoid responsiveness in this model. At least some of this paradox may be explained by the 48-hour time-point used for most experiments. Indeed, MuV output was lower in the Huh7.0 than Huh7.5 cells for the first 24–36 hours (data not shown). The 48 hour time-point was chosen for our experiments because retinoid effects were most obvious at this time. These findings are very similar to our observations with measles virus in the Huh 7.0/7.5 model where transfection of a dominant negative RIG-I eliminates the anti-viral activity of retinoids in the Huh 7.0 cells and transfection of a functional RIG-I gene into Huh 7.5 cells restores activity [47].

The Huh7.0/7.5 data are also intriguing because they suggest a larger role for RIG-I in defending against MuV than would have been predicted from the literature to date. It is widely thought that the double-stranded RNA sensor mda-5 is the primary target of the MuV V protein [81,82] and that RIG-I may respond primarily to Paramyxovirus defective interfering particles [83]. For several Paramyxoviruses, mda-5 signalling is inhibited by direct binding of the V protein and conserved residues in the helicase [82]. More recent data raises the possibility that Paramyxovirus V proteins may also target RIG-I indirectly by binding to laboratory of genetics and physiology 2 (LGP2) [84] Mutations in the carboxy-terminal domain of the V protein can result in a reduction or total loss of this interference [81]. In both NB4 and U937 cells, mda-5 expression is also increased by ATRA alone (data not shown). We are currently collecting wild-type (WT) MuV isolates to assess their susceptibility to retinoid-induced suppression and to correlate this suppression with V protein mutations. Our preliminary data (4 low-passage isolates to date) suggest that sensitivity to retinoid-induced suppression varies widely in WT MuV (50% suppressible) It is also interesting that retinoid sensitivity has been maintained in the two initially sensitive

WT isolates despite repeated *in vitro* passage in Vero cells in our laboratory.

The antiviral state created by MuV + ATRA was most profound in the initially uninfected bystander cells (Figure 5A-B) and could be transferred to fresh cells via the conditioned media leading to up-regulation of ISG expression (Figure 5C). Not surprisingly, since type I IFN responses are innate and non-specific, cells exposed to conditioned media from MuV + ATRA cells were relatively resistant to subsequent challenge with either MuV or MeV for less than 12 hours (Figure 6A-C). This last observation is consistent with the immediate and short-lived antiviral effects of type I IFNs [85].

The *Paramyxoviridae* including MeV, MuV, RSV, CDV, phocine distemper virus, Nipah virus and Hendra virus are among the most important human and animal pathogens. Commercial vaccines are not yet available for many of these viruses, and antiviral drugs are typically of little use [86]. Some of these viruses can have extraordinarily high mortality rates (for example, CDV in naïve seals and dogs, Nipah and Hendra viruses in man) [87]. The clinical evidence of benefit from retinoid therapy of MeV infection in children and CDV infection in ferrets is strong [17–19,78]. Our *in vitro* data suggest that ATRA may be far more potent that retinol in mediating antiviral effects. Our mechanistic studies in different tissue culture models of MuV infection suggest that common signalling pathways mediate these effects [46–48]. However, high doses of vitamin A in children with RSV infection have no benefit and may even cause harm [74,88]. In aggregate, these clinical and laboratory observations support further studies of the efficacy and mechanism of action of retinoids against a wider range of respiratory viruses in more sophisticated animal models, such as primates, or even clinical studies. It would be of particular interest to use retinoids other than retinol, ATRA in particular, in these latter studies to achieve more effective inhibition of viral replication. This conclusion is further supported by a recent study demonstrating that several synthetic retinoid analogues have much greater capacity to interfere with human herpes virus 8 (HHV8) replication *in vitro* than retinol [89].

Conclusions

In conclusion, this work has demonstrated that MuV can be inhibited *in vitro* by retinoids. This antiviral effect required RAR signalling, type I IFN signalling and functional RIG-I. The antiviral response was created in the initially uninfected bystander cells and was both short-lived and cross-protective against subsequent MuV or MeV challenge. This is the first work to demonstrate the antiviral effect of vitamin A on MuV and may contribute to better treatment options for MuV. We propose that IRF-1 is recruited to the RIG-I promoter under the influence of ATRA alone, and is required for the induction of RIG-I (47). In these models systems therefore, ATRA inhibits MuV replication through the RARα-dependent regulation of RIG-I and IRF-1 and via an IFN feedback loop.

Methods

Cells, reagents and viruses

All cell cultures were maintained at 37°C in a 5% CO_2 humidified incubator. U937 (ATCC, #CRL-1593.2), NB4 (M. Lanotte, INSERM UMR-S 1007, Paris, France) and R4, Huh7 and Huh7.5 (courtesy C. Richardson, Dalhousie University, Halifax, NS), Vero cells (ATCC, #CCL-81) were maintained as described in [47]. Retinol and All-trans retinoic acid (ATRA) (Sigma-Aldrich Fine Chemicals, Oakville, ON) stock solutions of 10^{-2} M were prepared in 100% DMSO and further dilutions were performed using RPMI. DMSO at equivalent final dilutions was used in all experiments as a control. All retinoids were stored in opaque eppendorf tubes at −80°C. The Jones MuV strain (ATCC, #VR-365) is a tissue culture-adapted virus that was, according to the supplier's web-site, extensively passaged in chicken embryos and Vero cells prior to purchase. Our MuV stock was initially plaque purified and then grown by infecting Vero cells with a maximum passage of three times from the original purchase (ATCC, #CCL-81) at a multiplicity of infection (MOI) of 0.001 at 33°C in a Cell-Stack 10 (Corning, Corning, NY). Harvested virus was concentrated by centrifugation at 15,752 x g for seven hours at 4°C in a fix-angle rotor, the pellet was resuspended in RPMI with gentle pipetting. The Chicago-1 MeV strain is a tissue culture-adapted genotype D3 virus (courtesy of W. Bellini, CDC, Atlanta, GA). MeV stock was grown as described in [47].

Cell culture infections

Cell lines were infected with MuV at the indicated MOIs. Media was removed and virus diluted in Hanks' Balanced Salt Solution with calcium and magnesium (Wisent, St-Bruno, QC). The virus was incubated with the cells for 1.5 hours, with gentle rocking at 15-minute intervals. The virus was removed and cells were resuspended in RPMI 1640 supplemented as previously described [46–48] using the specific MOIs and time points indicated in the figure legends and incubated at 37°C/5% CO_2.

Quantitative RT-PCR

RNA was extracted using Trizol (Invitrogen by Life Technologies, Burlington, ON) as per the manufacturer's instructions, and treated to remove possible genomic DNA contamination with Turbo DNAse (Ambion, Austin, TX). For experiments in which antibodies were used to block type I IFN signalling, an RNeasy Mini kit was used to extract RNA (Qiagen, Mississauga, ON). Equal quantities of RNA

were reverse-transcribed into cDNA for qPCR analysis using random primers. FAM-labelled TaqMan primer-probe assays for the following genes were obtained from ABI (Applied Biosystems by Life Technologies, Carlsbad CA): RIG-I, RARβ and IRF-1. The level of gene expression in untreated cells was used for calibration. Vic-labeled hGAPDH was used as the endogenous control.

Transwell

Transwell experiments (TW) were performed as previously described [47,48]. Briefly, TW membranes inserts with 0.02 μM pores served to separate infected cells in the outer chamber from the uninfected bystander cells of the inner chamber. Wells with no transwell inserts were used for control cultures. Preliminary experiments demonstrated that the presence/absence of the TW membrane had no impact on measured outcomes under control conditions.

Conditioned media

Supernatants were collected from TWs and used to treat fresh U937 cells. After 24 hours of incubation with the TW conditioned media, RNA was extracted and RT PCR performed. These samples were analyzed by qPCR for the expression of RIG-I.

Blocking antibody

Supernatants were collected from TWs and used to treat fresh U937 cells. These fresh cells were treated with anti-IFNAR2 blocking antibody (20 μg/μL, PBL Biomedical Laboratories, Piscataway, NJ) or isotype control antibody for one hour before infection and for the subsequent 24-hour incubation with the conditioned media. These samples were analyzed by qPCR for the expression of RIG-I.

Western blotting

Cells were infected with MuV and/or treated with ATRA at the indicated doses. 48 hours post infection, protein was harvested as previously described in [47]. The membranes were incubated in 5% non-fat milk or 5% BSA for 1 hour and incubated overnight at 4°C with primary antibody. Primary antibodies used were against phospho-STAT1 (Y701) (1/1000, BD Bioscience), Total STAT1 (1/1000, BD Bioscience) and β-actin (1/10000, Sigma). Following overnight incubation, membranes were washed three times for 10 minutes in TBS/0.1% Tween, incubated with secondary antibody (1/10000, GE Healthcare) at room temperature for 30 minutes, and washed three times for 10 minutes. The peroxidase-conjugated secondary antibodies were developed using a chemiluminescence kit according to the manufacturer's instructions (GE Healthcare).

Transfection

Huh 7.5 cells were seeded at 1.5×10^5 cell/mL, then were transfected with 3 μg of the RIG-I construct in a pcDNA3 plasmid (gift from J. Hiscott) or empty vector using a 3:1 ratio of FuGENE 6 (Roche, Toronto, ON) as per the manufacturer's instructions. At 18 hours post-transfection, cells were infected with MuV MOI 0.01 and at 48 hours post infection the cells and supernatants were quantified using plaque assay as previously described [46].

Viral challenge of bystander cells

Bystander cells from the TW inner chambers were pooled according to treatment and resuspended in Hanks' Balanced Salt Solution with calcium and magnesium (Wisent, St-Bruno, QC). Cells are infected with MuV or MeV at MOI 0.1 as described above and previously [46–48]. These cells were resuspended in RPMI 1640 (Wisent, St-Bruno, QC) supplemented with 10% heat-inactivated FBS (Wisent, St-Bruno, QC) and 0.1% gentamicin and incubated for the indicated time at 37°C/5% CO_2.

Tissue culture infectious dose$_{50}$ ($TCID_{50}$)

MuV concentrations were quantified by $TCID_{50}$. Briefly, Whole cells and supernatant were frozen at −80°C to lyse cells, samples were defrosted on ice, then serially diluted in Minimum Essential Medium Eagle (Wisent, St-Bruno, QC) supplemented with 3% heat-inactivated FBS (Wisent, St-Bruno, QC) and 0.1% gentamicin. Supernatants were not analysed separately in this series of experiments. Diluted virus was applied to Vero cells in 3% heat-inactivated FBS (Wisent, St-Bruno, QC) and 0.1% gentamicin in 96-well plates. The virus is incubated with the cells for 5 days at 37°C/5% CO_2. Syncytium formation was scored and $TCID_{50}$ was calculated using the Karber method [90,91].

Elisa

U937 cells were infected at an MOI of 0.01 with the indicated virus. At 48 hours post-infection, supernatant IFNα1 and IFNβ were measured by ELISA (PBL Interferon Source, Piscataway, NJ) as per the manufacturer's instructions.

Competing interests

The authors have no competing interest to declare.

Authors' contributions

KJS designed, completed, and analysed experiments, drafted and reviewed the manuscript; CT and LR designed and completed experiments; TZD and KHR drafted the model figure and revised the manuscript; WHM and BJW designed experiments and critically reviewed the manuscript. All authors read and approved the final manuscript.

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ASCORBIC ACID (VITAMIN C) TREATMENT OF WHOOPING COUGH*

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WHOOPING cough is an almost universal infectious disease, with its greatest infectivity in pre-school and school children. While some protection has been afforded against it by vaccination. treatment of the active disease has not progressed as has treatment of other infectious diseases such as scarlet fever and diphtheria. Madsen[1] reports that, of 1,842 vaccinated children, about 25 per cent escaped infection, while of 446 non-vaccinated children less than 2 per cent escaped. This decided improvement warrants the use of vaccines, but still leaves the infected child confronted with some weeks of unpleasantness and a not inconsiderable mortality rate. According to Tice,[2] in the registration area of the United States there were 7,518 deaths in 1934. In the years 1932-34 there were 45,755 cases of whooping cough reported to the Dominion Bureau of Vital Statistics, with 1,982 deaths. Of the fatal cases over 50 per cent occur in the first year of life. The non-fatal cases undergo a most disagreeable experience and lose considerable time from studies, in the case of the school-child. The disease is characterized by spasmodic coughing and vomiting, and this spasmodic or paroxysmal stage persists for weeks. How this paroxysmal stage originates, and why it should be so prolonged, has always intrigued investigators, and various hypotheses have been put forward. Among them is one suggested by Brown,[3] that a neurotropic toxin elaborated by the bacillus in the early catarrhal stage affects the vagus and respiratory centres and possibly the sensory nerve-endings in the upper respiratory mucosa. Fixation of this toxin in nervous tissue would explain the comparative failure of vaccines or convalescent serum to influence the course of the disease unless given in the incubation period or early in the catarrhal stage. Both exo- and endotoxins have been obtained from the Bordet-Gengou bacillus.

Ascorbic acid has been investigated by several workers from the standpoint of its detoxicating action. Grootton and Bezsonoff[4] record the results of mixing diphtheria toxin and ascorbic acid, incubating very briefly, and injecting the mixture into guinea-pigs. Unneutralized ascorbic acid completely destroyed the toxic action, but this effect was one of pH and not a specific effect. Ascorbic acid neutralized with soda and mixed with the toxin so altered its potency that, of four guinea-pigs receiving 4 M.L.D. of toxin each, one survived and the others died respectively on the 4th, 6th, and 9th day. Controls injected with 4 M.L.D. each of unaltered toxin all died on the 2nd day. These workers, in the same paper, tested the actual bactericidal action of ascorbic acid against various bacteria by adding varying amounts of the acid to the culture medium, bringing the mixture to a pH of 7.0, and inoculating with such organisms as staphylococcus, streptococcus, gonococcus, typhosus, Bordet-Gengou, etc. With 0.5 per cent ascorbic acid mixtures only the gonococcus and Bordet-Gengou bacillus were inhibited, as compared with controls. The gonococcus grew readily in a 0.2 per cent mixture. In a percentage of 0.008, ascorbic acid inhibited the growth of the Bordet-Gengou bacillus. Glacial acetic acid added to the culture medium in corresponding amounts, and then neutralized, failed to affect the growth of this bacillus.

Woringer and Sala[5] reported 4 cases of whooping cough complicated by scurvy occurring among a series of infants treated in their clinic. No scurvy appeared among the other children, although all were on exactly the same dietary regimen. They suggest that vitamin C is an essential part of the body's defence against the Bordet-Gengou bacillus, and that excessive demands made in the presence of such an infection may so deplete the vitamin stores of the tissues as to lead to the clinical condition of scurvy.

Gander and Niederberger[6] and Hochwald[7] report the use of ascorbic acid in the treatment of pneumonias. Pneumonia cases showed con-

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sistently a deficit in vitamin C. Administration of the vitamin produced an effect comparable with that of specific serum. The pulse and temperature subsided by crisis when the avitaminosis was completely relieved, as shown by beginning urinary excretion of the ascorbic acid. When small doses of ascorbic acid were given, the saturation point for the vitamin was reached slowly, and no clinical improvement was shown until this point was reached.

Various investigators[8, 9, 10] have shown that the tissues of normal children and young animals contain more vitamin C than those of normal older subjects, and that the saturation point, as judged by beginning urinary excretion, is attained in young subjects only by much larger doses than relative weights would indicate. This suggests a greater need of vitamin C by young animals, and so a greater storage of it in the presence of an ample supply.

From this evidence, ascorbic acid seemed to have possibilities in the treatment of whooping cough, and one of us (B.M.U.) has been using it in practice for the last two months or so. To date, we can report 9 cases, and 1 from another practitioner.* In each case, diagnosis was made from a history of contact with known cases together with personal observation of the typical cough, vomiting and nocturnal paroxysms. Cough plates or serological tests were not used in this preliminary investigation. Condensed case reports follow.

DISCUSSION

The short series of cases presented is too small to draw any statistical conclusions, but one fact stands out. Ascorbic acid has a definite effect in shortening the period of paroxysms from a matter of weeks to a matter of days. We have not checked by cough plates or otherwise in this preliminary work to see whether the infectivity subsides simultaneously with the spasmodic symptoms, but are continuing with a larger series of cases in which these and other tests will be employed.

* Case 4. We are indebted to Dr. C. H. A. Walton for details of this case.

TABLE

Case	*Age (years)*	*Sex*	*Contact*	*Duration of Symptoms*	*Treatment*	*Results*
1 R.T.	6	M	School	6 weeks—typical	150 mg. per day	7 days—cough reduced markedly 10 days—cough disappeared
2 C.H.	1½	M	Unknown Temperature 102 F. Bronchopneumonia when seen	3 weeks—typical 10 days "fever" at home	inhalations, sinapisms, expectorants } 3 days 175 mg. daily—11 dys.	No effect 7 days—temperature normal, cough reduced 14 days—cough disappeared
3 M.C.	12	M	School	10 days—typical	200 mg. daily	6 days—cough reduced 13 days—only occasional night coughs 15 days—all cough absent
4 J.P.	6	F	School	over 4 weeks—typical	200 mg. daily	3 days—cough less, no vomiting 7 days—occasional cough
5 B.O.	2½	M	Known case	2 weeks—typical	250 mg. daily	5 days—cough disappeared
6 H.F.	7	M	School	2 weeks—typical	375 mg. daily	4 days—cough less 9 days—night cough only 11 days—all cough absent
7 E.H.	22		Maid Child in house had whooping cough	4 dys., paroxysmal cough, vomited once, no whooping	500 mg. daily—3 days 125 mg. daily	4 days—cough less, no vomiting 6 days—coughed only once in 2 days 11 days—cough absent
8 B.P.	4	M	Known case	10 days—typical	500 mg. daily—4 days 250 mg. daily—4 days	5 days—cough disappeared
9 M.W.	6½	F	School	2 weeks—typical	500 mg. daily—4 days 250 mg. daily—5 days	4 days—cough reduced 7 days—coughed once in 24 hours 9 days—cough disappeared
10 W. C.	4½	F	Sister (Case 9)	1 week—typical	500 mg. daily—4 days 250 mg. daily—5 days	Same as for Case 9

The dosages used have been empirical, with a tendency to use larger doses early in the disease as our experience of its effects progressed. The acid is available at reasonable prices, and the danger of overdosage seems negligible. Animals have received 2,000 times their estimated requirements without any deleterious effects. Any excess is excreted by the kidneys.

CONCLUSIONS

1. A method has been described for the treatment of whooping cough by ascorbic acid (vitamin C).

2. Ascorbic acid definitely shortens the paroxysmal stage of the disease, particularly if relatively large doses are used early in the disease.

The ascorbic acid used by us was the Hoffmann-LaRoche product sold under the trade name of "Redoxon". Grootton and Bezsonoff[4] have shown that this product is identical chemically, physically and biologically with the original product prepared by Szent-Gyorgi.

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CHANGES IN CONDITIONED RESPONSES BROUGHT ABOUT BY ANÆSTHETICS AND SEDATIVES*

BY SIMON DWORKIN, WESLEY BOURNE AND BERNARD B. RAGINSKY

Montreal

PAVLOV[7] (1927) and his co-workers first observed that conditioned salivary reflexes could be modified by drugs like alcohol, caffeine, chloral hydrate and bromide. Recently Wolff and Gantt[8] (1935) studied the effects of amytal upon conditioned salivary secretion. The object of the present research was to extend the work to conditioned alimentary-motor responses of dogs and cats. From this viewpoint we have re-investigated the influence of alcohol and of amytal, and tested several new drugs, namely nembutal, avertin, paraldehyde, bulbocapnine, carbon dioxide, ethylene, nitrous oxide, morphia, and hyoscine.

Two dogs and two cats served as subjects. The dogs received sodium amytal and nembutal intravenously, avertin per rectum, alcohol and paraldehyde by stomach tube, and morphia, hyoscine and bulbocapnine subcutaneously. The gaseous anæsthetics were administered to the cats under a bell jar. We naturally waited for full recovery from one drug before we administered a new drug or even a different dose of the same drug.

The general procedure for establishing conditioned reflexes is by now well known. The measured and recorded response may be salivary secretion or any other easily observed reaction (*cf.* Liddell, 1934).

In our work a lid-lifting response was used. This particular training procedure was described by Dworkin[2] (1935). The stimuli selected comprised auditory, visual and tactile signals. The successive tests were made at intervals of 2 to 6 minutes. During these intervals the animals had been trained not to touch the lid of the food container. Consistent absence of response between stimuli, eventually developed by training, may be called "interval inhibition" (Fig. 1A). The animals were also trained to make two discriminations, (1) between two different buzzers—"coarse" discrimination, (2) between a loud and a quiet musical tone of fixed frequency —"fine" discrimination. The time of incidence of the signals, as well as that of the animals' response, was recorded graphically. Thus we had information as to the latent period, presence or absence of conditioned response, duration of conditioned and unconditioned phases, and finally the amount of interval inhibition.

The latent period of the positive responses varied between 1 and 3 seconds. Often it was just as short for a visual as for a tactile or auditory stimulus. Nevertheless, a loud sound usually evoked a response sooner than a quiet sound; similarly, the latent period for a strong light was often shorter than for a weak light. When a negative stimulus was turned on for differentiation there was at times a slight turning of the head away from the food container, and other signs of general irritation, but no attempt to raise the lid (see Fig. 1B).

RESULTS

Our observations indicate that the eleven drugs tested may be classed into three main

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SHORT REPORTS

Rotavirus neutralisation by human milk

There has been considerable publicity recently about the benefits of breast-feeding in giving protection from infection. We have investigated the effect of mother's serum and breast milk, taken daily for five days after birth, on rotavirus infection of cells in vitro.

Materials, methods, and results

Milk and blood samples were taken by staff at Birmingham Maternity Hospital and at Marston Green Maternity Hospital, Birmingham. Milks were clarified by centrifugation, and milks and sera were heated at 56 C for 30 minutes to inactivate complement.

Human rotavirus was obtained from the faeces of children with acute diarrhoea admitted to East Birmingham Hospital. The neutralisation test was carried out as previously described.[1 2] Human rotavirus infects but fails to replicate in LLC MK_2 cells and the infected cells can be detected by an indirect immunofluorescent technique. The neutralisation titre of a milk or serum was the dilution that gave a 50% or greater reduction of fluorescent foci compared with the control. The specific rotavirus fluorescent antibody titres of sera and milks were determined by their reaction with rabbit rotavirus infected LLC MK_2 cells[2] in an indirect immunofluorescent test.

The rotavirus neutralising titres of the randomly picked mothers' sera varied from 1/10 to 1/640 (see table). Most of the first milk samples had a neutralising titre close to that of the mother's serum, but this fell rapidly in the puerperium so that, by the fifth day, only the two mothers with the highest serum neutralising titres had milk titres of 1/5 or greater.

All the sera and milks were tested by indirect immunofluorescence for specific reaction with rotavirus infected cells. Specific fluorescence was given by all the sera and the early milks, but the titres were always less than the rotavirus neutralising titres (see table). Four- and five-day milk samples gave no reaction, but it was not possible to test them undiluted because of non-specific fluorescence.

The milk samples that did not neutralise human rotavirus at 1/5 dilution were tested undiluted; the virus was completely inactivated. The same result was obtained with these milks and lamb rotavirus. A high-speed aqueous supernatant of undiluted pasteurised cows' milk and an antibody-free glycoprotein prepared from cows' milk inactivated human rotavirus completely.

Comment

We have shown by neutralisation and immunofluorescent tests that human milk in the early puerperium contains rotavirus antibodies that decline to undetectable levels by five days after birth.

Fifth-day undiluted milks inactivated human rotavirus, but it was not possible to tell whether this was due to specific antibody. As they also inactivated lamb rotavirus, however, and human rotavirus was inactivated by cows' milk and its phenol-extracted glycoprotein, we suggest it may be due to a non-specific antiviral milk factor.[3 4]

Rotavirus infection in the first few days of life is frequent and largely asymptomatic, even in breast-fed babies,[5] at the time when there is a large amount of specific rotavirus antibody in the milk. The fact that undiluted human or cows' milk also inactivates human rotavirus, however, may be an important consideration in the current baby feeding discussions.

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Response of metastatic breast cancer to combination chemotherapy according to site

Despite the clear efficacy of combination chemotherapy in producing tumour regression in some patients with metastatic breast cancer, its precise role in the overall management of this condition remains controversial. Our experience with two chemotherapy regimens leads us to believe that the major site of symptomatic disease should be the most important factor determining the choice of systemic therapy. We briefly present the evidence for this view below.

Patients, methods, and results

The two regimens were as follows: (1) vincristine 1·5—2·0 mg and doxorubicin (Adriamycin) 40–100 mg intravenously on days 1 and 8; prednisolone 20 mg by mouth daily on days 1 to 14 of a 28-day cycle (VDP); or (2) methotrexate 30–50 mg, 5-fluorouracil 500–1000 mg intravenously on days 1 and 8 with cyclophosphamide 100 mg and prednis-

Milk and rotavirus antibodies

Case No	Test	Serum	Milk (days after delivery) 1	2	3	4	5	6	7	8
1	NT	640	320	320	80-160	20–40	20			20
	FA	160	320	10	20	5	<5			<5
2	NT	160	5*	80	20	5	5	<5		
	FA	40	<5	20	10	<5	<5	<5		
3	NT	160		>320	80	20				
	FA	40		20	10	5				
4	NT	80	160	80	20	5				
	FA	<10	<10	<10	<5	<5				
5*	NT	80		40	5	<5	<5			
	FA	10		<5	<5	<5				
6	NT	40	10	5	5	5	<5			<5
	FA	5	<5	<5	<5	<5	<5			<5
7	NT	40		20	5	5	5			
	FA	20		5	<5	<5	<5			
8	NT	20	40	40	10	5				
	FA	10	40	20	10	5				
9	NT	10	5	5	5	<5	<5			
	FA	20	<5	<5	<5	<5	<5			
10	NT	10		10	5	5	<5	<5		
	FA	10		5	<5	<5	<5	<5		

NT = Neutralisation test. The number is the reciprocal of the serum dilution causing 50% reduction in the fluorescent foci compared with the control.
FA = Fluorescent antibody. The number is the reciprocal of the greatest serum dilution showing fluorescence with rotavirus infected cells.
*This sample was very watery.

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Human milk mucin inhibits rotavirus replication and prevents experimental gastroenteritis.

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Author information

Abstract

Acute gastrointestinal infections due to rotaviruses and other enteric pathogens are major causes of morbidity and mortality in infants and young children throughout the world. Breast-feeding can reduce the rate of serious gastroenteritis in infants; however, the degrees of protection offered against rotavirus infection vary in different populations. The mechanisms associated with milk-mediated protection against viral gastroenteritis have not been fully elucidated. We have isolated a macromolecular component of human milk that inhibits the replication of rotaviruses in tissue culture and prevents the development of gastroenteritis in an animal model system. Purification of the component indicates that the antiviral activity is associated with an acidic fraction (pI = 4.0-4.6), which is free of detectable immunoglobulins. Furthermore, high levels of antiviral activity are associated with an affinity-purified complex of human milk mucin. Deglycosylation of the mucin complex results in the loss of antiviral activity. Further purification indicated that rotavirus specifically binds to the milk mucin complex as well as to the 46-kD glycoprotein component of the complex. Binding to the 46-kD component was substantially reduced after chemical hydrolysis of sialic acid. We have documented that human milk mucin can bind to rotavirus and inhibit viral replication in vitro and in vivo. Variations in milk mucin glycoproteins may be associated with different levels of protection against infection with gastrointestinal pathogens.

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Vitamin B6 prevents cognitive impairment in experimental pneumococcal meningitis.

Barichello T[1], Generoso JS[2], Simões LR[2], Ceretta RA[2], Dominguini D[3], Ferrari P[4], Gubert C[4], Jornada LK[3], Budni J[5], Kapczinski F[6], Quevedo J[7].

Author information

Abstract

Streptococcus pneumoniae is the relevant cause of bacterial meningitis, with a high-mortality rate and long-term neurological sequelae, affecting up to 50% of survivors. Pneumococcal compounds are pro-inflammatory mediators that induce an innate immune response and tryptophan degradation through the kynurenine pathway. Vitamin B6 acts as a cofactor at the active sites of enzymes that catalyze a great number of reactions involved in the metabolism of tryptophan, preventing the accumulation of neurotoxic intermediates. In the present study, we evaluated the effects of vitamin B6 on memory and on brain-derived neurotrophic factor (BDNF) expression in the brain of adult Wistar rats subjected to pneumococcal meningitis. The animals received either 10 µL of artificial cerebral spinal fluid (CSF) or an equivalent volume of S. pneumoniae suspension. The animals were divided into four groups: control, control treated with vitamin B6, meningitis, and meningitis treated with vitamin B6. Ten days after induction, the animals were subjected to behavioral tests: open-field task and step-down inhibitory avoidance task. In the open-field task, there was a significant reduction in both crossing and rearing in the control group, control/B6 group, and meningitis/B6 group compared with the training session, demonstrating habituation memory. However, the meningitis group showed no difference in motor and exploratory activity between training and test sessions, demonstrating memory impairment. In the step-down inhibitory avoidance task, there was a difference between training and test sessions in the control group, control/B6 group, and meningitis/B6 group, demonstrating aversive memory. In the meningitis group, there was no difference between training and test sessions, demonstrating impairment of aversive memory. In the hippocampus, BDNF expression decreased in the meningitis group when compared to the control group; however, adjuvant treatment with vitamin B6 increased BDNF expression in the meningitis group. Thus, vitamin B6 attenuated the memory impairment in animals subjected to pneumococcal meningitis.

KEYWORDS: BDNF; Pneumococcal meningitis; memory; vitamin B6

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Vitamin C for preventing and treating pneumonia.

Hemilä H[1], Louhiala P.

Author information

Abstract

BACKGROUND: Pneumonia is one of the most common serious infections, causing two million deaths annually among young children in low-income countries. In high-income countries pneumonia is most significantly a problem of the elderly.

OBJECTIVES: To assess the prophylactic and therapeutic effects of vitamin C on pneumonia.

SEARCH METHODS: We searched CENTRAL 2013, Issue 3, MEDLINE (1950 to March week 4, 2013), EMBASE (1974 to April 2013) and Web of Science (1955 to April 2013).

SELECTION CRITERIA: To assess the therapeutic effects of vitamin C, we selected placebo-controlled trials. To assess prophylactic effects, we selected controlled trials with or without a placebo.

DATA COLLECTION AND ANALYSIS: Two review authors independently read the trial reports and extracted data.

MAIN RESULTS: We identified three prophylactic trials which recorded 37 cases of community-acquired pneumonia in 2335 people. Only one was satisfactorily randomised, double-blind and placebo-controlled. Two trials examined military recruits and the third studied boys from "lower wage-earning classes" attending a boarding school in the UK during World War II. Each of these three trials found a statistically significant (80% or greater) reduction in pneumonia incidence in the vitamin C group. We identified two therapeutic trials involving 197 community-acquired pneumonia patients. Only one was satisfactorily randomised, double-blind and placebo-controlled. That trial studied elderly patients in the UK and found lower mortality and reduced severity in the vitamin C group; however, the benefit was restricted to the most ill patients. The other therapeutic trial studied adults with a wide age range in the former Soviet Union and found a dose-dependent reduction in the duration of pneumonia with two vitamin C doses. We identified one prophylactic trial recording 13 cases of hospital-acquired pneumonia in 37 severely burned patients; one-day administration of vitamin C had no effect on pneumonia incidence. The identified studies are clinically heterogeneous which limits their comparability. The included studies did not find adverse effects of vitamin C.

AUTHORS' CONCLUSIONS: The prophylactic use of vitamin C to prevent pneumonia should be further investigated in populations who have a high incidence of pneumonia, especially if dietary vitamin C intake is low. Similarly, the therapeutic effects of vitamin C should be studied, especially in patients with low plasma vitamin C levels. The current evidence is too weak to advocate prophylactic use of vitamin C to prevent pneumonia in the general population. Nevertheless, therapeutic vitamin C supplementation may be reasonable for pneumonia patients who have low vitamin C plasma levels because its cost and risks are low.

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A RANDOMIZED, CONTROLLED TRIAL OF VITAMIN A IN CHILDREN WITH SEVERE MEASLES

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Abstract *Background.* Measles kills about 2 million children annually, and there is no specific therapy for the disease. It has been suggested that vitamin A may be of benefit in the treatment of measles.

Methods. We conducted a randomized, double-blind trial involving 189 children who were hospitalized at a regional center in South Africa because of measles complicated by pneumonia, diarrhea, or croup. The children (median age, 10 months) were assigned to receive either vitamin A (total dose, 400,000 IU of retinyl palmitate, given orally; n = 92) or placebo (n = 97), beginning within five days of the onset of the rash. At base line, the characteristics of the two groups were similar.

Results. Although clinically apparent vitamin A deficiency is rare in this population, the children's serum retinol levels were markedly depressed (mean [±SEM], 0.405±0.021 μmol per liter [11.6±0.6 μg per deciliter]), and 92 percent of them had hyporetinemia (serum retinol level <0.7 μmol per liter [20 μg per deciliter]). Serum concentrations of retinol-binding protein (mean, 30.1±2.0 mg per liter) and albumin (mean, 33.4±0.5 g per liter) were also low. As compared with the placebo group, the children who received vitamin A recovered more rapidly from pneumonia (mean, 6.3 vs. 12.4 days, respectively; P<0.001) and diarrhea (mean, 5.6 vs. 8.5 days; P<0.001), had less croup (13 vs. 27 cases; P = 0.03), and spent fewer days in the hospital (mean, 10.6 vs. 14.8 days; P = 0.01). Of the 12 children who died, 10 were among those given placebo (P = 0.05). For the group treated with vitamin A, the risk of death or a major complication during the hospital stay was half that of the control group (relative risk, 0.51; 95 percent confidence interval, 0.35 to 0.74).

Conclusions. Treatment with vitamin A reduces morbidity and mortality in measles, and all children with severe measles should be given vitamin A supplements, whether or not they are thought to have a nutritional deficiency. (N Engl J Med 1990; 323:160-4.)

MEASLES remains a devastating disease, for which specific therapy is lacking. Hopes for its control and eventual eradication rest on immunization, but measles kills about 2 million children each year[1] and cripples an untold number through blindness[2] and lung disease.[3,4] The idea that vitamin A may have a protective effect in measles was first suggested more than 50 years ago[5] but was ignored until Barclay et al.,[6] in a randomized clinical trial, found twice as many deaths in the control group (12 of 92) as among children given high doses of vitamin A (6 of 88).[6] Although the overall results did not reach statistical significance, vitamin A was significantly protective in the group under two years of age.[6]

That vitamin A should be of benefit in measles is biologically plausible.[7] Measles depresses serum levels of vitamin A,[8-11] and hyporetinemia (a serum retinol level below 0.7 μmol per liter [20 μg per deciliter]) is associated with increased mortality from the disease, particularly in children under two years of age.[11] In almost every known infectious disease, vitamin A deficiency is known to result in greater frequency, severity, or mortality.[12] Increased susceptibility to infection was one of the first features of nutritional vitamin A deficiency to be recognized,[13] and even mild deficiency appears to be associated with an increased risk of pneumonia, diarrhea, and death in childhood.[14-17] According to Scrimshaw et al., "no nutritional deficiency in the animal kingdom is more consistently synergistic with infection than that of vitamin A."[12] They list nearly 50 studies (including 8 in humans) of diseases of bacterial, viral, or protozoan origin in which vitamin A deficiency resulted in increased frequency, severity, or mortality.[12] In fact, vitamin A is sometimes referred to as the "anti-infective" vitamin.[18]

We embarked on this study because measles is a pressing problem in our part of the world[19] and because the results of Barclay et al.[6] and the circumstantial evidence appeared promising. Subsequently, acting on the same evidence, the World Health Organization recommended routine vitamin A supplementation for all children with measles in regions where vitamin A deficiency was a recognized problem and suggested that elsewhere "in countries where the fatality rate of measles is 1% or higher it would be sensible to provide vitamin A supplements to all children diagnosed with measles."[20] One difficulty with this advice is that in the communities in which measles poses the greatest problem, the mortality rate is often unknown. Another is that the recommendation is based on the less than conclusive evidence from the only two studies to have addressed the question of vitamin A therapy in measles.[5,6] These are some of the reasons why vitamin A supplementation is still not given routinely to children who are seriously ill with measles in South Africa, and presumably elsewhere.

METHODS

Children with acute measles who required hospital admission for the treatment of associated complications were entered in a randomized, double-blind, placebo-controlled trial to assess the effect of oral vitamin A on morbidity and mortality. The study was limited by a priori considerations to a fixed termination date, with a maximal enrollment of 200 cases. It was conducted from March to July 1987 at the City Hospital for Infectious Diseases, a regional center serving a population of about 2 million in Cape Town and

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surrounding areas. The Medical Faculty's ethics and research committee approved the study protocol.

Patient Selection and Randomization

All children under 13 years of age who were referred to the hospital for admission with measles were eligible for entry into the trial. The criteria for exclusion were vitamin A therapy before admission, xerophthalmia on admission or thereafter, rash for more than four days, or lack of parental consent.

Patients in the trial were randomly assigned to receive either 400,000 IU (120 mg) of water-miscible vitamin A (retinyl palmitate; Arovit drops, Roche, Basel, Switzerland) or an identical-appearing placebo from syringes coded according to a random-number table. The senior ward nurse gave half the dose on admission and the remainder a day later, either by mouth or by nasogastric tube. The children were cared for by the regular ward staff. Concurrent therapy included oxygen, intravenous fluids, and antibiotics as appropriate, but no additional vitamin supplements. One of the study investigators assessed the patients each day. The treatment-assignment codes were broken only at the completion of the trial.

Initial Investigations

The children's weight and height were recorded, and a venous-blood sample was drawn on entry into the trial. The weights and heights were evaluated against the standards of the National Center for Health Statistics.[21] Hemoglobin levels, white-cell counts (by Coulter model S5, Coulter Electronics, Hialeah, Fla.), and differential counts were estimated, and serum was stored at −70°C. Serum levels of total protein and albumin were measured by automated analysis (Astra-8, Beckman Instruments, Brea, Calif.). Serum concentrations of vitamin A (as retinol) were measured by high-performance liquid chromatography (Dupont Instruments, Wilmington, Del.), with concentrations of vitamin E (as alpha-tocopherol) obtained incidentally.[22] A programmable integrator was used to quantify the chromatographic results (Spectra-Physics, San Jose, Calif.). Retinol-binding protein was measured by radial immunodiffusion with a commercial kit (LC-Partigen, Behringwerke, Marburg, Federal Republic of Germany). Chest radiography and other investigations were performed when indicated.

Table 1. Base-Line Clinical Findings in 189 Children with Measles, According to Treatment Group.*

Characteristic	No. of Patients	Placebo (N = 97)	Vitamin A (N = 92)
Age (mo)		*15.06 (8, 10, 15)*	*15.89 (8, 10, 17)*
<6	7	3	4
6–12	117	64	53
13–23	37	18	19
≥24	28	12	16
Male/female		56/41	53/39
Mixed race/black		29/68	24/68
Weight for age†	189	*81.5 (74, 84, 92)*	*85.7 (77, 85, 96)*
<5th percentile	95	51	44
Height for age†	178	*96.0 (93, 97, 100)*	*97.1 (93, 96, 101)*
<5th percentile	52	25	27
Weight for height†	178	*89.0 (82, 88, 95)*	*90.3 (84, 91, 97)*
<5th percentile	70	41	29
Rash (days)‡		*1.91 (1, 2, 2)*	*1.72 (1, 1.5, 2)*
Diarrhea	152	75	77
No pneumonia	30	13	17
Pneumonia	146	74	72
No diarrhea	24	12	12
Pneumonia and diarrhea	122	62	60
Herpes stomatitis	4	1	3
Measles croup§	13	4	9

*Values in italics are means, followed in parentheses by 25th percentiles, medians, and 75th percentiles. All other values are numbers of patients.

†Expressed as a percentage of the 50th percentile of the standards of the National Center for Health Statistics.

‡$P<0.05$ for the comparison between groups.

§No patients with measles croup required airway interventions.

Assessment of Outcomes

Outcomes were assessed solely on the basis of clinical criteria. The outcome variables used were death and the severity of illness, as indicated by the duration of the hospital stay; the duration of pneumonia or diarrhea; the incidence of "postmeasles" croup or herpes stomatitis; and the need for a transfer to the Red Cross War Memorial Children's Hospital for intensive care. Pneumonia was defined as the presence of tachypnea (frequency of respiration >40 per minute) with retractions, crackles, or wheezes. Diarrhea was defined as the passage of four or more liquid stools a day. Measles croup was defined as croup presenting on or within a day of admission. Croup that developed subsequently was categorized as postmeasles.

Statistical Analysis

The data were analyzed by computer with the Epi-Info program (version 3, USD, Stone Mountain, Ga.). Categorical data[23] (e.g., the number of patients per group) were evaluated by the chi-square test, with Yates' correction for continuity applied routinely,[24] or by Fisher's exact test when the expected number in a cell was five or less.[24] Confidence intervals for the relative risks were calculated according to the method of Greenland and Robins.[25] Continuous data[23] (e.g., vitamin level) were compared by the nonparametric Kruskal–Wallis test.[23,24] All P values reported are two-tailed, with values of less than 0.05 considered statistically significant.

Results

Exclusion of Patients

Of 224 patients under 13 years of age who were admitted to the hospital with measles during the study, 35 were excluded from the trial. In 12 of these cases the rash was present for five or more days, in 2 vitamin A had previously been given, in 18 consent could not be obtained because the child was unaccompanied by a parent on admission, and in 3 the parents refused consent. Hence, 189 patients were entered in the trial. There were no exclusions for xerophthalmia or withdrawals after entry.

Base-Line Characteristics

The placebo and treatment groups were generally comparable (Tables 1 and 2), except that the patients in the vitamin A group were admitted about 12 hours earlier in terms of the duration of the rash and had lower serum levels of total protein and albumin than those in the placebo group. Two thirds of the children were 12 months old or younger (median, 10 months; range, 2 months to 5 years), and most were boys (58 percent). Blacks predominated (72 percent), and the remainder were of mixed race. The five white patients admitted with measles were excluded: consent was refused in the cases of two, and three were more than 13 years old. The hospital is open to all. Immunization and socioeconomic factors are thought to account for differences in racial makeup between the study population and the general population 14 years of age or

under in Cape Town (57 percent mixed race, 25 percent black, 18 percent white).[27] Heights were not measured for 11 patients. Height for age was below the fifth percentile in 52 children (29 percent) — a prevalence similar to that in the local reference population.[28] Weight for age (below the fifth percentile in 50 percent), and weight for height (below the fifth percentile in 39 percent) were considered to reflect short-term weight losses from measles[29,30] rather than preexisting acute protein-energy malnutrition, since that occurs in 1 percent or less of the local reference population.[28] A combination of pneumonia and diarrhea was the usual indication for hospital admission (64 percent). Diarrhea (16 percent), pneumonia (13 percent), or measles croup (7 percent) appearing as isolated symptoms precipitated the other admissions.

Table 2. Base-Line Blood and Serum Values, According to Treatment Group.

Characteristic*	No. of Patients	Placebo	Vitamin A
		mean (25th, 50th, and 75th percentile)	
Hemoglobin (g/dl)	177	10.73 (10, 10.6, 11.5)	10.78 (10, 10.5, 11.7)
Hematocrit (%)	177	32.4 (30, 32.5, 35)	32.8 (30, 32, 35)
Leukocytes ($\times 10^{-9}$/liter)	177	8.63 (6.3, 7.7, 10.2)	8.99 (6.2, 8.15, 10.25)
Lymphocytes ($\times 10^{-9}$/liter)	177	3.39 (2, 3.1, 4.2)	3.42 (1.8, 2.9, 4.3)
Total protein (g/liter)†	155	58.54 (55, 57, 62)	53.94 (51, 54, 58)
Albumin (g/liter)†		34.5 (32, 34, 37)	32.4 (29, 33, 35)
RBP (mg/liter)	156	29.6 (14, 18, 30)	30.48 (14, 17, 37)
Vitamin A (retinol) (μg/dl)	156	12.19 (7.7, 10.7, 14.4)	10.95 (6.7, 9.5, 12.6)
Age <2 yr	131	12.84 (11.4, 15.1, 46.5)	11.1 (6.7, 9.5, 12.4)
Age ≥2 yr‡	25	8.38 (7.1, 8.1, 10.5)	10.29 (6.4, 10.5, 13.6)
Hyporetinemia	143	68§	75§
Vitamin E (mg/liter)	156	7.94 (5.5, 7.8, 9.4)	6.84 (4.7, 6.8, 8.8)

*Reference values for the characteristics shown are as follows[26]: hemoglobin, 11.5 to 15.5 g per deciliter; hematocrit, 35 to 45 percent; leukocytes, 6 to 17×10^9 cells per liter; total protein, 62 to 80 g per liter; albumin, 35 to 50 g per liter; retinol-binding protein, 22 to 45 mg per liter; vitamin A (as retinol), 30 to 80 μg per deciliter; vitamin E (as alpha-tocopherol), 5.0 to 20 mg per liter. No reference values are given for lymphocytes because of considerable variation with age. RBP denotes retinol-binding protein. To convert grams of hemoglobin per deciliter to millimoles per liter, multiply by 0.6206; to convert micrograms of vitamin A per deciliter to micromoles per liter, multiply by 0.03491; and to convert milligrams of vitamin E per liter to micromoles per liter, multiply by 23.22.

†$P<0.05$ for the comparison between groups.

‡In the placebo group, the retinol level was significantly lower in children ≥2 years old than in those <2 years old ($P = 0.026$).

§Indicates the number of cases of hyporetinemia (serum retinol concentration <0.7 μmol per liter [20 μg per deciliter]).

No blood samples were obtained from 15 patients, and only partial results were available for another 19 (Table 2). Serum levels were low for total protein (mean [±SE], 56.2±0.7 g per liter), albumin (mean, 33.4±0.46 g per liter), retinol-binding protein (mean, 30.1±2.02 mg per liter), and vitamin A as retinol (mean, 0.405±0.021 μmol per liter [11.6±0.6 μg per deciliter]). Low levels of total protein principally reflect depressed serum albumin concentrations ($r^2 = 72.6$ percent, $P<0.001$). Serum retinol levels were below the lower limit of the normal range (0.7 μmol per liter [20 μg per deciliter]) in 92 percent of the children (143 of 156), and 46 percent (72) had levels below 0.35 μmol per liter (10 μg per deciliter), placing them at risk for xerophthalmia,[31] although no cases of this were observed. Vitamin E levels were in the normal range.

Outcome

The children who received vitamin A had markedly diminished mortality and morbidity (Table 3), with no clinically apparent adverse effects. Of the 12 children who died (6.3 percent), 10 were in the placebo group ($P = 0.046$). The children who died were 5 to 29 months of age, and seven were boys. Death occurred 3 to 32 days after admission (median, 10.5). Pneumonia[3,32] caused 10 deaths, and the two remaining children died after 15 and 32 days, respectively, of fulminant sepsis following chronic diarrhea and measles-induced kwashiorkor. Croup was present as an incidental finding in 5 of the 10 children who died of pneumonia.

Cases of pneumonia lasted almost twice as long in the placebo group as in the vitamin A group ($P<0.001$), and 66 percent of the children with chronic pneumonia (>10 days) were in the placebo group ($P = 0.008$). Similarly, diarrhea continued for a third longer in the placebo group ($P<0.001$), and 72 percent of the children with chronic diarrhea were in that group ($P = 0.023$). Postmeasles croup was more common in the placebo group ($P = 0.033$), as was herpes stomatitis ($P = 0.08$). Finally, the hospital stay of the survivors was shorter by a third in the vitamin A–treated group ($P = 0.004$).

Overall, 77 children had adverse outcomes (Table 3), of whom 52 were in the placebo group ($P = 0.004$). As compared with the children in the placebo group, the children treated with vitamin A were at lower relative risk for death (relative risk, 0.21; 95 percent confidence interval, 0.05 to 0.94), prolonged pneumonia ≥10 days (relative risk, 0.44; 95 percent confidence interval, 0.24 to 0.80), prolonged diarrhea ≥10 days (relative risk, 0.40; 95 percent confidence interval, 0.19 to 0.86), postmeasles croup (relative risk, 0.51; 95 percent confidence interval, 0.28 to 0.92), airway intervention (relative risk, 0.35; 95 percent confidence interval, 0.10 to 1.26), herpes stomatitis (relative risk, 0.23; 95 percent confidence interval, 0.05 to 1.06), and the need for intensive care (relative risk, 0.38; 95 percent confidence interval, 0.13 to 1.16). The overall risk for an adverse outcome in children treated with vitamin A was half that in the control group (relative risk, 0.51; 95 percent confidence interval, 0.35 to 0.74). Of the 77 children who had adverse outcomes, only 2 were ≥2 years of age ($P = 0.002$), and the risk in a child ≥2 years old was substantially lower than in

Table 3. Mortality and Morbidity in 189 Children with Measles, According to Treatment Group.*

Characteristic	Placebo (N = 97)	Vitamin A (N = 92)	Relative Risk (95% CI)†	P Value
Death	10	2	0.21 (0.05–0.94)	0.046
Age at death (mo)				
<6	1	0		
6–12	7	1		
13–23	1	1		
≥24	1	0		
Pneumonia (days)				
Duration	*12.37 (5, 8, 17)*	*6.53 (3, 5, 8.5)*		<0.001
≥10	29	12	0.44 (0.24–0.80)	0.008
Diarrhea (days)				
Duration	*8.45 (5, 7, 10)*	*5.61 (3, 5, 7)*		<0.001
≥10	21	8	0.40 (0.19–0.86)	0.023
Postmeasles croup	27	13	0.51 (0.28–0.92)	0.033
With airway intervention	9	3	0.35 (0.10–1.26)	0.16
Herpes stomatitis	9	2	0.23 (0.05–1.06)	0.08
Intensive care	11	4	0.38 (0.13–1.16)	0.13
Adverse outcome‡	52	25	0.51 (0.35–0.74)	<0.001
Hospital stay (days)§	*15.24 (8, 11, 19)*	*10.52 (7, 9, 13)*		0.004

*In the columns representing the treatment groups, the values in italics are means, followed in parentheses by 25th percentiles, medians, and 75th percentiles. All other values are numbers of patients.

†Relative risk denotes the ratio of the incidence of an event in the vitamin A group to the incidence of the event in the placebo group. CI denotes confidence interval.

‡Defined as death, pneumonia ≥10 days in duration, diarrhea ≥10 days in duration, postmeasles croup, or transfer for intensive care.

§Refers to children who survived.

younger children (relative risk, 0.15; 95 percent confidence interval, 0.02 to 0.91). No child with a serum retinol concentration ≥0.7 μmol per liter (20 μg per deciliter) died, but the smallness of this group (n = 14) leaves the significance of the finding in doubt.

Discussion

The results of our randomized, controlled trial indicate a remarkable protective effect of vitamin A in severe measles, notwithstanding the provision of good general medical care and the presence of complicated advanced disease. Vitamin A reduced the death rate by more than half and the duration of pneumonia, diarrhea, and hospitalization by about one third. Vitamin A also appeared to reduce the incidence of herpes stomatitis and the need for intensive care. The consistency of benefit with respect to all measures of outcome is noteworthy, since mortality is not a sensitive criterion. Because of their reliance on mortality rates, previous studies of measles[5,6] lacked the statistical power to establish the benefit of vitamin A therapy.

The favorable response to vitamin A therapy may be understood in terms of the very high incidence (92 percent) of hyporetinemia in our patients (Table 2). Hyporetinemia implies a state of vitamin A deficiency at the tissue level, since there are virtually no peripheral-tissue stores of vitamin A except in the retina.[33-36] Serum retinol levels below 0.7 μmol per liter (20 μg per deciliter) appear to be inadequate for the body's biologic needs.[33] Oral vitamin A is absorbed well even in patients with diarrhea,[37] so the observed effects of treatment may reasonably be ascribed to correction of the tissue deficit of vitamin A. We do not know, however, whether the deficit was rectified by increases in the serum retinol concentration or by some other mechanism, since serum retinol levels were not measured after therapy.

Hyporetinemia appears almost invariable in children with severe measles,[8-11] as in this study, and the reduction in the serum retinol level is associated with increasingly severe disease.[11] Since many of these data come from populations in which nutritional vitamin A deficiency is a known problem,[8-10] it has been inferred that hyporetinemia in measles represents the exhaustion of hepatic stores.[6,7,20] There is a possible alternative mechanism, however. Hyporetinemia may occur in the presence of adequate hepatic stores of vitamin A when the stores are not mobilized fast enough to meet demand.[36] This has been found in fever, pneumonia, rheumatoid arthritis, hepatitis, acute tonsillitis, and rheumatic fever[36]; in protein-energy malnutrition[38]; and now also in measles.[8] Inadequate mobilization of hepatic stores may therefore underlie the hyporetinemia in children with severe measles from Kinshasa, Zaire,[11] and Cape Town, where nutritional vitamin A deficiency is uncommon. A study 25 years ago showed vitamin A deficiency to be rare in Cape Town, even in children with severe protein-energy malnutrition,[38] and it still appears to be rare. A search of the computer data-base listing of inpatients at our children's hospital, which predominantly serves the local underprivileged community, found only three instances of clinical vitamin A deficiency among 161,381 children admitted over a 13-year period, with no cases since 1985.

In view of the evidence that hyporetinemia may occur in the presence of adequate hepatic stores of vitamin A[38] and in populations not known to be deficient in vitamin A,[11] it would seem prudent to proceed on the assumption that previous nutritional adequacy may not ensure against the development of hyporetinemia in severe measles. For all children seriously ill with measles, vitamin A replacement should thus be provided at the dose given by Barclay et al.[6] (400,000 IU), which proved effective and safe in our study. A lower dose (100,000 to 200,000 IU) is recommended by the World Health Organization,[20] but its efficacy in measles has yet to be established.

It may be asked whether it is cost effective to advocate treatment with vitamin A for all children with

severe measles. Clearly, children under two years of age are at highest risk of an adverse outcome and derive the most benefit from vitamin A. When resources are scarce, such children should be given priority. In our study, however, half the children over two years of age were at risk of xerophthalmia because of serum retinol levels below 0.35 μmol per liter (10 μg per deciliter),[31] and hence they should have vitamin A prophylaxis. Thus, when resources permit, all children with severe measles should be given supplemental vitamin A.

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J Trop Pediatr. 1993 Dec;39(6):342-5. doi: 10.1093/tropej/39.6.342.

Routine high-dose vitamin A therapy for children hospitalized with measles.

Hussey GD[1], Klein M.

Author information

Abstract

Measles is without specific therapy and remains important globally as a cause of childhood death. In controlled studies, high-dose vitamin A therapy (Hi-VAT)--with 400,000 IU vitamin A--has been demonstrated to markedly reduce measles-associated morbidity and mortality. We performed a retrospective study of the hospital records of 1720 children < 15 years of age who were hospitalized for measles, to determine the extent to which these findings, in research settings, are applicable to the case management of measles under conditions of routine hospital practice. The outcomes were studied of children hospitalized during two non-consecutive 2 year periods (1985-6 and 1989-90). A policy of Hi-VAT for all children hospitalized with measles was started during the intervening period. As compared with the group of children on standard therapy (n = 1061), children receiving Hi-VAT (n = 651) had a shorter hospital stay (mean 10 versus 13 days; P < 0.001), a lower requirement for intensive care (4.3 versus 10.5 per cent; P < 0.001), and a lower death rate (1.6 versus 5 per cent; P < 0.001). No adverse effects of Hi-VAT therapy were observed. We conclude that a policy of high dose oral vitamin A (400,000 IU) supplementation in measles provides benefits which are equivalent to those previously observed only in controlled research trials, that it is highly cost effective, and that it should form part of the routine case management of all children hospitalized with measles.

PMID: 8133555 DOI: 10.1093/tropej/39.6.342

[Indexed for MEDLINE]

Format: Abstract

Nutr Rev. 1992 Oct;50(10):291-2.

Low serum retinol is associated with increased severity of measles in New York City children.

Caballero B[1], Rice A.

Author information

1 Department of International Health, Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD 21205.

Abstract

Children with no known prior vitamin A deficiency exhibited a significant decline in their serum retinol levels during the acute phase of measles. This decline in circulating retinol was associated with increased duration of fever, higher hospitalization rates, and decreased antibody titers.

PMID: 1436764

[Indexed for MEDLINE]

Format: Abstract

Full text links

PEDIATRICS
FINAL VERSION

Pediatrics. 1993 Jun;91(6):1176-81.

Measles severity and serum retinol (vitamin A) concentration among children in the United States.

Butler JC[1], Havens PL, Sowell AL, Huff DL, Peterson DE, Day SE, Chusid MJ, Bennin RA, Circo R, Davis JP.

Author information

Abstract

BACKGROUND: Studies in developing countries have shown that children with measles have low serum retinol concentrations and that lower retinol levels are associated with measles-related mortality. Vitamin A therapy has been shown to reduce mortality among African children with acute measles.

OBJECTIVES: To determine whether serum retinol concentration is low among children with measles in the United States and to determine whether retinol concentration is associated with illness severity.

SETTING: Pediatric referral hospital and clinic in Milwaukee, WI, during the measles outbreak of 1989-1990.

PATIENTS: One hundred fourteen patients < or = 5 years of age evaluated for serologically confirmed measles with serum obtained within 5 days following rash onset.

METHODS: Serum retinol concentration was determined by high-performance liquid chromatography. Clinical data were collected by hospital record review. A modified Pediatric Risk of Mortality (PRISM) score was used to assess physiologic instability as a measure of illness severity.

RESULTS: Retinol concentrations ranged from 0.25 to 1.18 mumol/L (median 0.58 mumol/L); 82 (72%) patients had low retinol concentration (< or = 0.70 mumol/L). Median retinol concentrations were lower among hospitalized patients (0.56 vs 0.70, P = .006) and patients with pneumonia (0.52 vs 0.64, P = .02) but higher among children with otitis media (0.63 vs 0.54, P = .01). Higher modified PRISM scores, reflecting greater physiologic instability, were associated with lower retinol concentration (beta coefficient -.0147, P = .025). In multivariate analysis, higher modified PRISM scores were associated with lower retinol concentration (beta coefficient -.0144, P = .025) even after controlling for hospitalization, presence of complications, race, age, receipt of Aid to Families With Dependent Children, gender, and interval from rash onset until serum was collected.

CONCLUSIONS: Among these children with measles in an urban United States community, retinol concentrations were depressed, and the degree of depression was associated with illness severity. Vitamin A therapy should be considered for children with measles in the United States who require hospitalization.

PMID: 8502524

[Indexed for MEDLINE]

Format: Abstract

Full text links

PMC FREE Full text

Br Med J. 1977 Jun 25;1(6077):1633-5.

Persistent measles infection in malnourished children.

Dossetor J, Whittle HC, Greenwood BM.

Abstract

Thirty malnourished and 25 well-nourished children were studied six to 31 days after the onset of a measles rash. Evidence of the virus was found in 40% of the malnourished children but in none of the well-nourished controls. Giant cells were found in the nasal secretions of five out of 17 malnourished children and measles antigen was detected in the lymphocytes of eight out of 28. The malnourished children showed depressed cell-mediated immunity to measles and candida antigens and a low response to meningococcal vaccine. Fifteen died from intercurrent infections. Malnutrition was thought to have depressed the immune response in these children, resulting in a severe and prolonged attack of measles. This, in turn, led to further damage to the immune system and more severe malnutrition. Thus these children were made susceptible to intercurrent infection.

PMID: 871699 PMCID: PMC1607735

[Indexed for MEDLINE] **Free PMC Article**

Format: Abstract

Full text links

OXFORD ACADEMIC

J Trop Pediatr. 2002 Dec;48(6):323-7. doi: 10.1093/tropej/48.6.323.

Vitamin A for the treatment of children with measles--a systematic review.

D'Souza RM[1], D'Souza R.

Author information

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Abstract

Vitamin A deficiency is a recognized risk factor for severe measles. WHO and UNICEF have recommended vitamin A for the treatment of measles but there are children still dying from measles. A systematic review, including the use of meta-analysis was done of randomized controlled trials comparing vitamin A with placebo obtained from a systematic search of the medical literature to determine whether vitamin A prevents mortality and pneumonia-specific mortality in children with measles. We identified five trials conducted in Africa, four in hospitals and one in a community that met the inclusion criteria. There were 445 children aged 6 months to 13 years supplemented with vitamin A and 478 with placebo. There was a 39 per cent reduction in overall mortality when vitamin A was used for the treatment of measles but this was not statistically significant (relative risk 0.61; 95 per cent confidence interval 0.32-1.12). When stratified by dose, 200 000 IU of vitamin A given for 2 days was associated with a reduction in overall mortality (0.36, 0.14-0.82) and pneumonia-specific mortality (0.33, 0.08-0.92) in hospitalized children in areas with high case fatality. Greater reduction in mortality was observed in children under the age of 2 years (0.17, 0.03-0.61). On the other hand, a single dose of 200 000 IU of vitamin A was not associated with reduced mortality (1.25, 0.48-3.1). There were no trials comparing a single dose with two doses of vitamin A. There were not enough studies to separate out the individual effects of age, dose, formulation, hospitalization and case fatality in the study area. We conclude that 200 000 IU of vitamin A repeated on 2 days should be used for the treatment of measles as recommended by WHO in children admitted to hospitals in areas where the case fatality is high.

PMID: 12521271 DOI: 10.1093/tropej/48.6.323

[Indexed for MEDLINE]

ScienceDaily
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Science News

from research organizations

Vitamin A supplements for children could save 600,000 lives a year, experts predict

Date: August 25, 2011

Source: BMJ-British Medical Journal

Summary: Children in low and middle income countries should be given vitamin A supplements to prevent death and illness, a new study concludes.

FULL STORY

Children in low and middle income countries should be given vitamin A supplements to prevent death and illness, concludes a study published online in the British Medical Journal.

The researchers argue that the effectiveness of vitamin A supplementation is now so well-established that further trials would be unethical, and they urge policymakers to provide supplements for all children at risk of deficiency.

Vitamin A is an essential nutrient that must be obtained through diet. Vitamin A deficiency in children increases vulnerability to infections like diarrhea and measles and may also lead to blindness. Globally, the World Health Organisation estimates that 190 million children under the age of 5 may be vitamin A deficient. But, despite widespread efforts, vitamin A programmes do not reach all children who could benefit.

So a team of researchers based in the UK and Pakistan analysed the results of 43 trials of vitamin A supplementation involving over 200,000 children aged 6 months to 5 years. Differences in study design and quality were taken into account to minimise bias.

They found vitamin A supplements reduced child mortality by 24% in low and middle income countries. It may also reduce mortality and disability by preventing measles, diarrhea and vision problems, including night blindness.

The authors say that, if the risk of death for 190 million vitamin A deficient children were reduced by 24%, over 600,000 lives would be saved each year and 20 million disability-adjusted life years (a measure of quantity and quality of life) would be gained.

Based on these results, the authors strongly recommend supplementation for children under 5 in areas at risk of vitamin A deficiency. They conclude: "The evidence for vitamin A is compelling and clear. Further trials comparing vitamin A with placebo would be unethical."

This view is supported in an accompanying editorial by two experts at Harvard School of Public Health, who say "effort should now focus on finding ways to sustain this important child survival initiative and fine tune it to maximise the number of lives saved."

Story Source:

Materials provided by **BMJ-British Medical Journal**. Note: Content may be edited for style and length.

Journal References:

1. E. Mayo-Wilson, A. Imdad, K. Herzer, M. Y. Yakoob, Z. A. Bhutta. **Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis**. BMJ, 2011; 343 (aug25 1): d5094 DOI: 10.1136/bmj.d5094
2. A. Thorne-Lyman, W. W. Fawzi. **Improving child survival through vitamin A supplementation**. BMJ, 2011; 343 (aug25 1): d5294 DOI: 10.1136/bmj.d5294

BMJ

BMJ 2011;343:d5094 doi: 10.1136/bmj.d5094

RESEARCH

Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis


OPEN ACCESS

Evan Mayo-Wilson *departmental lecturer*[1], Aamer Imdad *senior research officer*[2], Kurt Herzer *Marshall scholar*[1], Mohammad Yawar Yakoob *senior research officer*[2], Zulfiqar A Bhutta *Noordin Noormahomed Sheriff endowed professor and founding chair*[2]

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Abstract

Objective To determine if vitamin A supplementation is associated with reductions in mortality and morbidity in children aged 6 months to 5 years.

Design Systematic review and meta-analysis. Two reviewers independently assessed studies for inclusion. Data were double extracted; discrepancies were resolved by discussion. Meta-analyses were performed for mortality, illness, vision, and side effects.

Data sources Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Medline, Embase, Global Health, Latin American and Caribbean Health Sciences, metaRegister of Controlled Trials, and African Index Medicus. Databases were searched to April 2010 without restriction by language or publication status.

Eligibility criteria for selecting studies Randomised trials of synthetic oral vitamin A supplements in children aged 6 months to 5 years. Studies of children with current illness (such as diarrhoea, measles, and HIV), studies of children in hospital, and studies of food fortification or β carotene were excluded.

Results 43 trials with about 215 633 children were included. Seventeen trials including 194 483 participants reported a 24% reduction in all cause mortality (rate ratio=0.76, 95% confidence interval 0.69 to 0.83). Seven trials reported a 28% reduction in mortality associated with diarrhoea (0.72, 0.57 to 0.91). Vitamin A supplementation was associated with a reduced incidence of diarrhoea (0.85, 0.82 to 0.87) and measles (0.50, 0.37 to 0.67) and a reduced prevalence of vision problems, including night blindness (0.32, 0.21 to 0.50) and xerophthalmia (0.31, 0.22 to 0.45). Three trials reported an increased risk of vomiting within the first 48 hours of supplementation (2.75, 1.81 to 4.19).

Vitamin A supplementation reduced incidence of measles by 50% (37%-67%).

Conclusions Vitamin A supplementation is associated with large reductions in mortality, morbidity, and vision problems in a range of settings, and these results cannot be explained by bias. Further placebo controlled trials of vitamin A supplementation in children between 6 and 59 months of age are not required. However, there is a need for further studies comparing different doses and delivery mechanisms (for example, fortification). Until other sources are available, vitamin A supplements should be given to all children at risk of deficiency, particularly in low and middle income countries.

Introduction

Vitamin A refers to a subclass of retinoic acids[1] long understood to help regulate immune function and to reduce morbidity of infectious diseases.[2] Vitamin A is required for normal functioning of the visual system, maintenance of cell function for growth, epithelial integrity, production of red blood cells, immunity, and reproduction.[3] Different forms of vitamin A include β carotene, which is found in plants, and preformed vitamin A, which is found in animal sources. Vitamin A is an essential nutrient that cannot be synthesised so it must be obtained through diet.[1]

Vitamin A deficiency increases vulnerability to a range of illnesses including diarrhoea, measles, and respiratory infections.[3 4] These are leading causes of mortality among children in low and middle income countries,[5] where risk of infection and risk of mortality can be compounded by coexisting undernutrition.[6] The bioavailability of provitamin A carotenoids in fruit and vegetables is lower than once believed,[7 8] and it is difficult for children to fulfil their daily requirements through plant foods alone. Consequently, vitamin A deficiency is

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Extra material supplied by the author (see http://www.bmj.com/content/343/bmj.d5094/suppl/DC1)

Appendix 1: Search strategy for other databases

common among children whose families cannot afford eggs and dairy products.

Preformed vitamin A (retinol, retinal, retinoic acid, and retinyl esters) is the most active in humans; it is usually used in supplements in the form of retinyl esters.[1 3] High intake of synthetic vitamin A over a prolonged period can lead to toxicity,[9] but toxicity from food sources is rare. Periodic supplementation should not cause serious adverse effects.[10]

Previous meta-analyses suggested that vitamin A supplementation for children in developing countries is associated with up to 30% reductions in mortality,[11-13] especially deaths from diarrhoea and measles. The World Health Organization has long recommended vitamin A supplementation for children aged under 5 and for pregnant and breastfeeding mothers.[14] The Countdown to 2015 identified 68 "priority countries" in which over 90% of the world's maternal and childhood deaths occur[15]; the programme aims to hold governments accountable for their commitments to Millennium Development Goals. Vitamin A is now being provided in many low and middle income countries with coverage rates of 86%.[15] Nonetheless, some critics have questioned the value and effectiveness of vitamin A supplementation programmes, and several studies have been conducted since initial recommendations were made.[16 17]

We undertook a review to synthesise all available evidence for vitamin A supplementation in children aged 6 months to 5 years, adding to previous reviews by investigating effects on mortality and the illnesses that lead to death. By investigating all effects in the same review, we provided current estimates of treatment effects and identified potential pathways through which vitamin A supplementation might reduce mortality. A complete protocol was peer reviewed and published by the Cochrane Collaboration, and the review is available in the Cochrane Library.[18]

Methods

We evaluated the effect of prophylactic synthetic oral vitamin A supplementation compared with no treatment or placebo. We planned to conduct five subgroup analyses:

- Dose: WHO recommended dose (up to 100 000 IU for children aged 6-11 months and 200 000 IU for children aged 1-5 years) *v* lower and higher doses
- Frequency: high (doses within 6 months) *v* low (1 dose or ≥6 month interval)
- Location: by continent
- Age: 6-12 months *v* 1-5 years
- Sex: boys *v* girls.

Eligibility criteria

Types of trials—Randomised controlled trials including cluster trials and factorial trials were included irrespective of publication status or language.

Types of participants—At the time of recruitment, children had to be aged 6 months to 5 years and apparently healthy. Children in hospital at the time of recruitment were excluded.

Types of interventions—Included studies examined synthetic oral vitamin A supplementation compared with no treatment or placebo, irrespective of dose or frequency. Studies of food fortification and β carotene supplementation were excluded as their effects can differ.

Types of outcome measures

Primary—We examined all cause mortality at the longest follow-up. We also analysed outcomes within the first year and more than one year after supplementation.

Secondary—We analysed cause specific mortality from diarrhoea, lower respiratory tract infection, measles, and meningitis. We compared the incidence and prevalence of diarrhoea, lower respiratory tract infection, measles, malaria, meningitis, Bitot's spots, night blindness, and xerophthalmia. Adverse events were noted and analysed when possible (vomiting and bulging fontanelle). Finally, we examined vitamin A status (serum retinol) as a continuous and dichotomous outcome.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 2), Medline (see box), Embase, Global Health, Latin American Database (LILACS), metaRegister of Controlled Trials, and African Index Medicus (see appendix 1 on bmj.com). All searches were conducted on 27 April 2010. To identify ongoing and unpublished trials, we used the WHO international clinical trials registry, which searches multiple trial registries. Reference lists of reviews, included studies, and excluded studies were searched for additional citations. We contacted organisations and researchers by email and by phone. Two authors (from AI, KH, and MYY) independently screened abstracts and resolved differences with a third author (EMW).

Assessment of bias

Studies were assessed with the Cochrane Collaboration's risk of bias tool.[19] Two authors rated each study for risk of bias from sequence generation (was the method truly random?), allocation concealment (before enrolment, were participants' group assignments disguised?), blinding of participants, assessors, and providers (was assignment adequately disguised after randomisation?), selective outcome reporting (were all outcome measures reported?), and incomplete data (do the results account for all participants randomised?). Risk of bias for each domain was rated as high (seriously weakens confidence in the results), low (unlikely to seriously alter the results), or unclear. Discrepancies were resolved through discussion. The primary analysis was repeated without studies at high risk of bias for sequence generation.

Data management

Two independent people, at least one of whom was an author, completed data extraction and assessments of risk of bias online with Distiller software.[20] We collected data on the time points and measures (both collected and reported) and recruitment, inclusion/exclusion criteria, co-interventions, dose, frequency, duration, age, sex, setting, and location.

Statistical analysis

For continuous outcomes, we calculated the standardised mean difference, Hedges' g.[21] For dichotomous outcomes, we calculated an overall risk ratio. For incidence data, risk ratio (events per child) and rate ratio (events per child year) were combined because these ratios use the same scale and can be interpreted in the same way for these studies (the duration of studies was short and there was no interaction between the intervention and time at risk). All outcomes are reported with 95% confidence intervals, and overall effects are weighted by the inverse of variance with a fixed effect model. In the case of

Search strategy for Medline

Medline (1950 to April (week 2) 2010)

1. exp infant/ or exp child/ or exp child, preschool/
2. (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3. 1 or 2
4. exp Vitamin A/
5. (retinol$ or retinal$ or aquasol a or vitamin a).ab,ti.
6. 4 or 5
7. randomised controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. drug therapy.fs.
12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. 3 and 6 and 17

cluster randomised controlled trials, we used adjusted estimates reported by the authors. Where results did not control for clustering, we contacted authors to request the intracluster correlation coefficient. If authors were unable to provide this, we used design effects calculated previously[11] to calculate it using Cochrane methods.[19] For estimated values, we conducted sensitivity analyses using larger and smaller design effects to determine if the results were robust.

Missing data were noted for each outcome. When the numbers of dropouts were not reported, we contacted the authors. When analyses were reported for completers as well as controlled for dropouts (for example, imputed with regression methods), we used the latter.

Statistical heterogeneity was assessed by visual inspection of forest plots, by performing χ^2 tests (assessing the P value), and by calculating the I^2 statistic,[22 23] which describes the percentage of observed heterogeneity that would not be expected by chance. If the P value was less than 0.10 and I^2 exceeded 50%, we considered heterogeneity to be substantial. In subgroup analyses, we tested differences between groups with χ^2. To assess the possibility of small study bias, we compared random effects estimates with fixed effects estimates, drew funnel plots for outcomes with 10 or more studies, and conducted a trim and fill analysis,[24] which yields an effect adjusted for funnel plot asymmetry. Meta-analysis was conducted with RevMan[25] and Biostat CMA (comprehensive meta-analysis)[26] and a summary of results was prepared with the GRADE system.[27]

Results

Trial flow

We included 43 trials[28-69] reported in 90 papers; 39 (90%) reported data that could be included in a meta-analysis (fig 1⇓). The others reported outcomes that were not relevant to the review[35] and data that were not available by group[43] or were incomplete.[62 66] Post hoc, we included two studies in which participants were assigned using quasi-random methods (alternating assignment) as described below.[41 65]

Eight trials nearly met the inclusion criteria but were excluded because they were not randomised controlled trials,[70-73] were designed to treat diarrhoea[74] or Bitot's spots,[75] focused on children with HIV, [76] or did not include an eligible comparison.[77]

Two trials could not be assessed at this time. One including 36 children could not be located and is unlikely to affect the results.[78] One completed trial, the deworming and vitamin A (DEVTA) trial, seems likely to meet the eligibility criteria and could be included in further updates of this review.[79] To assess how the results of that trial could affect the conclusions of our review, we conducted a sensitivity analysis for the primary outcome.

Study characteristics

Trials included 215 633 participants with a median sample size of 480, ranging from 35[66] to over 29 000.[63] The 39 trials that were analysed included 215 043 participants (99.8% of children included in the review).

Of the 43 included trials, 37 compared vitamin A supplementation with placebo. Four used factorial designs, combining vitamin A supplementation with other treatments such as zinc[46 51 62] or deworming.[55] In one trial,[51] raw data were not available and we could not identify outcome data for an eligible comparison. Different doses were combined for the main analysis in one trial.[40]

The median of the mean ages was 30.5 months. Most trials assigned equal numbers of boys and girls; three studies favoured boys by more than 10%.[45 54 57] When trials reported outcomes at multiple time points, we analysed the longest follow-up; most studies lasted about one year. Table 1⇓ describes characteristics for individual studies, and table 2⇓ shows counts for subgroup characteristics.

Risk of bias

Figure 2 shows the risk of bias ratings[19] for each trial.⇓ Three trials were at high risk of bias for sequence generation (not truly random), and these included 41 139 participants.[29 41 65] In two

quasi-random studies (included post hoc), the authors and the Cochrane editors agreed that the methods of assignment had the desirable characteristics of randomisation and were at no greater risk of bias than other included studies. Only one study was at high risk of bias because of inadequate allocation concealment, but concealment of the allocation sequence was not sufficiently described in 27 trials.

Lack of blinding of assessors created a high risk of bias in only two studies, but it was unclear if assessors were blind in 14 trials. Two studies were at high risk of bias for failing to blind project staff, and 13 trials were unclear on this issue. At the trial level, nine were at high risk of bias for missing data and 12 were unclear, though missing data for the primary outcome was not a concern.

Only four studies seemed to be completely free from selective outcome reporting. It was unclear if 24 trials reported all outcomes, but the primary outcome (mortality) was known for almost all participants in the review. To test for bias, the primary analysis was repeated without studies at high risk of bias for sequence generation.

Quantitative data synthesis

All cause mortality

Mortality (fig 3⇓) was reported in 17 trials including 194 483 children (90% of the children in the review); one reported no events and was not analysed.[45] Thus, 16 trials were included in the primary meta-analysis. Two studies[41 65] randomised households, and we treated them as if they had randomised individuals. Previously reported design effects[11] were used to calculate intracluster correlation coefficients for six cluster randomised studies.[37 52 56 63 68 69] The coefficients were consistent, and we imputed an intracluster correlation coefficient of 0.002 for all studies in which clustering was not considered in the original analysis. A sensitivity analysis was conducted for all cause mortality with coefficients of 0 and 0.01 for those studies in which the mean design effect was estimated.

Vitamin A was associated with a 24% reduction in all cause mortality (0.76, 95% confidence interval 0.69 to 0.83; fig 3), though there was moderate heterogeneity (χ^2=29.10, df=15, P=0.02; I^2=48%). Only five trials[36 38 48 56 68] (7% of trials) measured mortality after 13 months, and the effect was similar (0.75, 0.64 to 0.88) with substantial and significant heterogeneity (χ^2=9.29, df=4, P=0.05; I^2=57%).

We then added a study awaiting assessment to the analysis.[79] In an analysis of 17 trials, this study (the deworming and vitamin A trial) accounted for 65.2% of the combined effect (fig 4⇓), which remained significant (0.88, 0.84 to 0.94) with substantial and significant heterogeneity (χ^2=44.31, df=16, P<0.001; I^2=64%). Though the benefit of vitamin A decreased by half (24% to 12%), the result remained clinically important. As we were unable to assess the trial, we cannot explain this substantially different result; its impacts on the conclusions of this review are considered below.

Of those in the main analysis, 10 trials were conducted in Asia, five in Africa, and one in Latin America. There was no clear difference (P=0.12) between the Asia subgroup (0.69, 0.61 to 0.79) and the Africa subgroup (0.85, 0.73 to 0.98), though the Latin American trial reported no effect (1.00, 0.14 to 7.08). We planned to compare trials in urban and rural areas, but only two urban trials reported the primary outcome; an analysis comparing 1982 and 192 501 participants would be difficult to interpret.

Four trials reported separate effects for children aged 6-12 months (0.59, 0.43 to 0.82) and children aged 1-5 years (0.68, 0.57 to 0.82); the subgroups did not differ significantly (P=0.46). Five trials reported separate effects for boys (0.80, 0.66 to 0.97) and girls (0.79, 0.65 to 0.95), which were not significantly different (P=0.89). Notably, effects for sex and age subgroups are all larger than the overall result, and these results should be interpreted with caution.

Only one trial providing small frequent doses reported mortality data, and the effects were larger (0.46, 0.30 to 0.71) than the effects for the WHO recommended dose delivered every four to six months (0.81, 0.72 to 0.90) or the recommended dose delivered once (0.66, 0.52 to 0.83). Differences between subgroups were significant (P=0.02), but only the greater effect for small frequent doses seems clinically plausible (fig 5⇓).

Of the trials at high risk of bias from sequence generation, only one contributed to primary analysis, and it reported no effect (1.06, 0.82 to 1.37), indicating that these trials were not likely to inflate the combined effect.

The primary analysis was repeated with a random effects model, and the overall estimate was slightly larger; thus, heterogeneity is partially explained by small studies reporting larger effects (0.71, 0.61 to 0.84), which could be related to bias or to clinical differences (such as better implementation in small trials). We drew a funnel plot and conducted a trim and fill analysis (fig 6⇓). There was some evidence of asymmetry (five studies trimmed), but the overall effect was strongly influenced by five studies that accounted for over 80% of the weighted mean, and there was no effect of replacing missing studies (adjusted value rate ratio=0.80, 0.73 to 0.87).

We also conducted a sensitivity analysis to determine if the intracluster correlation coefficients used to adjust for clustering influenced the overall effect. The size of the effect was slightly smaller when these trials were treated as if they had randomised individuals (0.81, 0.75 to 0.89) and was unchanged when we increased the coefficient to 0.01 (0.75, 0.68 to 0.83). Adjusting three studies for which the intracluster correlation coefficients was unknown did not affect our conclusions; further inflating their standard errors would increase the size of the overall effect.

Cause specific mortality

Vitamin A supplementation was associated with a 27% reduction in deaths from diarrhoea. Differences in deaths from measles and meningitis were not significant (table 3⇓).

Morbidities

Morbidity was measured in different ways, and we combined all available data whenever possible. For example, for diarrhoea we included all types of diarrhoea (mild, moderate, and severe). Pneumonia and lower respiratory tract infection outcomes were combined post hoc because pneumonia is a type of lower respiratory tract infection and many studies did not have complete diagnostic information.

Overall, there was a 15% decrease in diarrhoea incidence (fig 7⇓) and a 50% decrease in incidence of measles (fig 8⇓); heterogeneity in the former analysis was substantial, but heterogeneity in the second was not important. Only one trial reported incidence of malaria, which showed a reduction, and effects on lower respiratory infections were not significant (table 3⇓). Few studies reported prevalence data; results for diarrhoea and malaria were not significant, and there were no data for measles.

Vision

Evidence for vision outcomes was based on a small number of small studies. The available studies suggest a large reduction in the incidence and prevalence of night blindness and a large reduction in the prevalence of xerophthalmia, but effects on Bitot's spots and the incidence of xerophthalmia were not significant (table 4⇓).

Vitamin A deficiency

Serum concentrations were measured in a small number of small studies. These suggest that vitamin A supplementation reduces the proportion of children who are deficient and increases vitamin A serum concentrations (table 4⇓), but heterogeneity was substantial. These results could be influenced by bias, and serum concentrations might be a poor indicator of vitamin A status.

Adverse events

Three trials reported that high doses of vitamin A triple the risk of vomiting within 48 hours. Results for fontanelle side effects were not significant in one study (table 4), and two studies that measured the outcome could not be analysed.

Discussion

Comparable with previous reviews, this review shows that vitamin A supplementation is associated with large and important reductions in mortality for children in low and middle income countries. This adds substantively to previous reviews[11-13] in providing a plausible pathway and indicating that vitamin A supplementation reduces the incidence of and mortality from diarrhoea and measles. Vitamin A also reduces precursors to blindness. While there was a slight increase in the risk of vomiting within 48 hours, there was no evidence of serious adverse events as a result of periodic supplementation. Most trials did not measure vitamin A serum concentrations at baseline as children are unlikely to experience serious harm under these conditions; continuous supplementation, however, might lead to toxicity and cause more severe side effects. It is unclear if smaller more frequent doses would lead to the same minor side effects observed in this review.[9]

Vitamin A deficiency is common during childhood in many low and middle income countries, even among populations whose diets rely heavily on vegetables and fruits.[80] The reasons are multiple and include widespread maternal undernutrition, poor dietary quality, and losses during diarrhoea.[81 82] WHO estimates that 122 countries have a moderate to severe public health problem.[83]

Strengths and limitations

For the primary outcome, the evidence in this review is strong. Sixteen studies were analysed, which included a large number of children. Subgroup and sensitivity analyses show that the result is robust and the effects of bias were not important.

For the primary outcome, the quality of the evidence was "high" on the GRADE scale[27]—that is, further trials are unlikely to change the conclusion that vitamin A supplementation has a large and significant effect (table 3). It seems unlikely that the primary outcome is significantly overestimated because of bias from any source. Almost all studies were randomised with appropriate methods for sequence generation, and allocation was well concealed. It was easy to blind participants and providers, and most trials reported that people were unaware of the treatments being provided. Furthermore, lack of blinding might underestimate rather than overestimate effects—for example, a teacher might give extra food to a child receiving a placebo. Failure to blind assessors is unlikely to influence mortality data. Risks of selective outcome reporting and publication bias are low; the primary analysis included nearly all participants who had been randomised, and all studies large enough to make a difference in this analysis are probably known.

Two trials at high risk of bias for sequence generation were included post hoc, but steps to maintain allocation concealment and blinding minimised the possibility that participants were treated differently between groups. In the first, participants were assigned alternately by household.[41] The second used a random starting point and alternating distribution of red or green pills; the manufacturer held the code until the study was completed.[65] The decision to include these studies was made before data were extracted, and the one study that contributed to the primary outcome[41] reported no effect (1.06, 0.82 to 1.37). The decision to include these studies did not result in an overestimation of the primary outcome.

This review makes an important contribution by identifying several pathways though which vitamin A could reduce mortality. Much of the reduction in all cause mortality is probably explained by reductions in death from diarrhoea and measles, which are leading contributors to child mortality in low and middle income countries.[5] This hypothesis is strengthened by a review indicating that vitamin A supplementation prevents acute diarrhoea from becoming chronic.[84] Though the overall effect for mortality from measles was not significant, the trend was consistent with the overall results, and the therapeutic effects of vitamin A supplementation for measles are well established.[78]

For the secondary outcomes, the quality of the evidence was variable on the GRADE scale (tables 3 and 4), though evidence for measles incidence was high quality. We downgraded ratings for diarrhoea and measles mortality to "moderate" because of uncertainty about the size of the effects; these results are consistent with other findings and consistent with biological mechanisms through which vitamin A supplementation could cause an overall reduction in mortality.

In general, large studies examined effects on mortality while small studies measured illness, vision, and vitamin A serum concentrations. A few studies measured growth, though we did not include this as an outcome. Different outcomes are appropriate for studies with different purposes, but many secondary analyses include only a small proportion of the participants in the review. Recent evidence suggests that the prevalence of selective reporting of outcomes is high and that this might substantially bias systematic reviews.[85 86] If outcomes were reported selectively, addition of unreported data might influence the observed effects in some secondary analyses; we have more confidence in the internal validity of the primary outcome than the secondary outcomes.

Secondary outcomes also have less external validity than the primary analysis, and differences in the size of included studies could mask differences in the size of the analyses. For example, the primary analysis includes 16 trials while analyses for incidence of diarrhoea and serum concentration include 12 and 13 trials. Only five trials appear in both the primary analysis and the diarrhoea analysis, and only three appear in both the primary and serum analyses. While the primary outcome includes 194 483 participants (90% of those randomised), the analysis of incidence of diarrhoea includes only 37 710 (17%) and the serum analysis includes 6623 (that is, less than 3% of participants in the review). To draw attention to these differences

in external validity and risk of bias, tables 3 and 4 include the number of participants in each analysis as a percentage of those randomised.[87]

Comparison with earlier reviews

Landmark reviews of vitamin A for children appeared in 1993.[11 13] Since then, nine studies contributing 30% of the children in this review have improved the quality of the evidence for vitamin A supplementation in children aged under 5 years.

For the primary outcome, we conducted a cumulative meta-analysis (fig 9⇓) to show how the effect has shifted with the addition of studies over time. That is, each point on the plot shows the combined effect of the new study and all studies reported before it, and the weight is the combined weight of all studies up to that time. Eight trials were included in a 1993 review,[11] which reported a 23% reduction in all cause mortality (0.77, 0.70 to 0.86). Eight trials were added to this analysis (one additional trial reported no events), and the overall estimate has changed by 1%. The overall effect is not meaningfully different from the result of the first trial published in 1986. Therefore, this review confirms that previous estimates remain valid, finding little evidence of secular trends.

Supplementation in other populations is more controversial. A recent review of vitamin A supplementation for children aged under 6 months found no overall effect, but differences between regional subgroups might have been important.[88]

Comparison with the deworming and vitamin A (DEVTA) trial

The most important qualification of these findings is that a large study, awaiting assessment, found no benefit of vitamin A supplementation. Some reviews have found only fair agreement between the results of meta-analyses and the results of large trials[89]; in extreme cases, large trials might indicate that the combined results of smaller trials are incorrect in magnitude or direction.[90] When the results of large trials differ from the results of small trials, commonly used methods for meta-analysis could be inappropriate.[91] All things being equal (such as risk of bias and implementation), researchers and clinicians have been advised to trust large simple trials rather than meta-analyses of small trials.[92 93]

The deworming and vitamin (DEVTA) trial is the largest randomised controlled trial ever conducted, including about a million children in 72 clusters, more than four times the number of children in this review. The trial registration describes a factorial study comparing deworming and vitamin A, which was delivered every six months for two years.[79] The study began in 1999 and recruitment closed in 2004. The authors were contacted several times before our review was completed, but they did not provide information about the conduct of the study. We are unaware of any published results. We were therefore unable to assess eligibility, potential risk of bias, implementation of the intervention, or the generalisability of results. The authors did provide an early analysis of the primary outcome (rate ratio=0.96, 0.89 to 1.03), as well as analyses of cause specific mortality and vitamin A serum concentration.

Details that might explain differences between DEVTA and our review were not available, but we find it unlikely that the results of our review can be explained by small study bias. Small studies could differ from mega-trials, but five trials in this review included more than 20 000 participants and nine included more than 10 000 participants. Furthermore, when the mortality data for DEVTA are included, results of the primary analysis remain significant with a fixed effect model, and that effect remains clinically meaningful.

Heterogeneity

Statistical heterogeneity suggests there might be differences in the effects of vitamin A supplementation across settings and populations, and we conducted prespecified subgroup analyses for all analyses with 10 or more studies.

Trials were conducted in 18 countries. As described above, vitamin A supplementation was associated with significant reductions in mortality in both Asia and Africa. While the difference between subgroups for the primary outcome was not significant, biochemical concentrations of vitamin A seem lower in Asia than in Africa,[83] and our results are consistent with the hypothesis that the benefits of supplementation in Asia might be greater.[94]

For ethical reasons, some trials provided supplements to all children with symptoms of vitamin A deficiency (such as Bitot's spots). Exclusion of such children limits the magnitude of effects on vision outcomes, and such restrictions could contribute to observed heterogeneity across other outcomes in this review. Universal supplementation could result in larger benefits than those reported here.

A non-representative subset of studies reported data by age and sex, but these comparisons cannot be interpreted meaningfully except insofar as vitamin A supplementation was associated with significant reductions in mortality for all subgroups. All studies reporting the primary outcome used the standard dose recommended by WHO (table 2), except for one.[52] While differences between these subgroups were significant, the results might be a statistical artefact; it is possible that small frequent doses will lead to large reductions in mortality, but it seems unlikely that a single supplement is more effective than multiple supplements of the same dose.

Though we did not find evidence of specific contributors to heterogeneity in this review, effects might differ according to baseline vitamin A status, the availability of other nutrients, or the prevalence of disease—for example, concomitant nutrient deficiencies could impair the bioavailability of vitamin A supplementation[95] and differences in the prevalence of pathogens, sanitation, immunisation, and access to healthcare could affect the relative impact of vitamin A supplementation. Heterogeneity might be related to differences in the implementation of interventions, details of which are routinely under-reported in trials.[96] For example, it is essential that providers distribute capsules effectively, that capsules have been stored properly and remain active, and that children ingest the supplements.

Subgroup analyses in this review were limited by the available data, and meta-analyses of group level data to explore individual level moderators should be interpreted with caution. Further analyses with individual patient data from randomised controlled trials and observational studies would be more informative.

Implications for policy

Vitamin A deficiency is a common condition that contributes to illness, blindness, and death; supplements can reduce these problems for children aged under 5 in low and middle income countries. National and regional supplementation programmes could be among the world's most cost effective public health interventions.[97] If the risk of death for 190 million children deficient in vitamin A were reduced by 24%, estimates from

2008 suggest that over 600 000 lives could be saved each year[98] and 20 million disability adjusted life years would be gained.[99]

Although vitamin A supplementation has been available in many countries for over a decade, direct evidence for its contribution to reducing child mortality is not available. Many countries have experienced significant reductions in child mortality,[5 100] and vitamin A supplementation programmes might have contributed to these declines.

Supplementation responds to an immediate need, but, in the long term, good nutrition requires reliable access to various fresh foods. Fortification, food distribution programmes, and horticultural developments might provide more permanent solutions. For example, growers could increase access to agricultural products like the orange fleshed sweet potato.[101] Vitamin A could be added to rice, though fortification programmes must minimise risk of toxicity. Until such long term solutions are in place, supplementation should continue. As access to vitamin A increases, it will be important to continue to identify at risk groups and to deliver supplements to them.

Our review suggests potential pathways through which vitamin A supplementation reduces mortality. Increased vaccination against measles and other diseases will reduce the effect of vitamin A supplementation if its primary effect is to prevent infection; widespread supplementation, however, will remain important because vitamin A affects other systems—for example, supplementation can prevent blindness.

Based on these results, we strongly recommend vitamin A supplementation for children aged under 5 in areas at risk of vitamin A deficiency. Despite widespread efforts, vitamin A programmes do not reach all children who could benefit.[15] Universal distribution could be achieved in several ways. Vitamin A supplementation can be provided when children receive other services like vaccinations,[102] and it can be provided on a large scale. Child health days or other strategies might be used to increase awareness,[103] and vitamin A uptake could be increased through national food programmes[104] or through delivery by community health workers.[105]

Implications for future research

The effectiveness of vitamin A supplementation is so well established that further placebo controlled studies are not required. Nevertheless, this review does not identify the most effective dose or frequency of delivery. Large doses in the included studies were effective. Smaller, more frequent doses might produce larger reductions in mortality; more complex and burdensome programmes, however, could result in lower coverage. We suggest that policymakers consider including trials of dose and frequency in vitamin A distribution programmes. Other studies might investigate different delivery channels, including food supplementation, horticultural innovations, improved access to food, or psychosocial programmes to increase uptake of foods rich in vitamin A.

Conclusions

Our review reaffirms compelling evidence that vitamin A supplements can prevent death and illness in children aged 6 months to 5 years. Supplements are inexpensive and have few side effects. Further trials are needed to determine the most effective dose and frequency of supplementation, but placebo controlled trials would be unethical. Policymakers should continue working to provide supplements for all children at risk of deficiency, particularly those in low and middle income countries.

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Data sharing: Detailed tables and effects for each study are available from our Cochrane Review (www.cochrane.org).

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What is already known on this topic

Vitamin A is an essential nutrient; it must be obtained through diet

In low and middle income countries, many people (especially children) do not eat enough vitamin A

Vitamin A deficiency is related to vision problems and increased susceptibility to infectious disease and death

WHO recommends vitamin A supplements for children, pregnant women, and breastfeeding mothers

What this study adds

There have been 43 trials of vitamin A for children aged 6 months to 5 years old, including about 215 633 children

In low and middle income countries, vitamin A supplementation is associated with a 24% reduction in mortality

Vitamin A supplementation might reduce mortality by preventing measles and diarrhoea; it also prevents blindness

The evidence for vitamin A is compelling and clear; further trials comparing vitamin A with placebo would be unethical

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Tables

Table 1| Characteristics of included studies in review of effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

Study	Country	Age (months)	No of participants	Follow-up (months)	Dose (1000 IU)	Frequency*
Agarwal 1995[28]	India	0-72	17 778†	15, 27	50 at 1-6 m; 100 at >6 m	0, 4, 8, 12 m
Arya 2000[29]	India	9-12	256	24 hour	100	1 dose
Bahl 1999[30]	India	6-9	618	4	100	1 dose
Barreto 1994[31]	Brazil	6-48	1240	12	100 at <12 m; 200 ≥12 m	0, 4, 8, 12 m
Benn 1997[32]	Guinea Bissau	6-9	462	12	100	1 dose
Biswas 1994[33]	India	12-71	180	6	200	1 dose
Cheng 1993[34]	China	6-36	198	12	100 at <12 m; 200 ≥12 m	4, 10 m
Cherian 2003[35]	India	6-9	395	6	100	1 dose
Chowdhury 2002[8,36]	India	<120	1520	15	50 at <6 m; 100 at 6-12 m; 200 at >12m	0, 5, 10 m
Daulaire 1992‡[37]	Nepal	1-59	7197†	5	50 at <6 m; 100 at 6-12 m; 200 at ≥12 m	1 dose
Dibley 1996[38]	Indonesia	6-47	1405	24	103 at <12 m; 206 at ≥12 m	0, 4, 8, 12, 16, 20, 24 m
Donnen 1998‡[39]	Congo (Zaire)	0-72	235	12	100 at <12 m; 200 at ≥12 m	0, 6, 12 m
Florentino 1990[40]	Philippines	12-72	2471	1 week	100, 200§	1 dose
Herrera 1992[41]	Sudan	9-72	28 753	18	200	0, 6, 12, 18 m
Kartasamita 1995[42]	Indonesia	12-54	267	12	200	0, 6, 12 m
Lima 2010‡[43]	Brazil	2-108	79	36	100 at <12 m; 200 at ≥12 m	0, 4, 8m
Lin 2008[45]	China	24-84	70	3	100	0, 0.5, 1, 1.5, 2, 2,5, 3 m
Lin 2009[44]	China	6-84	86	3	100	0, 1, 2, 3 m
Long 2006[46]	Mexico	6-15	786	12	20 at <12 m; 45 at ≥12 m	0, 2, 4, 6, 8, 10, 12 m
Long 2007[47]	Mexico	6-15	195	12	20 at <12 m; 45 at ≥12 m	0, 2, 4, 6, 8, 10, 12 m
Pant 1996‡[48]	Nepal	6-120	25 301†	24	100 at 6-12 m; 200 at ≥12 m	1 dose
Pinnock 1986[49]	Australia	1-48	147	20 weeks	3.9	3/week for 20 weeks
Pinnock 1988[50]	Australia	0-24	206	12	14	Weekly for 1 year
Rahman 2001[51]	Bangladesh	12-35	800	6	200	1 dose
Rahmathullah 1990[52]	India	6-60	15 419†	12	8.333	Weekly for 1 year
Ramakrishnan 1995[53]	India	6-36	583	12	100 at <12 m; 200 at ≥12 m	0, 4, 8, 12 m
Ranjini 2001[54]	India	12-60	61	6	200	1 dose
Reddy 1986[55]	India	12-60	487	12	200	1 dose
Ross 1993 health[56]	Ghana	6-59	1455	12	100 at 6-12 m; 200 at ≥12 m	0, 4, 8, 12 m
Ross 1993 survival[56]	Ghana	6-90	21 906†	12	100 at 6-12 m; 200 at ≥12 m	0, 4, 8, 12, 16, 20, 24 m
Semba 1992[57]	Indonesia	36-72	236	1	200	1 dose
Semba 1995[58]	Indonesia	6	336	6	100	1 dose
Sempertegui 1999[59]	Ecuador	6-36	400	9	10	Weekly for 40 w
Shankar 1999[60]	Papa New Guinea	6-60	480	13	100 at <12 m; 200 at ≥12 m	0, 4, 8, 12 m
Sinha 1976[61]	India	2-54	306	12	200	0, 4, 8, 12 m
Smith 1999[62]	Belize	26-66	51	6	10	Weekly for 26 w
Sommer 1986‡[63]	Indonesia	0-71	29 236†	9-13	200	0, 6 m
Stabell 1995[64]	Guinea Bissau	6	68	30	100	0, 3 m
Stansfield 1993[65]	Haiti	6-83	13 651	12	100 at 6-11 m; 200 at ≥12 m	0, 4, 8 m
van Agtmaal 1988[66]‡	Thailand	37	30	4	200	1 dose
Venkatarao 1996[67]	India	6	612	6	200	1 dose
Vijyagharvan 1990[68]	India	12-60	15 775†	12	200	0, 6, 12 m
West 1991[69]	Nepal	6-72	28 630†	16	100 at 6-11 m; 200 at ≥12 m	0, 4, 8, 12 m

Table 1 (continued)

Study	Country	Age (months)	No of participants	Follow-up (months)	Dose (1000 IU)	Frequency*

*Several studies did not explicitly state number of doses received. We assumed that children received doses at baseline and end point—for example, "every 4 months for 1 year" appears as 0, 4, 8, and 12 months.

†Cluster randomised.

‡Compared vitamin A with treatment as usual (control group did not receive placebo).

§Two eligible intervention groups combined for analysis.

¶Mean.

Table 2| Subgroup analyses for all cause mortality at longest follow-up in studies of effect of vitamin A supplementation in children aged under 5

Subgroup (test for difference)	All trials	No (%) in primary analysis		Fixed effect rate ratio (95% CI)	Heterogeneity: I^2 (%); Q
		Trials	Participants		
All studies[28-69]	43	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)
Location (P=0.12):					
All	—	16 (37)	194 483 (90)	—	—
Africa[33 39 41 56 64]	6	5 (12)	52 811 (25)	0.85 (0.73 to 0.98)	59%; 9.81 (P=0.04)
Australia[49 50]	2	0	0	—	—
Asia[28-30 33-38 40 42 44 45 48 51-55 57 58 60 61 63 66-69]	28	10 (23)	140 432 (65)	0.69 (0.61 to 0.79)	40%; 15.00 (P=0.09)
Latin America[31 43 46 47 59 62 65]	7	1 (2)	1240 (<1)	1.00 (0.14 to 7.08)	—
Setting (NA):					
All	—	16 (37)	194 483 (90)	—	—
(Peri)urban [29 30 32 33 35 36 42 43 45-47 49-51 54 59]	16	2 (5)	1982 (<1)	NA	NA
Rural[28 31 34 37-41 44 48 52 53 55-58 60-69]	27	14 (33)	192 501 (89)	NA	NA
Dose (P=0.02):					
All	—	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)
WHO (single)[29 30 32 33 36 37 40 48 51 54 55 57 58 66 67]	15	4 (9)	33 572 (16)	0.66 (0.52 to 0.83)	0%; 2.15 (P=0.54)
WHO (4-6m)[28 31 34 36 38 39 41-47 53 56 60 61 63-65 68 69]	18	11 (26)	147 933 (69)	0.81 (0.72 to 0.90)	48%; 19.17 (P=0.04)
More frequent[44-47 49 50 52 59 62 64]	10	1 (2)	15 419 (7)	0.46 (0.30 to 0.71)	—
Age* (P=0.46):					
All	—	5 (12)	61 544 (29)	0.66 (0.56 to 0.77)	0.0%; 6.77 (P=0.45)
6-12 months[28-32 34-39 41 44 44 46-50 52 53 56 58-61 64-65 67 69]	32	4 (9)	4739 (2)	0.59 (0.43 to 0.82)	15%; 3.51 (P=0.32)
12-60 months[28 31 33 34 36-57 59-66 68 69]	37	4 (9)	56 805 (26)	0.68 (0.57 to 0.81)	0.0%; 2.72 (P=0.44)
Sex† (P=0.89):					
All	—	5 (12)	85 568 (40)	0.80 (0.70 to 0.91)	34%; 10.69 (P=0.15)
Males[28-69]	43	5 (12)	43 567 (20)	0.80 (0.66 to 0.97)	62%; 7.79 (P=0.05)
Females[28-69]	43	5 (12)	42 001 (20)	0.79 (0.65 to 0.95)	0.0%; 2.87 (P=0.41)
With DEVTA[28-69 79]	44	17 (39)	1 194 483 (98)	0.88 (0.84 to 0.94)	64%; 44.31 (P<0.001)

NA=not available; planned analysis not conducted; DEVTA=deworming and vitamin A trial.

*For primary outcome, trials reported mortality for children <12 months,[33] children >12 months,[64] or both.[38 53 70]

†One trial reporting data by sex reported no events,[46] and four trials appear in both analysis.[38 42 64 70]

Table 3| Summary of pooled analyses for mortality and illness in studies of effect of vitamin A supplementation in children aged under 5

Outcome	No (%) of trials (n=43)	No (%) of participants (n=215 633)	Rate ratio (95% CI), fixed effect	Heterogeneity: I^2; χ^2	Follow-up (weeks)	Quality of evidence (GRADE)
Primary outcome						
All cause mortality[31 32 36-39 41 45 48 52 56 63 68 69 107]	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)	12-96	High
Cause specific mortality						
Diarrhoea[28 36 37 41 52 56 67]	7 (16)	90 951 (42)	0.72 (0.57 to 0.91)	2%; 6.12 (P=0.41)	48-104	Moderate
Measles[28 37 41 52 56]	5 (12)	88 261 (41)	0.80 (0.51 to 1.24)	0%; 0.40 (P=0.98)	52-104	Moderate
Meningitis[28 36 56]	3 (7)	41 204 (19)	0.57 (0.17 to 1.88)	0%; 0.75 (P=0.69)	48-108	Low
LRTI[28 36 37 41 52 56 67]	7 (16)	90 951 (42)	0.78 (0.54 to 1.14)	14%; 7.00 (P=0.32)	48-104	Low
Illness						
Diarrhoea:						
Incidence[29 31 33 34 36 38 40 41 47 53 59 60 67]	13 (30)	37 710(17)	0.85 (0.82 to 0.87)	95%; 217.99 (P<0.01)	24-60	Low
Prevalence[35 47 65]	2 (5)	14 437 (7)	1.08 (1.05 to 1.12)	87%; 15.76 (P<0.01)	48	Very low
Malaria:						
Incidence[60]	1 (2)	480 (<1)	0.73 (0.60 to 0.88)	NA	52	Very low
Prevalence[56]	2 (5)	23 361 (11)	0.72 (0.41 to 1.28)	0%; 0.02 (P=0.88)	48	Moderate
Measles:						
Incidence[30-32 36 41 58]	6 (14)	19 566 (9)	0.50 (0.37 to 0.67)	0%; 0.55 (0.99);	16-78	High
Prevalence	0 (0)	0 (0)	NA	NA	NA	NA
LRTI:						
Incidence[31 34 36 42 47 59 67]	7 (16)	18 179 (8)	1.14 (0.95 to 1.37)	22%; 7.66 (0.26)	24-60	Very low
Prevalence[46]	1 (2)	786 (0.4)	0.46 (0.21 to 1.03)	NA	48	Very low

LRTI=lower respiratory tract infection.

Table 4| Summary of pooled analyses for admission to hospital, vision, vitamin A deficiency, and adverse events in studies of effect of vitamin A supplementation in children aged under 5

Outcome	No (%) of trials (n=43)	No (%) of participants (n=215 633)	Rate ratio (95% CI), fixed effect	Heterogeneity: I^2; χ^2	Follow-up (weeks)	Quality of evidence (GRADE)
Admission to hospital						
All cause[56]	1 (2)	1185 (0.5)	0.64 (0.40 to 1.02)	NA	48	Very low
Diarrhoea[34]	1 (2)	198 (<1)	0.25 (0.01 to 6.11)	NA	48	Very low
LRTI[34]	1 (2)	198 (<1)	0.11 (0.01 to 2.06)	NA	48	Very low
Vision						
Bitot's spots:						
Incidence[41]	1 (2)	28 753 (13)	0.93 (0.76 to 1.14)	NA	72	Very low
Prevalence[48 61 63 69]	4 (9)	63 278 (29)	0.45 (0.33 to 0.61)	64%; 8.25 (P=0.04)	36-96	Moderate
Night blindness:						
Incidence[41]	1 (2)	28 753 (13)	0.53 (0.28 to 0.99)	NA	72	Low
Prevalence[63 69]	2 (5)	22 972 (11)	0.32 (0.21 to 0.50)	0%; 0.19 (P=0.66)	52-68	Moderate
Xerophthalmia:						
Incidence[31 41 69]	3 (7)	58 623 (27)	0.85 (0.70 to 1.03)	63%; 2.69 (P=0.10)	48-72	Low
Prevalence[31 63 69]	2 (5)	57 866 (27)	0.31 (0.22 to 0.45)	0%; 0.22 (P=0.64)	36-64	Moderate
Vitamin A deficiency						
Number deficient[38 54 56 60]	4 (9)	2262 (1)	0.71 (0.65 to 0.78)	78%; 13.58 (P<0.01)	24-96	High
Serum concentration[34 38 42 44 49 50 54-57 59 60]	13 (30)	6623 (3)	g=0.31 (0.26 to 0.36)	95%; 270.23 (P<0.01)	4-96	Moderate
Adverse events						
Vomiting[29 40 61]	3 (7)	2994 (1)	2.75 (1.81 to 4.19)	21%; 2.53 (P=0.28)	48 hours	Very low
Bulging fontanelle[29 30 64]	3 (7)	885 (<1)	5.00 (0.24 to 103.72)	NA	48 hours	Low

NA=not available; LRTI=lower respiratory tract infection.

Figures

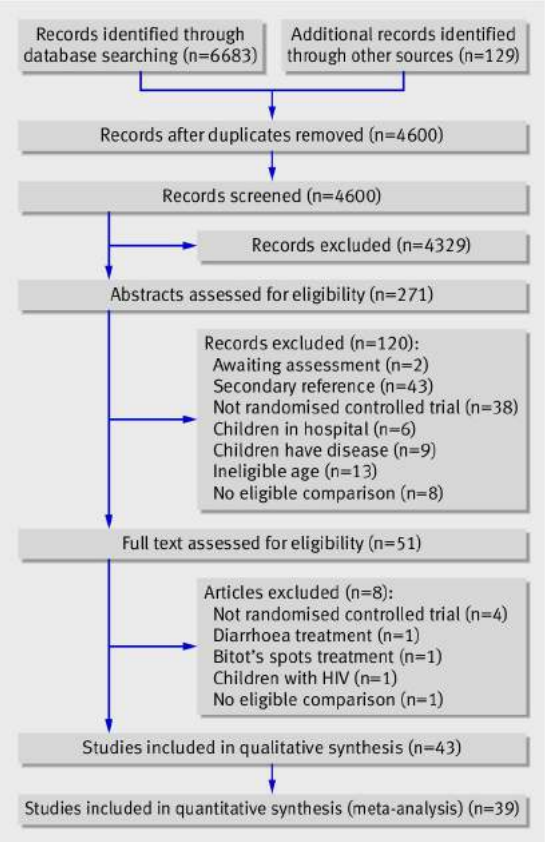

Fig 1 Identification of studies to include in review of effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

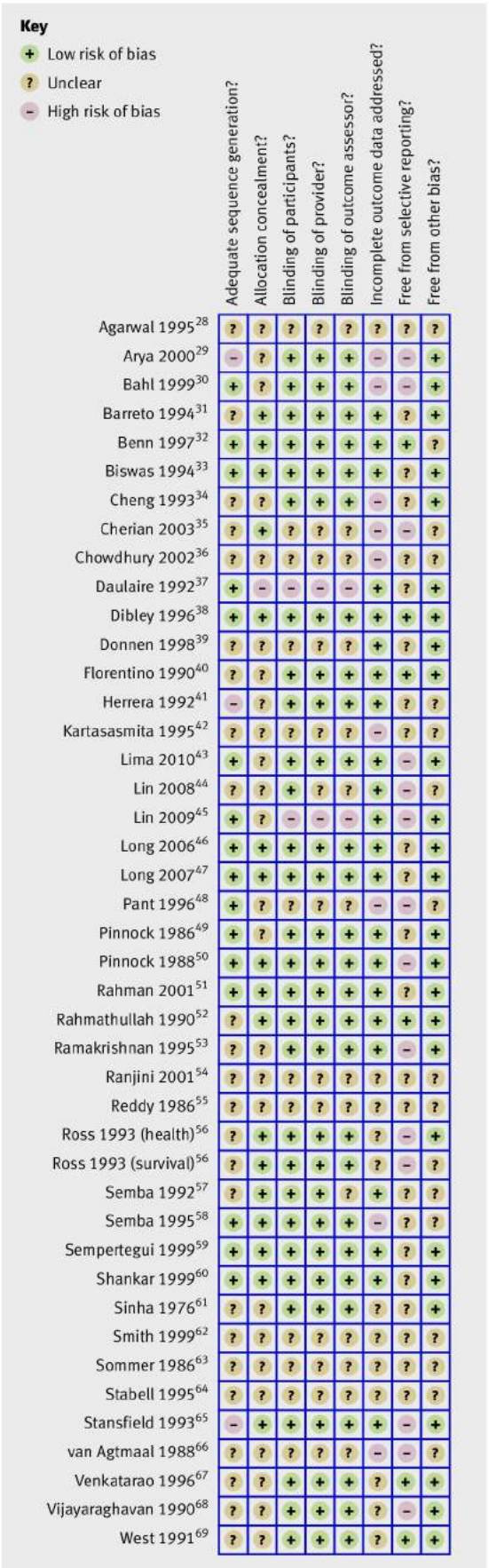

Fig 2 Assessment of risk of bias in studies on effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

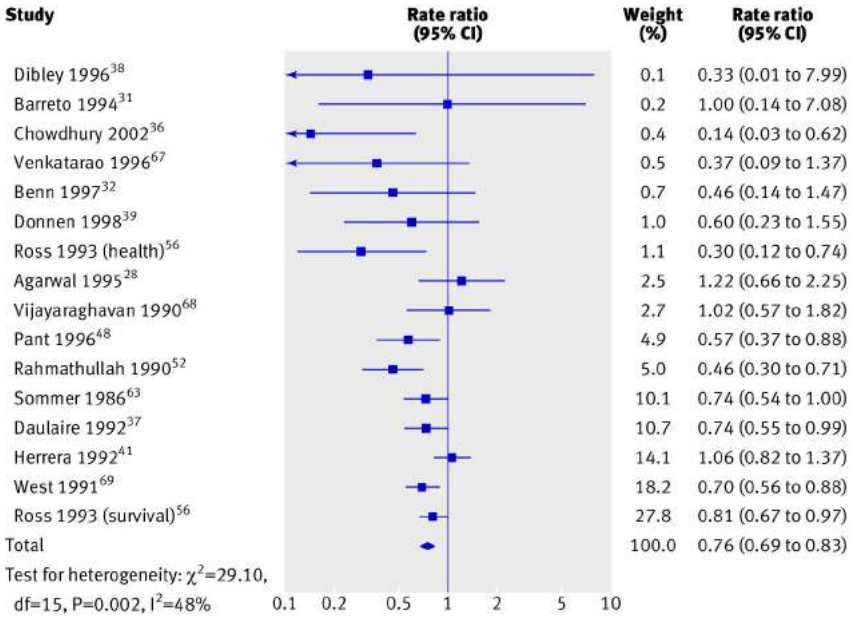

Fig 3 All cause mortality in studies on effect of vitamin A supplementation in children aged under 5

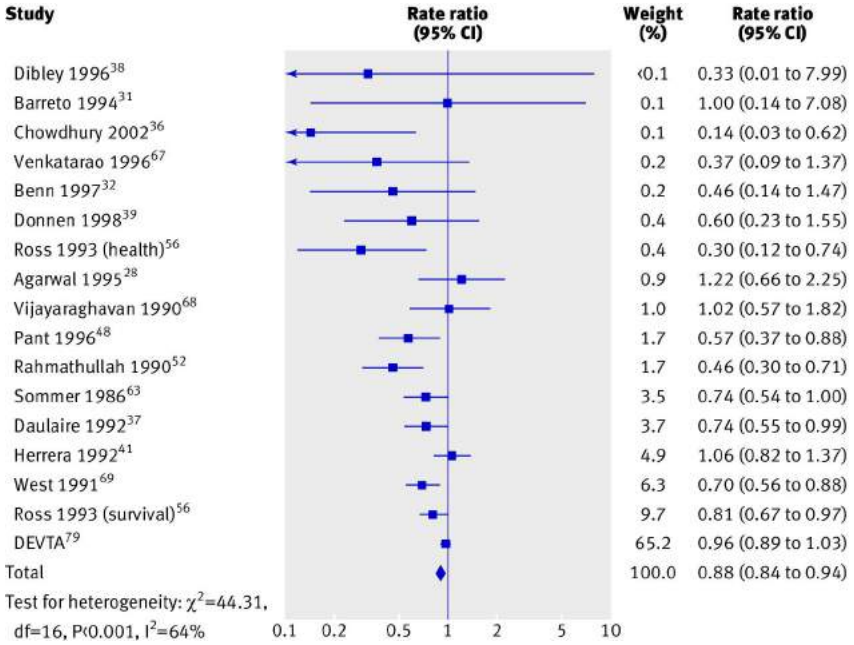

Fig 4 All cause mortality sensitivity analysis in studies on effect of vitamin A supplementation in children aged under 5, including deworming and vitamin A (DEVTA) trial

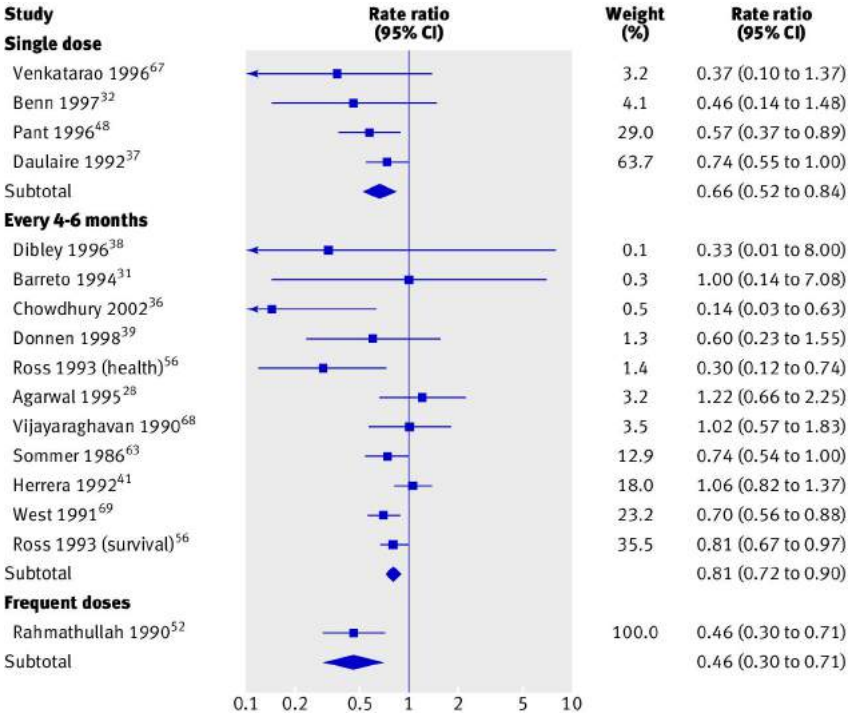

Fig 5 All cause mortality by dose in studies on effect of vitamin A supplementation in children aged under 5

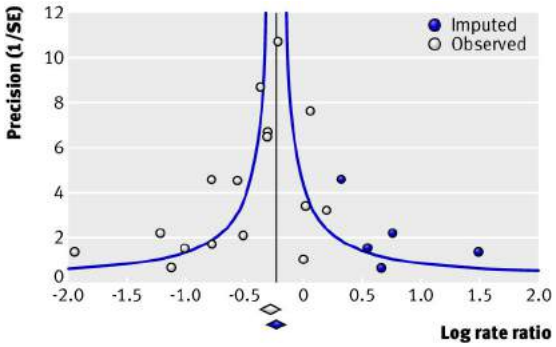

Fig 6 Mortality funnel plot with trim and fill in studies on effect of vitamin A supplementation in children aged under 5. Observed=included studies. Imputed=observed effects trimmed to make funnel plot symmetrical, opposite effects imputed, trimmed studies and imputed effects replaced

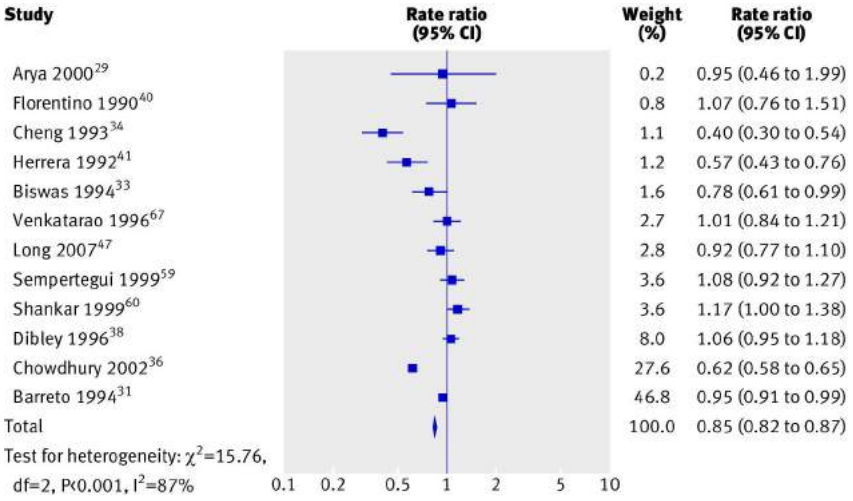

Fig 7 Incidence of diarrhoea in studies on effect of vitamin A supplementation in children aged under 5

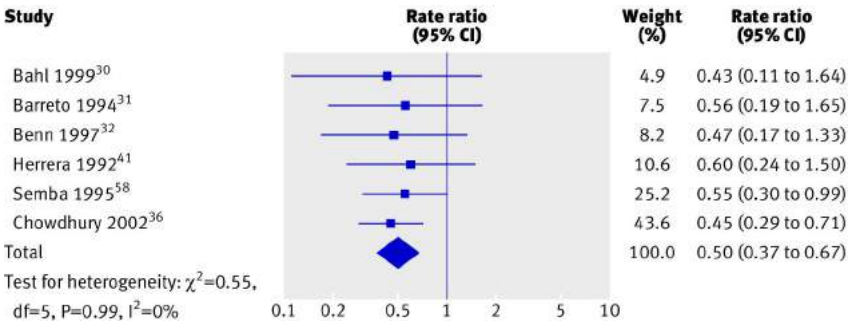

Fig 8 Incidence of measles in studies on effect of vitamin A supplementation in children aged under 5

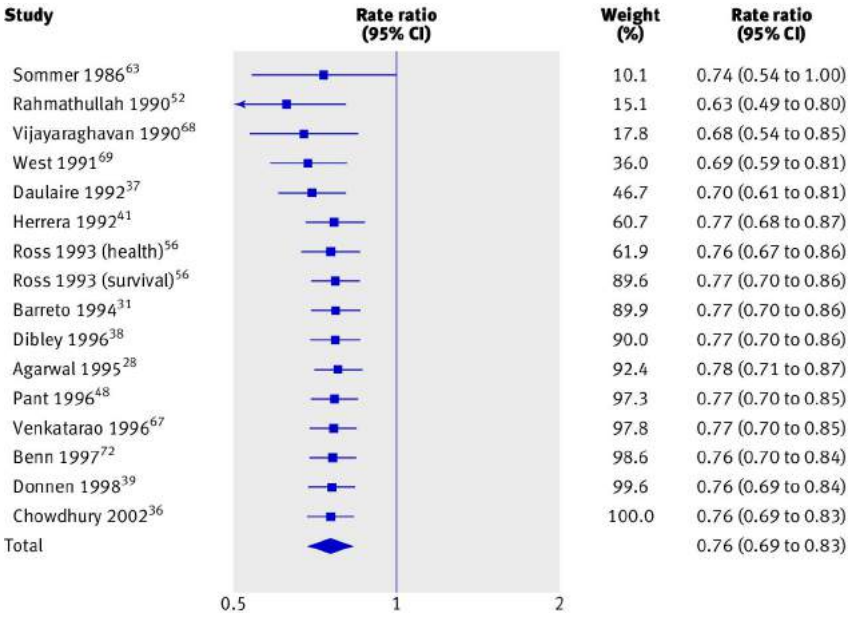

Fig 9 All cause mortality cumulative meta-analysis in studies on effect of vitamin A supplementation in children aged under 5

Format: Abstract

Full text links

ELSEVIER FULL-TEXT ARTICLE

Antiviral Res. 2008 Oct;80(1):45-53. doi: 10.1016/j.antiviral.2008.04.003. Epub 2008 May 19.

Retinoids inhibit measles virus in vitro via nuclear retinoid receptor signaling pathways.

Trottier C[1], Chabot S, Mann KK, Colombo M, Chatterjee A, Miller WH Jr, Ward BJ.

Author information

Abstract

Measles virus (MV) infects 30 million children every year, resulting in more than half a million deaths. Vitamin A (retinol) treatment of acute measles can reduce measles-associated mortality by 50-80%. We sought to determine whether or not retinoids can act directly to limit MV output from infected cells. Physiologic concentrations of retinol were found to inhibit MV output in PBMC and a range of cell lines of epithelial and endothelial origin (40-50%). Near complete inhibition of viral output was achieved in some cells/lines treated with all-trans retinoic acid (ATRA) and 9-cis RA (9cRA). Important attenuation of the anti-MV effect of retinoids in R4 cells, a subclone of a retinoid-responsive cell line (NB4) deficient in RAR signaling, demonstrates that this effect is mediated at least in part by nuclear retinoid receptor signaling pathways. Inhibition of MV replication could not be fully explained as a result of retinoid effects on cell differentiation, proliferation or viability, particularly at low retinoid concentrations (1-10nM). These data provide the first evidence that retinoids can directly inhibit MV in vitro, and raise the possibility that retinoids may have similar actions in vivo.

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[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

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Full text links

FASEB J. 2009 Sep;23(9):3203-12. doi: 10.1096/fj.09-129288. Epub 2009 May 15.

Retinoids inhibit measles virus through a type I IFN-dependent bystander effect.

Trottier C[1], Colombo M, Mann KK, Miller WH Jr, Ward BJ.

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Abstract

Measles-associated mortality can be decreased in response to treatment with vitamin A. Our goal was to understand the mechanism by which vitamin A and other retinoids reduce measles virus (MeV) replication in vitro. MeV is known to inhibit type I interferon (IFN) signaling, and retinoids are increasingly implicated in modulating innate immunity. Type I IFN blocking antibodies abrogated the inhibitory effects of all-trans retinoic acid (ATRA) on MeV replication (EC(50) of ATRA: 3.17 x 10(-8) M). IFN-stimulated genes (ISGs) are up-regulated by ATRA in MeV-infected U937 cell cultures starting at 12 h and reaching a plateau at 24 h postinfection when compared to either treatment or infection alone. We found that this increased gene expression occurs in uninfected cells by using a transwell system where the uninfected cells were separated from infected cells by a membrane with 0.02-muM pores. Uninfected bystander cells from the ATRA-treated transwells did not support substantial viral replication when subsequently infected with MeV. In the absence of ATRA, the cells from the uninfected chamber did not up-regulate ISG expression and were not protected from subsequent challenge with virus. These results demonstrate that retinoids inhibit MeV replication by up-regulating elements of the innate immune response in uninfected bystander cells, making them refractory to productive infection during subsequent rounds of viral replication.

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Poliomyelitis

Epidemiology and Prevention of Vaccine-Preventable Diseases
The Pink Book: Course Textbook - 12th Edition (April 2011)

On this Page

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The words polio (grey) and myelon (marrow, indicating the spinal cord) are derived from the Greek. It is the effect of poliomyelitis virus on the spinal cord that leads to the classic manifestation of paralysis.

Poliomyelitis

- First described by Michael Underwood in 1789
- First outbreak described in U.S. in 1843
- More than 21,000 paralytic cases reported in the U.S. in 1952
- Global eradication within next decade

Records from antiquity mention crippling diseases compatible with poliomyelitis. Michael Underwood first described a debility of the lower extremities in children that was recognizable as poliomyelitis in England in 1789. The first outbreaks in Europe were reported in the early 19th century, and outbreaks were first reported in the United States in 1843. For the next hundred years, epidemics of polio were reported from developed countries in the Northern Hemisphere each summer and fall. These epidemics became increasingly severe, and the average age of persons affected rose. The increasingly older age of persons with primary infection increased both the disease severity and number of deaths from polio. Polio reached a peak in the United States in 1952, with more than 21,000 paralytic cases. However, following introduction of effective vaccines, polio incidence declined rapidly. The last case of wild-virus polio acquired in the United States was in 1979, and global polio eradication may be achieved within the next decade.

Poliovirus

Poliovirus is a member of the enterovirus subgroup, family Picornaviridae. Enteroviruses are transient inhabitants of the gastrointestinal tract, and are stable at acid pH. Picornaviruses are small, ether-insensitive viruses with an RNA genome.

There are three poliovirus serotypes (P1, P2, and P3). There is minimal heterotypic immunity between the three serotypes. That is, immunity to one serotype does not produce significant immunity to the other serotypes.

Poliovirus

- Enterovirus (RNA)
- Three serotypes: 1, 2, 3
- Minimal heterotypic immunity between serotypes
- Rapidly inactivated by heat, formaldehyde, chlorine, ultraviolet light

The poliovirus is rapidly inactivated by heat, formaldehyde, chlorine, and ultraviolet light.

Pathogenesis

The virus enters through the mouth, and primary multiplication of the virus occurs at the site of implantation in the pharynx and gastrointestinal tract. The virus is usually present in the throat and in the stool before the onset of illness. One week after onset there is less virus in the throat, but virus continues to be excreted in the stool for several weeks. The virus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the central nervous system.

Poliomyelitis Pathogenesis

- Entry into mouth
- Replication in pharynx, GI tract, local lymphatics
- Hematologic spread to lymphatics and central nervous system

Replication of poliovirus in motor neurons of the anterior horn and brain stem results in cell destruction and causes the typical manifestations of poliomyelitis.

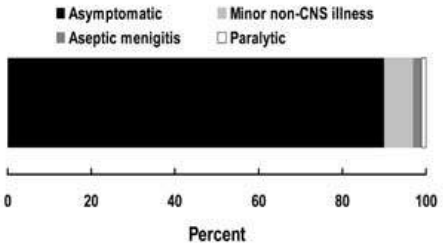
- Viral spread along nerve fibers
- Destruction of motor neurons

Clinical Features

The incubation period for poliomyelitis is commonly 6 to 20 days with a range of 3 to 35 days.

The response to poliovirus infection is highly variable and has been categorized on the basis of the severity of clinical presentation.

Outcomes of poliovirus infection



Up to 95% of all polio infections are inapparent or asymptomatic. Estimates of the ratio of inapparent to paralytic illness vary from 50:1 to 1,000:1 (usually 200:1). Infected persons without symptoms shed virus in the stool and are able to transmit the virus to others.

Approximately 4%–8% of polio infections consist of a minor, nonspecific illness without clinical or laboratory evidence of central nervous system invasion. This clinical presentation is known as abortive poliomyelitis, and is characterized by complete recovery in less than a week. Three syndromes observed with this form of poliovirus infection are upper respiratory tract infection (sore throat and fever), gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhea), and influenza-like illness. These syndromes are indistinguishable from other viral illnesses.

Nonparalytic aseptic meningitis (symptoms of stiffness of the neck, back, and/or legs), usually following several days after a prodrome similar to that of minor illness, occurs in 1%–2% of polio infections. Increased or abnormal sensations can also occur. Typically these symptoms will last from 2 to 10 days, followed by complete recovery.

Fewer than 1% of all polio infections result in flaccid paralysis. Paralytic symptoms generally begin 1 to 10 days after prodromal symptoms and progress for 2 to 3 days. Generally, no further paralysis occurs after the temperature returns to normal. The prodrome may be biphasic, especially in children, with initial minor symptoms separated by a 1- to 7-day period from more major symptoms. Additional prodromal signs and symptoms can include a loss of superficial reflexes, initially increased deep tendon reflexes and severe muscle aches and spasms in the limbs or back. The illness progresses to flaccid paralysis with diminished deep tendon reflexes, reaches a plateau without change for days to weeks, and is usually asymmetrical. Strength then begins to return. Patients do not experience sensory losses or changes in cognition.

Many persons with paralytic poliomyelitis recover completely and, in most, muscle function returns to some degree. Weakness or paralysis still present 12 months after onset is usually permanent.

Paralytic polio is classified into three types, depending on the level of involvement. Spinal polio is most common, and during 1969–1979, accounted for 79% of paralytic cases. It is characterized by asymmetric paralysis that most often involves the legs. Bulbar polio leads to weakness of muscles innervated by cranial nerves and accounted for 2% of cases during this period. Bulbospinal polio, a combination of bulbar and spinal paralysis, accounted for 19% of cases.

The death-to-case ratio for paralytic polio is generally 2%–5% among children and up to 15%–30% for adults (depending on age). It increases to 25%–75% with bulbar involvement.

*Less than 1% of all polio infections result in "paralytic polio". Of those cases, 2–5% result in death among children.

Laboratory Diagnosis

Viral Isolation

Poliovirus may be recovered from the stool or pharynx of a person with poliomyelitis. Isolation of virus from the cerebrospinal fluid (CSF) is diagnostic, but is rarely accomplished.

If poliovirus is isolated from a person with acute flaccid paralysis, it must be tested further, using oligonucleotide mapping (fingerprinting) or genomic sequencing, to deter-mine if the virus is “wild type” (that is, the virus that causes polio disease) or vaccine type (virus that could derive from a vaccine strain).

Serology

Neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized; therefore, a fourfold rise in antibody titer may not be demonstrated.

Cerebrospinal Fluid

In poliovirus infection, the CSF usually contains an increased number of white blood cells (10–200 cells/mm3, primarily lymphocytes) and a mildly elevated protein (40–50 mg/100 mL).

Epidemiology

Occurrence

At one time poliovirus infection occurred throughout the world. Transmission of wild poliovirus was interrupted in the United States in 1979, or possibly earlier. A polio eradication program conducted by the Pan American Health Organization led to elimination of polio in the Western Hemisphere in 1991. The Global Polio Eradication Program has dramatically reduced

poliovirus transmission throughout the world. In 2009, only 1,579 confirmed cases of polio were reported globally and polio was endemic in four countries.

Reservoir

Humans are the only known reservoir of poliovirus, which is transmitted most frequently by persons with inapparent infections. There is no asymptomatic carrier state except in immune deficient persons.

Transmission

Person-to-person spread of poliovirus via the fecal-oral route is the most important route of transmission, although the oral-oral route may account for some cases.

Temporal Pattern

Poliovirus infection typically peaks in the summer months in temperate climates. There is no seasonal pattern in tropical climates.

Communicability

Poliovirus is highly infectious, with seroconversion rates among susceptible household contacts of children nearly 100%, and greater than 90% among susceptible household contacts of adults. Persons infected with poliovirus are most infectious from 7 to 10 days before and after the onset of symptoms, but poliovirus may be present in the stool from 3 to 6 weeks.

Poliovirus Epidemiology

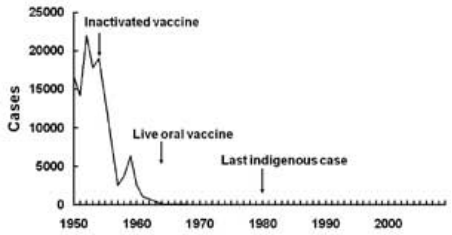
- Reservoir - Human
- Transmission - Fecal-oral
  Oral-oral possible
- Communicability - 7-10 days before onset
  Virus present in stool 3 to 6 weeks

Secular Trends in the United States

Before the 18th century, polioviruses probably circulated widely. Initial infections with at least one type probably occurred in early infancy, when transplacentally acquired maternal antibodies were high. Exposure throughout life probably provided continual boosting of immunity, and paralytic infections were probably rare. (This view has been recently challenged based on data from lameness studies in developing countries).

In the immediate prevaccine era, improved sanitation allowed less frequent exposure and increased the age of primary infection. Boosting of immunity from natural exposure became more infrequent and the number of susceptible persons accumulated, ultimately resulting in the occurrence of epidemics, with 13,000 to 20,000 para-lytic cases reported annually.

Poliomyelitis - United States, 1950-2009



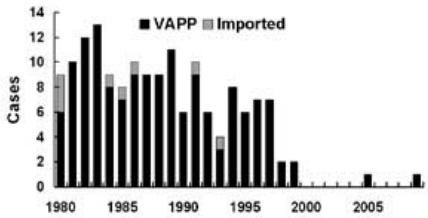
*See article "The Truth About the Polio Vaccines" under Incentives, Marketing, and Misconduct.

In the early vaccine era, the incidence dramatically decreased after the introduction of inactivated polio vaccine (IPV) in 1955. The decline continued following oral polio vaccine (OPV) introduction in 1961. In 1960, a total of 2,525 paralytic cases were reported, compared with 61 in 1965.

The last cases of paralytic poliomyelitis caused by endemic transmission of wild virus in the United States were in 1979, when an outbreak occurred among the Amish in several Midwest states. The virus was imported from the Netherlands.

From 1980 through 1999, a total of 152 confirmed cases of paralytic poliomyelitis were reported, an average of 8 cases per year. Six cases were acquired outside the United States and imported. The last imported case was reported in 1993. Two cases were classified as indeterminant (no poliovirus isolated from samples obtained from the patients, and patients had no history of recent vaccination or direct contact with a vaccine recipient). The remaining 144 (95%) cases were vaccine-associated paralytic polio (VAPP) caused by live oral polio vaccine.

Poliomyelitis - United States, 1980-2009



In order to eliminate VAPP from the United States, ACIP recommended in 2000 that IPV be used exclusively in the United States. The last case of VAPP acquired in the United States was reported in 1999. In 2005, an unvaccinated U.S. resident was infected with polio vaccine virus in Costa Rica and subsequently developed VAPP. A second case of VAPP from vaccine-derived poliovirus was reported in 2009. Also in 2005, several asymptomatic infections with a vaccine-derived poliovirus were detected in unvaccinated children in Minnesota. The source of the vaccine virus has not been determined, but it appeared to have been circulating among humans for at least 2 years based on genetic changes in the virus. No VAPP has been reported from this virus.

Poliovirus Vaccines

Inactivated poliovirus vaccine (IPV) was licensed in 1955 and was used extensively from that time until the early 1960s. In 1961, type 1 and 2 monovalent oral poliovirus vaccine (MOPV) was licensed, and in 1962, type 3 MOPV was licensed. In 1963,

Poliovirus Vaccine

- 1955 - Inactivated vaccine
- 1961 - Types 1 and 2 monovalent OPV

trivalent OPV was licensed and largely replaced IPV use. Trivalent OPV was the vaccine of choice in the United States and most other countries of the world after its introduction in 1963. An enhanced-potency IPV was licensed in November 1987 and first became available in 1988. Use of OPV was discontinued in the United States in 2000.

- 1962 - Type 3 monovalent OPV
- 1963 - Trivalent OPV
- 1987 - Enhanced-potency IPV (IPV)

Characteristics

Inactivated poliovirus vaccine

Two enhanced forms of inactivated poliovirus vaccine are currently licensed in the U.S., but only one vaccine (IPOL, sanofi pasteur) is actually distributed. This vaccine contains all three serotypes of polio vaccine virus. The viruses are grown in a type of monkey kidney tissue culture (Vero cell line) and inactivated with formaldehyde. The vaccine contains 2-phenoxyethanol as a preservative, and trace amounts of neomycin, streptomycin, and polymyxin B. It is supplied in a single-dose prefilled syringe and should be administered by either subcutaneous or intramuscular injection.

Inactivated Polio Vaccine

- Contains 3 serotypes of vaccine virus
- Grown on monkey kidney (Vero) cells
- Inactivated with formaldehyde
- Contains 2-phenoxyethanol, neomycin, streptomycin, polymyxin B

Oral poliovirus vaccine

Trivalent OPV contains live attenuated strains of all three serotypes of poliovirus in a 10:1:3 ratio. The vaccine viruses are grown in monkey kidney tissue culture (Vero cell line). The vaccine is supplied as a single 0.5-mL dose in a plastic dispenser. The vaccine contains trace amounts of neomycin and streptomycin. OPV does not contain a preservative.

Oral Polio Vaccine

- Contains 3 serotypes of vaccine virus
- Grown on monkey kidney (Vero) cells
- Contains neomycin and streptomycin
- Shed in stool for up to 6 weeks following vaccination

Live attenuated polioviruses replicate in the intestinal mucosa and lymphoid cells and in lymph nodes that drain the intestine. Vaccine viruses are excreted in the stool of the vaccinated person for up to 6 weeks after a dose. Maximum viral shedding occurs in the first 1–2 weeks after vaccination, particularly after the first dose.

Vaccine viruses may spread from the recipient to contacts. Persons coming in contact with fecal material of a vaccinated person may be exposed and infected with vaccine virus.

Immunogenicity and Vaccine Efficacy

Inactivated poliovirus vaccine

IPV is highly effective in producing immunity to poliovirus and protection from paralytic poliomyelitis. Ninety percent or more of vaccine recipients develop protective antibody to all three poliovirus types after two doses, and at least 99% are immune following three doses. Protection against paralytic disease correlates with the presence of antibody.

Inactivated Polio Vaccine

- Highly effective in producing immunity to poliovirus
- 90% or more immune after 2 doses
- At least 99% immune after 3 doses
- Duration of immunity not known with certainty

IPV appears to produce less local gastrointestinal immunity than does OPV, so persons who receive IPV are more readily infected with wild poliovirus than OPV recipients.

The duration of immunity with IPV is not known with certainty, although it probably provides protection for many years after a complete series.

Oral poliovirus vaccine

OPV is highly effective in producing immunity to poliovirus. A single dose of OPV produces immunity to all three vaccine viruses in approximately 50% of recipients. Three doses produce immunity to all three poliovirus types in more than 95% of recipients. As with other live-virus vaccines, immunity from oral poliovirus vaccine is probably lifelong. OPV produces excellent intestinal immunity, which helps prevent infection with wild virus.

Oral Polio Vaccine

- Highly effective in producing immunity to poliovirus
- Approximately 50% immune after 1 dose
- More than 95% immune after 3 doses
- Immunity probably lifelong

Serologic studies have shown that seroconversion following three doses of either IPV or OPV is nearly 100% to all three vaccine viruses. However, seroconversion rates after three doses of a combination of IPV and OPV are lower, particularly to type 3 vaccine virus (as low as 85% in one study). A fourth dose (most studies used OPV as the fourth dose) usually produces seroconversion rates similar to three doses of either IPV or OPV.

Vaccination Schedule and Use

Trivalent OPV was the vaccine of choice in the United States (and most other countries of the world) since it was licensed in 1963. The nearly exclusive use of OPV led to elimination of wild-type poliovirus from the United States in less than 20 years. However, one case of VAPP occurred for every 2 to 3 million doses of OPV administered, which resulted in 8 to 10 cases of VAPP each year in the United States (see Adverse Reactions section for more details on VAPP). From 1980 through 1999, VAPP accounted for 95% of all cases of paralytic poliomyelitis reported in the United States.

Polio Vaccination Recommendations, 1996-1999

- Increased use of IPV (sequential IPV-OPV schedule) recommended in 1996
- Intended to reduce the risk of vaccine-associated paralytic polio

In 1996, ACIP recommended an increase in use of IPV through a sequential schedule of IPV followed by OPV. This recommendation was intended to reduce the occurrence of vaccine-associated paralytic polio. The sequential schedule was expected to eliminate VAPP among vaccine recipients by producing humoral immunity to polio vaccine viruses with inactivated polio vaccine prior to exposure to live vaccine virus. Since OPV was still used for the third and fourth doses of the polio vaccination schedule, a risk of VAPP would continue to exist among contacts of vaccinees, who were exposed to live vaccine virus in the stool of vaccine recipients.

The sequential IPV–OPV polio vaccination schedule was widely accepted by both providers and parents. Fewer cases of VAPP were reported in 1998 and 1999, suggesting an impact of the increased use of IPV. However, only the complete discontinuation of use of OPV would lead to complete elimination of VAPP. To further the goal of complete elimination of paralytic polio in the United States, ACIP recommended in July 1999 that inactivated polio vaccine be used exclusively in the United States beginning in 2000. OPV is no longer routinely available in the United States. Exclusive use of IPV eliminated the shedding of live vaccine virus, and eliminated any indigenous VAPP.

A primary series of IPV consists of three doses. In infancy, these primary doses are integrated with the administration of other routinely administered vaccines. The first dose may be given as early as 6 weeks of age but is usually given at 2 months of age, with a second dose at 4 months of age. The third dose should be given at 6–18 months of age. The recommended interval between the primary series doses is 2 months. However, if accelerated protection is needed, the minimum interval between each of the first 3 doses of IPV is 4 weeks.

The final dose in the IPV series should be administered at 4 years of age or older. A dose of IPV on or after age 4 years is recommended regardless of the number of previous doses. The minimum interval from the next-to-last to final dose is 6 months.

When DTaP-IPV/Hib (Pentacel) is used to provide 4 doses at ages 2, 4, 6, and 15-18 months, an additional booster dose of age-appropriate IPV-containing vaccine (IPV or DTaP-IPV [Kinrix]) should be administered at age 4-6 years. This will result in a 5-dose IPV vaccine series, which is considered acceptable by ACIP. DTaP-IPV/Hib is not indicated for the booster dose at 4-6 years of age. ACIP recommends that the minimum interval from dose 4 to dose 5 should be at least 6 months to provide an optimum booster response.

Shorter intervals between doses and beginning the series at a younger age may lead to lower seroconversion rates. Consequently, ACIP recommends the use of the minimum age (6 weeks) and minimum intervals between doses in the first 6 months of life only if the vaccine recipient is at risk for imminent exposure to circulating poliovirus (e.g., during an outbreak or because of travel to a polio-endemic region).

Only IPV is available for routine polio vaccination of children in the United States. A polio vaccination schedule begun with OPV should be completed with IPV. If a child receives both types of vaccine, four doses of any combination of IPV or OPV by 4–6 years of age is considered a complete poliovirus vaccination series. A minimum interval of 4 weeks should separate all doses of the series.

There are three combination vaccines that contain inactivated polio vaccine. Pediarix is produced by GlaxoSmithKline and contains DTaP, hepatitis B and IPV vaccines. Pediarix is licensed for the first 3 doses of the DTaP series among children 6 weeks through 6 years of age. Kinrix is also produced by GSK and contains DTaP and IPV. Kinrix is licensed only for the fifth dose of DTaP and fourth dose of IPV among children 4 through 6 years of age. Pentacel is produced by sanofi pasteur and contains DTaP, Hib and IPV. It is licensed for the first four doses of the component vaccines among children 6 weeks through 4 years of age. Pentacel is not licensed for children 5 years or older. Additional information about these combination vaccines is in the Pertussis chapter of this book.

(VAPP)
- Continued risk of VAPP for contacts of OPV recipients

Polio Vaccination Schedule

Age	Vaccine	Minimum Interval
2 months	IPV	--
4 months	IPV	4 weeks
6-18 months	IPV	4 weeks
4-6 years	IPV	6 months

Polio Vaccination Recommendations

- Exclusive use of IPV recommended in 2000
- OPV no longer routinely available in the United States
- Indigenous VAPP eliminated

Schedules That Include Both IPV and OPV

- Only IPV is available in the United States
- Schedule begun with OPV should be completed with IPV
- Any combination of 4 doses of IPV and OPV by 4-6 years of age constitutes a complete series

Combination Vaccines That Contain IPV

- Pediarix
  - DTaP, Hepatitis B and IPV
- Kinrix
  - DTaP and IPV
- Pentacel
  - .DTaP, Hib and IPV

Polio Vaccination of Adults

- Routine vaccination of U.S. residents 18 years of age and older not necessary or recommended
- May consider vaccination of travelers to polio-endemic countries and selected laboratory workers

Polio Vaccination of Adults

Routine vaccination of adults (18 years of age and older) who reside in the United States is not necessary or recommended because most adults are already immune and have a very small risk of exposure to wild poliovirus in the United States.

Some adults, however, are at increased risk of infection with poliovirus. These include travelers to areas where poliomyelitis is endemic or epidemic (currently limited to South Asia, the eastern Mediterranean, and Africa), laboratory workers handling specimens that may contain polioviruses, and healthcare personnel in close contact with patients who may be excreting wild

polioviruses. In addition, members of specific population groups with a current disease caused by wild polioviruses (e.g., during an outbreak) are also at increased risk.

Recommendations for poliovirus vaccination of adults in the above categories depend upon the previous vaccination history and the time available before protection is required.

- For unvaccinated adults (including adults without a written record of prior polio vaccination) at increased risk of exposure to poliomyelitis, primary immunization with IPV is recommended. The recommended schedule is two doses separated by 1 to 2 months, and a third dose given 6 to 12 months after the second dose. The minimum interval between the second and the third doses is 6 months.

Polio Vaccination of Unvaccinated Adults

- Use standard IPV schedule if possible (0, 1-2 months, 6-12 months)
- May separate first and second doses by 4 weeks if accelerated schedule needed
- The minimum interval between the second and third doses is 6 months

In some circumstances time will not allow completion of this schedule. If 8 weeks or more are available before protection is needed, three doses of IPV should be given at least 4 weeks apart. If 4 to 8 weeks are available before protection is needed, two doses of IPV should be given at least 4 weeks apart. If less than 4 weeks are available before protection is needed, a single dose of IPV is recommended. In all instances, the remaining doses of vaccine should be given later, at the recommended intervals, if the person remains at increased risk.

- Adults who have previously completed a primary series of 3 or more doses and who are at increased risk of exposure to poliomyelitis should be given one dose of IPV. The need for further supplementary doses has not been established. Only one supplemental dose of polio vaccine is recommended for adults who have received a complete series (i.e., it is not necessary to administer additional doses for subsequent travel to a polio endemic country).
- Adults who have previously received less than a full primary course of OPV or IPV and who are at increased risk of exposure to poliomyelitis should be given the remaining doses of IPV, regardless of the interval since the last dose and type of vaccine previously received. It is not necessary to restart the series of either vaccine if the schedule has been interrupted.

Polio Vaccination of Previously Vaccinated Adults

- Previously complete series
  - administer one dose of IPV
- Incomplete series
  - administer remaining doses in series
  - no need to restart series

Contraindications and Precautions to Vaccination

Severe allergic reaction (anaphylaxis) to a vaccine component, or following a prior dose of vaccine, is a contraindication to further doses of that vaccine. Since IPV contains trace amounts of streptomycin, neomycin, and polymyxin B, there is a possibility of allergic reactions in persons sensitive to these antibiotics. Persons with allergies that are not anaphylactic, such as skin contact sensitivity, may be vaccinated.

Moderate or severe acute illness is a precaution for IPV.

Polio Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose of vaccine
- Moderate or severe acute illness

Breastfeeding does not interfere with successful immunization against poliomyelitis with IPV. IPV may be administered to a child with diarrhea. Minor upper respiratory illnesses with or without fever, mild to moderate local reactions to a prior dose of vaccine, current antimicrobial therapy, and the convalescent phase of an acute illness are not contraindication for vaccination with IPV.

Contraindications to combination vaccines that contain IPV are the same as the contraindications to the individual components (e.g., DTaP, hepatitis B).

Adverse Reactions Following Vaccination

Minor local reactions (pain, redness) may occur following IPV. No serious adverse reactions to IPV have been documented. Because IPV contains trace amounts of streptomycin, polymyxin B, and neomycin, allergic reactions may occur in persons sensitive to these antibiotics.

Polio Vaccines Adverse Reactions

- Rare local reactions (IPV)
- No serious reactions to IPV have been documented
- Paralytic poliomyelitis (OPV)

Vaccine-Associated Paralytic Poliomyelitis

Vaccine-associated paralytic polio is a rare adverse reaction following live oral poliovirus vaccine. Inactivated poliovirus vaccine does not contain live virus, so it cannot cause VAPP. The mechanism of VAPP is believed to be a mutation, or reversion, of the vaccine virus to a more neurotropic form. These mutated viruses are called revertants. Reversion is believed to occur in almost all vaccine recipients, but it only rarely results in paralytic disease. The paralysis that results is identical to that caused by wild virus, and may be permanent.

VAPP is more likely to occur in persons 18 years of age and older than in children, and is much more likely to occur in immunodeficient children than in those who are immunocompetent. Compared with immunocompetent children, the risk of VAPP is almost 7,000 times higher for persons with certain types of immunodeficiencies, particularly B-lymphocyte disorders (e.g., agammaglobulinemia and hypogammaglobulinemia), which reduce the synthesis of immune globulins. There is no procedure available for identifying

Vaccine-Associated Paralytic Polio

- Increased risk in persons 18 years and older
- Increased risk in persons with immunodeficiency

persons at risk of paralytic disease, except excluding older persons and screening for immunodeficiency.

- No procedure available for identifying persons at risk of paralytic disease
- 5-10 cases per year with exclusive use of OPV
- Most cases in healthy children and their household contacts

From 1980 through 1998, 152 cases of paralytic polio were reported in the United States; 144 (95%) of these cases were VAPP, and the remaining eight were in persons who acquired documented or presumed wild-virus polio outside the United States. Of the 144 VAPP cases, 59 (41%) occurred in healthy vaccine recipients (average age 3 months). Forty-four (31%) occurred in healthy contacts of vaccine recipients (average age 26 years), and 7 (5%) were community acquired (i.e., vaccine virus was recovered but there was no known contact with a vaccine recipient). Thirty-four (24%) of VAPP cases occurred in persons with immunologic abnormalities (27 in vaccine recipients and 7 in contacts of vaccine recipients). None of the vaccine recipients were known to be immunologically abnormal prior to vaccination.

Vaccine-Associated Paralytic Polio (VAPP) 1980-1998

- Healthy recipients of OPV - 41%
- Healthy contacts of OPV recipients - 31%
- Community acquired - 5%
- Immunodeficient - 24%

The risk of VAPP is not equal for all OPV doses in the vaccination series. The risk of VAPP is 7 to 21 times higher for the first dose than for any other dose in the OPV series. From 1980 through 1994, 303 million doses of OPV were distributed and 125 cases of VAPP were reported, for an overall risk of VAPP of one case per 2.4 million doses. Forty-nine paralytic cases were reported among immunocompetent recipients of OPV during this period. The overall risk to these recipients was one VAPP case per 6.2 million OPV doses. However, 40 (82%) of these 49 cases occurred following receipt of the first dose, making the risk of VAPP one case per 1.4 million first doses. The risk for all other doses was one per 27.2 million doses. The reason for this difference by dose is not known with certainty, but it is probably because the vaccine virus is able to replicate longer in a completely nonimmune infant. This prolonged replication increases the chance of the emergence of a revertant virus that may cause paralysis. The situation is similar for contacts. A nonimmune child may shed virus longer, increasing the chance of exposure of a contact.

The last case of VAPP acquired in the United States was reported in 1999. As noted previously, a U.S. resident with VAPP was reported in 2005, but the vaccine virus infection was acquired in Costa Rica.

Vaccine Storage and Handling

IPV may be shipped without refrigeration provided it is delivered within 4 days. It should be maintained at 35°–46°F (2°–8°C). The vaccine should be clear and colorless. Any vaccine showing particulate matter, turbidity, or change in color should be discarded.

Outbreak Investigation and Control

Collect preliminary clinical and epidemiologic information (including vaccine history and contact with OPV vaccines) on any suspected case of paralytic polio. Notify CDC, (404-639-8255) after appropriate local and state health authorities have been notified. Intensify field investigation to verify information and collect appropriate specimens for viral isolation and serology.

Polio Eradication

- Last case in United States in 1970
- Western Hemisphere certified polio free in 1994
- Last isolate of type 2 poliovirus in India in October 1999
- Global eradication goal

A single case of paralytic poliomyelitis demands immediate attention. If the evidence indicates vaccine-associated disease, no outbreak control program is needed. If, however, evidence indicates wild virus (for example, two cases in a community), all unvaccinated persons in the epidemic area who are 6 weeks of age and older and whose vaccine histories are uncertain should be vaccinated.

Polio Eradication

Following the widespread use of poliovirus vaccine in the mid-1950s, the incidence of poliomyelitis declined rapidly in many industrialized countries. In the United States, the number of cases of paralytic poliomyelitis reported annually declined from more than 20,000 cases in 1952 to fewer than 100 cases in the mid-1960s. The last documented indigenous transmission of wild poliovirus in the United States was in 1979.

Wild Poliovirus 1988

In 1985, the member countries of the Pan American Health Organization adopted the goal of eliminating poliomyelitis from the Western Hemisphere by 1990. The strategy to achieve this goal included increasing vaccination coverage; enhancing surveillance for suspected cases (i.e., surveillance for acute flaccid paralysis); and using supplemental immunization strategies such as national immunization days, house-to-house vaccination, and containment activities. Since 1991, when the last wild-virus–associated indigenous case was reported from Peru, no additional cases of poliomyelitis have been confirmed despite intensive surveillance. In September 1994, an international commission certified the Western Hemisphere to be free of indigenous wild poliovirus. The commission based its judgment on detailed reports from national certification commissions that had been convened in every country in the region.

In 1988, the World Health Assembly (the governing body of the World Health Organization) adopted the goal of global eradication of poliovirus by the year 2000. Although this goal was not achieved, substantial progress has been made. One type of poliovirus appears to have already been eradicated. In 1988, an estimated 350,000 cases of paralytic polio occurred, and the disease was endemic in more than 125 countries. By 2006, fewer than 2,000 cases were reported globally—a reduction of more than 99% from 1988—and polio remained endemic in only four countries. In addition, one type of poliovirus appears to have already been eradicated. The last isolation of type 2 virus was in India in October 1999.

Wild Poliovirus 2008

The polio eradication initiative is led by a coalition of international organizations that includes WHO, the United Nations Children's Fund (UNICEF), CDC, and Rotary International. Other bilateral and multilateral organizations also support the initiative. Rotary International has contributed more than $600 million to support the eradication initiative. Current information on the status of the global polio eradication initiative is available on the World Health Organization website .

Postpolio Syndrome

After an interval of 30–40 years, 25%–40% of persons who contracted paralytic poliomyelitis in childhood experience new muscle pain and exacerbation of existing weakness, or develop new weakness or paralysis. This disease entity is referred to as postpolio syndrome. Factors that increase the risk of postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from the acute illness, and female sex. The pathogenesis of postpolio syndrome is thought to involve the failure of oversized motor units created during the recovery process of paralytic poliomyelitis. Postpolio syndrome is not an infectious process, and persons experiencing the syndrome do not shed poliovirus.

For more information, or for support for persons with post-polio syndrome and their families, contact:

Post-Polio Health International
4207 Lindell Boulevard #110
St. Louis, MO 63108-2915
314-534-0475

Selected References

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Format: Abstract

J Toxicol Environ Health A. 2011;74(14):903-16. doi: 10.1080/15287394.2011.573736.

A positive association found between autism prevalence and childhood vaccination uptake across the U.S. population.

Delong G[1].

Author information

Abstract

The reason for the rapid rise of autism in the United States that began in the 1990s is a mystery. Although individuals probably have a genetic predisposition to develop autism, researchers suspect that one or more environmental triggers are also needed. One of those triggers might be the battery of vaccinations that young children receive. Using regression analysis and controlling for family income and ethnicity, the relationship between the proportion of children who received the recommended vaccines by age 2 years and the prevalence of autism (AUT) or speech or language impairment (SLI) in each U.S. state from 2001 and 2007 was determined. A positive and statistically significant relationship was found: The higher the proportion of children receiving recommended vaccinations, the higher was the prevalence of AUT or SLI. A 1% increase in vaccination was associated with an additional 680 children having AUT or SLI. Neither parental behavior nor access to care affected the results, since vaccination proportions were not significantly related (statistically) to any other disability or to the number of pediatricians in a U.S. state. The results suggest that although mercury has been removed from many vaccines, other culprits may link vaccines to autism. Further study into the relationship between vaccines and autism is warranted.

PMID: 21623535 DOI: 10.1080/15287394.2011.573736

[Indexed for MEDLINE]

MeSH terms

LinkOut - more resources

J Inorg Biochem. 2011 Nov;105(11):1489-99. doi: 10.1016/j.jinorgbio.2011.08.008. Epub 2011 Aug 23.

Do aluminum vaccine adjuvants contribute to the rising prevalence of autism?

Tomljenovic L[1], Shaw CA.

Author information

Abstract

Autism spectrum disorders (ASD) are serious multisystem developmental disorders and an urgent global public health concern. Dysfunctional immunity and impaired brain function are core deficits in ASD. Aluminum (Al), the most commonly used vaccine adjuvant, is a demonstrated neurotoxin and a strong immune stimulator. Hence, adjuvant Al has the potential to induce neuroimmune disorders. When assessing adjuvant toxicity in children, two key points ought to be considered: (i) children should not be viewed as "small adults" as their unique physiology makes them much more vulnerable to toxic insults; and (ii) if exposure to Al from only few vaccines can lead to cognitive impairment and autoimmunity in adults, is it unreasonable to question whether the current pediatric schedules, often containing 18 Al adjuvanted vaccines, are safe for children? By applying Hill's criteria for establishing causality between exposure and outcome we investigated whether exposure to Al from vaccines could be contributing to the rise in ASD prevalence in the Western world. Our results show that: (i) children from countries with the highest ASD prevalence appear to have the highest exposure to Al from vaccines; (ii) the increase in exposure to Al adjuvants significantly correlates with the increase in ASD prevalence in the United States observed over the last two decades (Pearson r=0.92, p<0.0001); and (iii) a significant correlation exists between the amounts of Al administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3-4 months of age (Pearson r=0.89-0.94, p=0.0018-0.0248). The application of the Hill's criteria to these data indicates that the correlation between Al in vaccines and ASD may be causal. Because children represent a fraction of the population most at risk for complications following exposure to Al, a more rigorous evaluation of Al adjuvant safety seems warranted.

PMID: 22099159 DOI: 10.1016/j.jinorgbio.2011.08.008

[Indexed for MEDLINE]

PubMed

Format: Abstract

Altern Ther Health Med. 2008 Nov-Dec;14(6):46-53.

A possible central mechanism in autism spectrum disorders, part 1.

Blaylock RL[1].

Author information

Abstract

The autism spectrum disorders (ASD) are a group of related neurodevelopmental disorders that have been increasing in incidence since the 1980s. Despite a considerable amount of data being collected from cases, a central mechanism has not been offered. A careful review of ASD cases discloses a number of events that adhere to an immunoexcitotoxic mechanism. This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain. It has now been shown that chronic microglial activation is present in autistic brains from age 5 years to age 44 years. A considerable amount of evidence, both experimental and clinical, indicates that repeated microglial activation can initiate priming of the microglia and that subsequent stimulation can produce an exaggerated microglial response that can be prolonged. It is also known that one phenotypic form of microglia activation can result in an outpouring of neurotoxic levels of the excitotoxins, glutamate and quinolinic acid. Studies have shown that careful control of brain glutamate levels is essential to brain pathway development and that excesses can result in arrest of neural migration, as well as dendritic and synaptic loss. It has also been shown that certain cytokines, such as TNF-alpha, can, via its receptor, interact with glutamate receptors to enhance the neurotoxic reaction. To describe this interaction I have coined the term immunoexcitotoxicity, which is described in this article.

PMID: 19043938

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

PubMed

Format: Abstract

J Toxicol Environ Health A. 2010;73(24):1665-77. doi: 10.1080/15287394.2010.519317.

Hepatitis B vaccination of male neonates and autism diagnosis, NHIS 1997-2002.

Gallagher CM[1], Goodman MS.

Author information

Abstract

Universal hepatitis B vaccination was recommended for U.S. newborns in 1991; however, safety findings are mixed. The association between hepatitis B vaccination of male neonates and parental report of autism diagnosis was determined. This cross-sectional study used weighted probability samples obtained from National Health Interview Survey 1997-2002 data sets. Vaccination status was determined from the vaccination record. Logistic regression was used to estimate the odds for autism diagnosis associated with neonatal hepatitis B vaccination among boys age 3-17 years, born before 1999, adjusted for race, maternal education, and two-parent household. Boys vaccinated as neonates had threefold greater odds for autism diagnosis compared to boys never vaccinated or vaccinated after the first month of life. Non-Hispanic white boys were 64% less likely to have autism diagnosis relative to nonwhite boys. Findings suggest that U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period. Nonwhite boys bore a greater risk.

PMID: 21058170 DOI: 10.1080/15287394.2010.519317

[Indexed for MEDLINE]

MeSH terms, Substances

LinkOut - more resources

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Aluminium in brain tissue in autism

Matthew Mold [a], Dorcas Umar [b], Andrew King [c], Christopher Exley [a]

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https://doi.org/10.1016/j.jtemb.2017.11.012

Abstract

Autism spectrum disorder is a neurodevelopmental disorder of unknown aetiology. It is suggested to involve both genetic susceptibility and environmental factors including in the latter environmental toxins. Human exposure to the environmental toxin aluminium has been linked, if tentatively, to autism spectrum disorder. Herein we have used transversely heated graphite furnace atomic absorption spectrometry to measure, for the first time, the aluminium content of brain tissue from donors with a diagnosis of autism. We have also used an aluminium-selective fluor to identify aluminium in brain tissue using fluorescence microscopy. The aluminium content of brain tissue in autism was consistently high. The mean (standard deviation) aluminium content across all 5 individuals for each lobe were 3.82(5.42), 2.30(2.00), 2.79(4.05) and 3.82(5.17) μg/g dry wt. for the occipital, frontal, temporal and parietal lobes respectively. These are some of the highest values for aluminium in human brain tissue yet recorded and one has to question why, for example, the aluminium content of the occipital lobe of a 15 year old boy would be 8.74 (11.59) μg/g dry wt.? Aluminium-selective fluorescence microscopy was used to identify aluminium in brain tissue in 10 donors. While aluminium was imaged associated with neurones it appeared to be present intracellularly in microglia-like cells and other inflammatory non-neuronal cells in the meninges, vasculature, grey and white matter. The pre-eminence of intracellular aluminium associated with non-neuronal cells was a standout observation in autism brain tissue and may offer clues as to both the origin of the brain aluminium as well as a putative role in autism spectrum disorder.

Previous article

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Keywords

Human exposure to aluminium; Human brain tissue; Autism spectrum disorder; Transversely heated atomic absorption spectrometry; Aluminium-selective fluorescence microscopy

1. Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental conditions of unknown cause. It is highly likely that both genetic [1] and environmental [2] factors are associated with the onset and progress of ASD while the mechanisms underlying its aetiology are expected to be multifactorial [3], [4], [5], [6]. Human exposure to aluminium has been implicated in ASD with conclusions being equivocal [7], [8], [9], [10]. To-date the majority of studies have used hair as their indicator of human exposure to aluminium while aluminium in blood and urine have also been used to a much more limited extent. Paediatric vaccines that include an aluminium adjuvant are an indirect measure of infant exposure to aluminium and their burgeoning use has been directly correlated with increasing prevalence of ASD [11]. Animal models of ASD continue to support a connection with aluminium and to aluminium adjuvants used in human vaccinations in particular [12]. Hitherto there are no previous reports of aluminium in brain tissue from donors who died with a diagnosis of ASD. We have measured aluminium in brain tissue in autism and identified the location of aluminium in these tissues.

2. Materials and methods

2.1. Measurement of aluminium in brain tissues

Ethical approval was obtained along with tissues from the Oxford Brain Bank (15/SC/0639). Samples of cortex of approximately 1 g frozen weight from temporal, frontal, parietal and occipital lobes and hippocampus (0.3 g only) were obtained from 5 individuals with ADI-R-confirmed (Autism Diagnostic Interview-Revised) ASD, 4 males and 1 female, aged 15–50 years old (Table 1).

Table 1. Aluminium content of occipital (O), frontal (F), temporal (T) and parietal (P) lobes and hippocampus (H) of brain tissue from 5 donors with a diagnosis of autism spectrum disorder.

Donor ID	Gender	Age	Lobe	Replicate	[Al] μg/g
A1	F	44	O	1	0.49
				2	4.26
				3	0.33
				Mean (SD)	1.69 (2.22)
			F	1	0.98
				2	1.10
				3	0.95
				Mean (SD)	1.01 (0.08)
			T	1	1.13
				2	1.16
				3	1.12
				Mean (SD)	1.14 (0.02)
			P	1	0.54
				2	1.18
				3	NA
				Mean (SD)	0.86 (0.45)
			All	Mean (SD)	1.20 (1.06)
A2	M	50	O	1	3.73
				2	7.87
				3	3.49
				Mean (SD)	5.03 (2.46)
			F	1	0.86
				2	0.88
				3	1.65
				Mean (SD)	1.13 (0.45)
			T	1	1.31
				2	1.02
				3	2.73
				Mean (SD)	1.69 (0.92)
			P	1	18.57
				2	0.01
				3	0.64
				Mean (SD)	6.41 (10.54)

			Hip.	1	1.42
			All	Mean (SD)	3.40 (5.00)
A3	M	22	O	1	0.64
				2	2.01
				3	0.66
				Mean (SD)	1.10 (0.79)
			F	1	1.72
				2	4.14
				3	2.73
				Mean (SD)	2.86 (1.22)
			T	1	1.62
				2	4.25
				3	2.57
				Mean (SD)	2.81 (1.33)
			P	1	0.13
				2	3.12
				3	5.18
				Mean (SD)	2.82 (1.81)
			All	Mean (SD)	2.40 (1.58)
A4	M	15	O	1	2.44
				2	1.66
				3	22.11
				Mean (SD)	8.74 (11.59)
			F	1	1.11
				2	3.23
				3	1.66
				Mean (SD)	2.00 (1.10)
			T	1	1.10
				2	1.83
				3	1.54
				Mean (SD)	1.49 (0.37)
			P	1	1.38
				2	6.71
				3	NA
				Mean (SD)	4.05 (3.77)
			Hip.	1	0.02
			All	Mean (SD)	3.73 (6.02)

A5	M	33	O	1	3.13
				2	2.78
				3	1.71
				Mean (SD)	2.54 (0.74)
			F	1	2.97
				2	8.27
				3	NA
				Mean (SD)	5.62 (3.75)
			T	1	1.71
				2	1.64
				3	17.10
				Mean (SD)	6.82 (8.91)
			P	1	5.53
				2	2.89
				3	NA
				Mean (SD)	4.21 (1.87)
			All	Mean (SD)	4.77 (4.79)

The aluminium content of these tissues was measured by an established and fully validated method [13] that herein is described only briefly. Thawed tissues were cut using a stainless steel blade to give individual samples of ca 0.3 g (3 sample replicates for each lobe except for hippocampus where the tissue was used as supplied) wet weight and dried to a constant weight at 37 °C. Dried and weighed tissues were digested in a microwave (MARS Xpress CEM Microwave Technology Ltd.) in a mixture of 1 mL 15.8 M HNO_3 (Fisher Analytical Grade) and 1 mL 30% w/v H_2O_2 (BDH Aristar). Digests were clear with no fatty residues and, upon cooling, were made up to 5 mL volume using ultrapure water (cond.<0.067 μS/cm). Total aluminium was measured in each sample by transversely heated graphite furnace atomic absorption spectrometry (TH GFAAS) using matrix-matched standards and an established analytical programme alongside previously validated quality assurance data [13].

2.2. Fluorescence microscopy

All chemicals were from Sigma Aldrich (UK) unless otherwise stated. Where available frontal, parietal, occipital, temporal and hippocampal tissue from 10 donors (3 females and 7 males) with a diagnosis of ASD was supplied by the Oxford Brain Bank as three 5 μm thick serial paraffin-embedded brain tissue sections per lobe for each donor (Table S1). Tissue sections mounted on glass slides were placed in a slide rack and de-waxed and rehydrated via transfer through 250 mL of the following reagents: 3 min in Histo-Clear (National Diagnostics, US), 1 min in fresh Histo-Clear, 2 min in 100% v/v ethanol (HPLC grade) and 1 min in 95, 70, 50 & 30% v/v ethanol followed by rehydration in ultrapure water (cond.<0.067 μS/cm) for 35 s. Slides were agitated every 20 s in each solvent and blotted on tissue paper between transfers to minimise solvent carry-over. Rehydrated brain tissue sections were carefully outlined with a PAP pen for staining, in order to form a hydrophobic barrier around the periphery of tissue sections. In between staining, tissue sections were kept hydrated with ultrapure water and stored in moisture chambers, to prevent sections from drying out. Staining was staggered to allow for accurate incubation times of brain tissue sections. We have developed and optimised the fluor lumogallion as a selective stain for aluminium in cells [14] and human tissues [15]. Lumogallion (4-chloro-3-(2,4-dihydroxyphenylazo)-2-hydroxybenzene-1-sulphonic acid, TCI Europe N.V. Belgium) was prepared at ca 1 mM via dilution in a 50 mM PIPES (1,4-Piperazinediethanesulphonic acid) buffer, adjusted to pH 7.4 with NaOH. Lumogallion staining was performed via the addition of 200 μL of the staining solution to rehydrated brain tissue sections that were subsequently incubated at ambient temperature away from light for 45 min. Sections for autofluorescence analyses were incubated for 45 min in 200 μL 50 mM PIPES buffer only, pH 7.4. Following staining, glass slides containing tissue sections were washed six times with 200 μL aliquots of 50 mM PIPES buffer, pH 7.4, prior to rinsing for 30 s in ultrapure water. Serial sections numbered 1 and 2 for each lobe were incubated in 50 mM PIPES buffer, pH 7.4 or stained with 1 mM lumogallion in the same buffer, respectively, to ensure consistency across donor tissues.

All tissue sections were subsequently mounted under glass coverslips using the aqueous mounting medium, Fluoromount™. Slides were stored horizontally for 24 h at 4 °C away from light, prior to analysis via fluorescence microscopy.

Stained and mounted human brain tissue sections were analysed via the use of an Olympus BX50 fluorescence microscope, equipped with a vertical illuminator and BX-FLA reflected light fluorescence attachment (mercury source). Micrographs were obtained at X 400 magnification by use of a X 40 Plan-Fluorite objective (Olympus, UK). Lumogallion-reactive aluminium and related autofluorescence micrographs were obtained via use of a U-MNIB3 fluorescence filter cube (excitation: 470–495 nm, dichromatic mirror: 505 nm, longpass emission: 510 nm, Olympus, UK). Light exposure and transmission values were fixed across respective staining treatment conditions and images were obtained using the CellD software suite (Olympus, Soft Imaging Solutions, SiS, GmbH). Lumogallion-reactive regions identified through sequential screening of stained human brain tissue sections were additionally imaged on autofluorescence serial sections, to assess the contribution of the fluorophore. The subsequent merging of fluorescence and bright-field channels was achieved using Photoshop (Adobe Systems Inc. US). When determining intracellular staining the type of cells stained were estimated by their size and shape in the context of the brain area sampled and their surrounding cellular environment.

3. Results

3.1. Aluminium content of brain tissues

The aluminium content of all tissues ranged from 0.01 (the limit of quantitation) to 22.11 μg/g dry wt. (Table 1). The aluminium content for whole brains (n = 4 or 5 depending upon the availability of hippocampus tissue) ranged from 1.20 (1.06) μg/g dry wt. for the 44 year old female donor (A1) to 4.77 (4.79) μg/g dry wt. for a 33 year old male donor (A5). Previous measurements of brain aluminium, including our 60 brain study [13], have allowed us to define loose categories of brain aluminium content beginning with ≤1.00 μg/g dry wt. as pathologically benign (as opposed to 'normal'). Approximately 40% of tissues (24/59) had an aluminium content considered as pathologically-concerning (≥2.00 μg/g dry wt.) while approximately 67% of these tissues had an aluminium content considered as pathologically-significant (≥3.00 μg/g dry wt.). The brains of all 5 individuals had at least one tissue with a pathologically-significant content of aluminium. The brains of 4 individuals had at least one tissue with an aluminium content ≥5.00 μg/g dry wt. while 3 of these had at least one tissue with an aluminium content ≥10.00 μg/g dry wt. (Table 1). The mean (SD) aluminium content across all 5 individuals for each lobe were 3.82(5.42), 2.30(2.00), 2.79(4.05) and 3.82(5.17) μg/g dry wt. for the occipital, frontal, temporal and parietal lobes respectively. There were no statistically significant differences in aluminium content between any of the 4 lobes.

3.2. Aluminium fluorescence in brain tissues

We examined serial brain sections from 10 individuals (3 females and 7 males) who died with a diagnosis of ASD and recorded the presence of aluminium in these tissues (Table S1). Excitation of the complex of aluminium and lumogallion emits characteristic orange fluorescence that appears increasingly bright yellow at higher fluorescence intensities. Aluminium, identified as lumogallion-reactive deposits, was recorded in at least one tissue in all 10 individuals. Autofluorescence of immediately adjacent serial sections confirmed lumogallion fluorescence as indicative of aluminium. Deposits of aluminium were significantly more prevalent in males (129 in 7 individuals) than females (21 in 3 individuals). Aluminium was found in both white (62 deposits) and grey (88 deposits) matter. In females the majority of aluminium deposits were identified as extracellular (15/21) whereas in males the opposite was the case with 80 out of 129 deposits being intracellular. We were only supplied with 3 serial sections of each tissue and so we were not able to do any staining for general morphology which meant that it was not always possible to determine which subtype of cell was showing aluminium fluorescence.

Aluminium-loaded mononuclear white blood cells, probably lymphocytes, were identified in the meninges and possibly in the process of entering brain tissue from the lymphatic system (Fig. 1). Aluminium could be clearly seen inside cells as either discrete punctate deposits or as bright yellow fluorescence. Aluminium was located in inflammatory cells associated with the vasculature (Fig. 2). In one case what looks like an aluminium-loaded lymphocyte or monocyte was noted within a blood vessel lumen surrounded by red blood cells while another probable lymphocyte showing intense yellow fluorescence was noted in the adventitia (Fig. 2b). Glial cells including microglia-like cells that showed positive aluminium fluorescence were often observed in brain tissue in the vicinity of aluminium-stained extracellular deposits (Fig. 3, Fig. 4). Discrete deposits of aluminium approximately 1 μm in diameter were clearly visible in both round and amoeboid glial cell bodies (e.g. Fig. 3b). Intracellular aluminium was identified in likely neurones and glia-like cells and often in the vicinity of or co-localised with lipofuscin (Fig. 5). Aluminium-selective fluorescence microscopy was successful in identifying aluminium in extracellular and intracellular locations in neurones and non-neuronal cells and across all brain tissues studied (Fig. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5). The method only identifies aluminium as evidenced by large areas of brain tissue without any characteristic aluminium-positive fluorescence (Fig. S1).

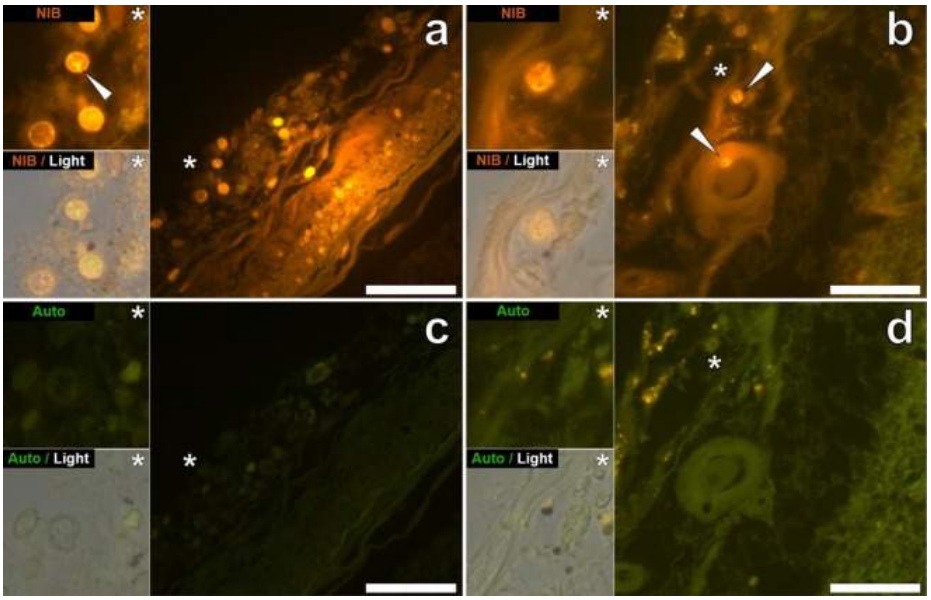

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Fig. 1. Mononuclear inflammatory cells (probably lymphocytes) in leptomeningeal membranes in the hippocampus and frontal lobe of a 50-year-old male donor (A2), diagnosed with autism. Intracellular lumogallion-reactive aluminium was noted via punctate orange fluorescence emission (white arrows) in the hippocampus **(a)** and frontal lobe **(b)**. A green autofluorescence emission was detected in the adjacent non-stained (5 μm) serial section **(c & d)**. Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification ×400, scale bars: 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

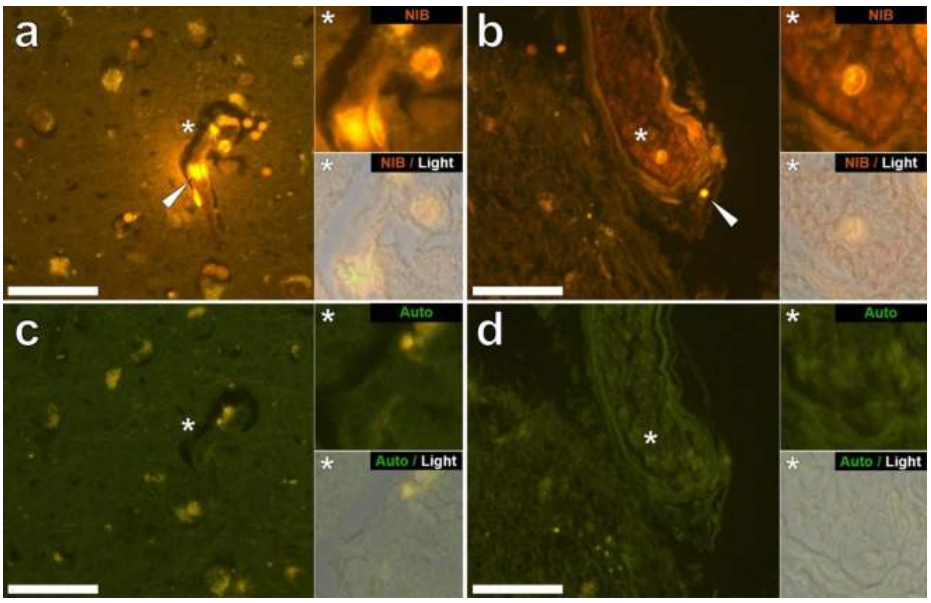

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Fig. 2. Intracellular lumogallion-reactive aluminium in the vasculature of the hippocampus of a 50-year-old male donor (A2), diagnosed with autism. Aluminium-loaded inflammatory cells noted in the hippocampus in the vessel wall (white arrow) **(a)** and depicting punctate orange fluorescence in the lumen **(b)** are highlighted. An inflammatory cell in the vessel adventitia was also noted (white arrow) **(b)**. Lumogallion-reactive aluminium was identified via an orange fluorescence emission **(a & b)** versus a green autofluorescence emission **(c & d)** of the adjacent non-stained (5 μm) serial section. Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification ×400, scale bars: 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

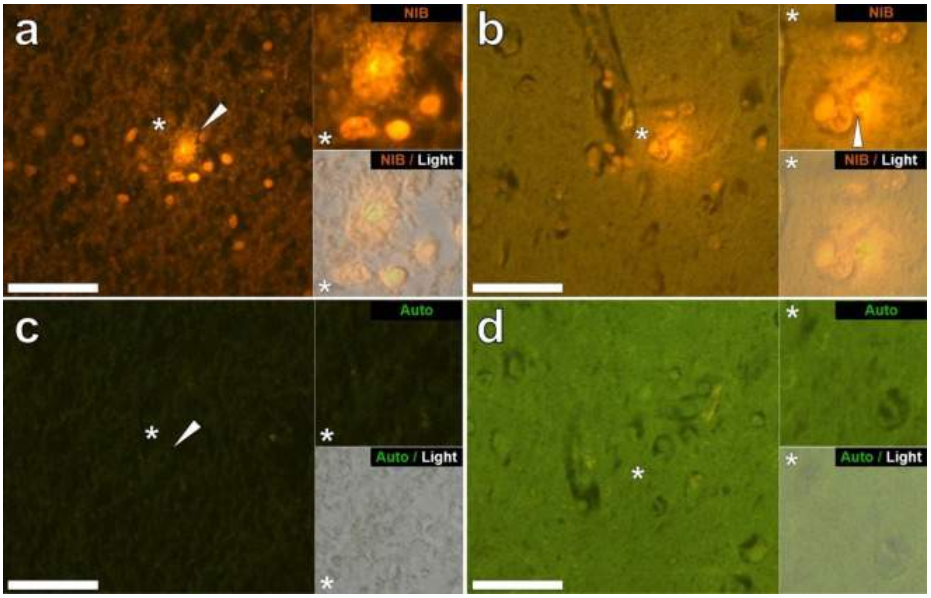

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Fig. 3. Intracellular aluminium in cells morphologically compatible with glia and neurones in the hippocampus of a 15-year-old male donor (A4), diagnosed with autism. Lumogallion reactive cellular aluminium identified within glial-like cells in the hippocampus **(a)** and producing a punctate orange fluorescence in glia surrounding a likely neuronal cell within the parietal lobe **(b)** are highlighted (white arrows). Lumogallion-reactive aluminium was identified via an orange fluorescence emission **(a & b)** versus a green autofluorescence emission **(c & d)** of the subsequent non-stained (5 μm) serial section (white arrow/asterisk). Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification ×400, scale bars: 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

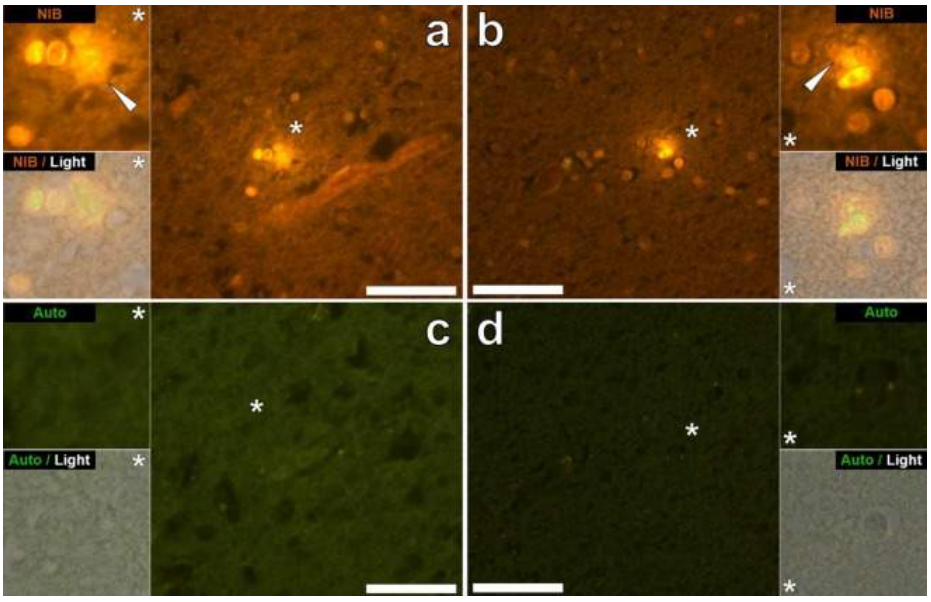

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Fig. 4. Intracellular aluminium in cells morphologically compatible with microglia within the parietal and temporal lobes of 29-year-old (A8) and 15-year-old (A4) male donors, diagnosed with autism. Lumogallion-reactive extracellular aluminium (white arrows) producing an orange fluorescence emission was noted around likely microglial cells in the parietal **(a)** and temporal lobes **(b)** of donors A8 and A4 respectively. Non-stained adjacent (5 μm) serial sections, produced a weak green autofluorescence emission of the identical area imaged in white **(c)** and grey matter **(d)** of the respective lobes. Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification ×400, scale bars: 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

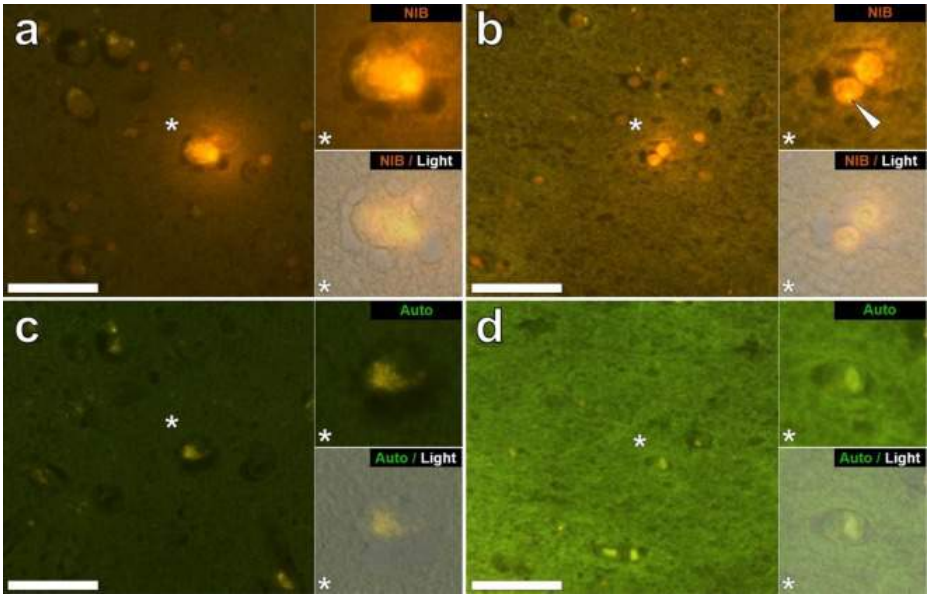

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Fig. 5. Lumogallion-reactive aluminium in likely neuronal and glial cells in the temporal lobe and hippocampus of a 14-year-old male donor (A10), diagnosed with autism. Intraneuronal aluminium in the temporal lobe **(a)** was identified via an orange fluorescence emission, co-deposited with lipofuscin as revealed by a yellow fluorescence in the non-stained autofluorescence serial (5 μm) section **(c)**. Intracellular punctate orange fluorescence (white arrow) was observed in glia in the hippocampus **(b)** producing a green autofluorescence emission on the non-stained section **(d)**. Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification ×400, scale bars: 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

The aluminium content of brain tissues from donors with a diagnosis of ASD was extremely high (Table 1). While there was significant inter-tissue, inter-lobe and inter-subject variability the mean aluminium content for each lobe across all 5 individuals was towards the higher end of all previous (historical) measurements of brain aluminium content, including iatrogenic disorders such as dialysis encephalopathy [13], [15], [16], [17], [18], [19]. All 4 male donors had significantly higher concentrations of brain aluminium than the single female donor. We recorded some of the highest values for brain aluminium content ever measured in healthy or diseased tissues in these male ASD donors including values of 17.10, 18.57 and 22.11 μg/g dry wt. (Table 1). What discriminates these data from other analyses of brain aluminium in other diseases is the age of the ASD donors. Why, for example would a 15 year old boy have such a high content of aluminium in their brain tissues? There are no comparative data in the scientific literature, the closest being similarly high data for a 42 year old male with familial Alzheimer's disease (fAD) [19].

Aluminium-selective fluorescence microscopy has provided indications as to the location of aluminium in these ASD brain tissues (Fig. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5). Aluminium was found in both white and grey matter and in both extra- and intracellular locations. The latter were particularly pre-eminent in these ASD tissues. Cells that morphologically appeared non-neuronal and heavily loaded with aluminium were identified associated with the meninges (Fig. 1), the vasculature (Fig. 2) and within grey and white matter (Fig. 3, Fig. 4, Fig. 5). Some of these cells appeared to be glial (probably astrocytic) whilst others had elongated nuclei giving the appearance of microglia [5]. The latter were sometimes seen in the environment of extracellular aluminium deposition. This implies that aluminium somehow had crossed the blood-brain barrier and was taken up by a native cell namely the microglial cell. Interestingly, the presence of occasional aluminium-laden inflammatory cells in the vasculature and the leptomeninges opens the possibility of a separate mode of entry of aluminium into the brain i.e. intracellularly. However, to allow this second scenario to be of significance one would expect some type of intracerebral insult to occur to allow egress of lymphocytes and monocytes from the vasculature [20]. The identification herein of non-neuronal cells including inflammatory cells, glial cells and microglia loaded with aluminium is a standout observation for ASD. For example, the majority of aluminium deposits identified in brain tissue in fAD were extracellular and nearly always associated with grey matter [19]. Aluminium is cytotoxic [21] and its association herein with inflammatory cells in the vasculature, meninges and central nervous system is unlikely to be benign. Microglia heavily loaded with aluminium while potentially remaining viable, at least for some time, will inevitably be compromised and dysfunctional microglia are thought to be involved in the aetiology of ASD [22], for example in disrupting synaptic pruning [23]. In addition the suggestion from the data herein

that aluminium entry into the brain via immune cells circulating in the blood and lymph is expedited in ASD might begin to explain the earlier posed question of why there was so much aluminium in the brain of a 15 year old boy with an ASD.

A limitation of our study is the small number of cases that were available to study and the limited availability of tissue. Regarding the latter, having access to only 1 g of frozen tissue and just 3 serial sections of fixed tissue per lobe would normally be perceived as a significant limitation. Certainly if we had not identified any significant deposits of aluminium in such a small (the average brain weighs between 1500 and 2000 g) sample of brain tissue then such a finding would be equivocal. However, the fact that we found aluminium in every sample of brain tissue, frozen or fixed, does suggest very strongly that individuals with a diagnosis of ASD have extraordinarily high levels of aluminium in their brain tissue and that this aluminium is pre-eminently associated with non-neuronal cells including microglia and other inflammatory monocytes.

5. Conclusions

We have made the first measurements of aluminium in brain tissue in ASD and we have shown that the brain aluminium content is extraordinarily high. We have identified aluminium in brain tissue as both extracellular and intracellular with the latter involving both neurones and non-neuronal cells. The presence of aluminium in inflammatory cells in the meninges, vasculature, grey and white matter is a standout observation and could implicate aluminium in the aetiology of ASD.

Competing interests

The authors declare that they have no competing interests.

Author contributions

CE designed the study, carried out tissue digests and TH GFAAS. DU carried out tissue digests and TH GFAAS. AK carried out brain neuropathology on sections prepared by MM. MM carried out all microscopy and with CE wrote the manuscript. All authors read and approved the manuscript.

Acknowledgements

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Appendix A. Supplementary data

The following are Supplementary data to this article:

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JOURNAL OF
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Full Length Research Paper

Impact of environmental factors on the prevalence of autistic disorder after 1979

Theresa A. Deisher* **Ngoc V. Doan** **Angelica Omaiye** **Kumiko Koyama** **Sarah Bwabye**

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Abstract

The aim of this study was to investigate a previously overlooked, universally introduced environmental factor, fetal and retroviral contaminants in childhood vaccines, absent prior to change points (CPs) in autistic disorder (AD) prevalence with subsequent dose-effect evidence and known pathologic mechanisms of action. Worldwide population based cohort study was used for the design of this study. The United States, Western Australia, United Kingdom and Denmark settings were used. All live born infants who later developed autistic disorder delivered after 1 January 1970, whose redacted vaccination and autistic disorder diagnosis information is publicly available in databases maintained by the US Federal Government, Western Australia, UK, and Denmark. The live births, grouped by father's age, were from the US and Australia. The children vaccinated with MMRII, Varicella and Hepatitis A vaccines varied from 19 to 35 months of age at the time of vaccination. Autistic disorder birth year change points were identified as 1980.9, 1988.4 and 1996 for the US, 1987 for UK, 1990.4 for Western Australia, and 1987.5 for Denmark. Change points in these countries corresponded to introduction of or increased doses of human fetal cell line-manufactured vaccines, while no relationship was found between paternal age or Diagnostic and Statistical Manual (DSM) revisions and autistic disorder diagnosis. Further, linear regression revealed that Varicella and Hepatitis A immunization coverage was significantly correlated to autistic disorder cases. R software was used to calculate change points. Autistic disorder change points years are coincident with introduction of vaccines manufactured using human fetal cell lines, containing fetal and retroviral contaminants, into childhood vaccine regimens. This pattern was repeated in the US, UK, Western Australia and Denmark. Thus, rising autistic disorder prevalence is directly related to vaccines manufactured utilizing human fetal cells. Increased paternal age and DSM revisions were not related to rising autistic disorder prevalence.

Key words: Autism disorder, change point, vaccine, paternal age.

Format: Abstract

Issues Law Med. 2015 Spring;30(1):47-70.

Epidemiologic and Molecular Relationship Between Vaccine Manufacture and Autism Spectrum Disorder Prevalence.

Deisher TA, Doan NV, Koyama K, Bwabye S.

Abstract

OBJECTIVES: To assess the public health consequences of fetal cell line manufactured vaccines that contain residual human fetal DNA fragments utilizing laboratory and ecological approaches including statistics, molecular biology and genomics.

METHOD: MMR coverage and autism disorder or autism spectrum disorder prevalence data for Norway, Sweden and the UK were obtained from public and government websites as well as peer reviewed published articles. Biologically, the size and quantity of the contaminating fetal DNA in Meruvax II and Havrix as well as the propensity of various cell lines for cellular and nuclear uptake of primitive human DNA fragments were measured and quantified using gel electrophoresis, fluorescence microscopy and fluorometry. Lastly, genomic analysis identified the specific sites where fetal DNA fragment integration into a child's genome is most likely to occur.

RESULTS: The average MMR coverage for the three countries fell below 90% after Dr. Wakefield's infamous 1998 publication but started to recover slowly after 2001 until reaching over 90% coverage again by 2004. During the same time period, the average autism spectrum disorder prevalence in the United Kingdom, Norway and Sweden dropped substantially after birth year 1998 and gradually increased again after birth year 2000. Average single stranded DNA and double stranded DNA in Meruvax II were 142.05 ng/vial and 35.00 ng/vial, respectively, and 276.00 ng/vial and 35.74 ng/vial in Havrix respectively. The size of the fetal DNA fragments in Meruvax II was approximately 215 base pairs. There was spontaneous cellular and nuclear DNA uptake in HFF1 and NCCIT cells. Genes that have been linked to autism (autism associated genes; AAGs) have a more concentrated susceptibility for insults to genomic stability in comparison to the group of all genes contained within the human genome. Of the X chromosome AAGs, 15 of 19 have double strand break motifs less than 100 kilobases away from the center of a meiotic recombination hotspot located within an exon.

CONCLUSION: Vaccines manufactured in human fetal cell lines contain unacceptably high levels of fetal DNA fragment contaminants. The human genome naturally contains regions that are susceptible to double strand break formation and DNA insertional mutagenesis. The "Wakefield Scare" created a natural experiment that may demonstrate a causal relationship between fetal cell-line manufactured vaccines and ASD prevalence.

PMID: 26103708

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Newborn immune activation may have long-term negative impact on brain function

New research shows that triggering the immune system in infant mice produces symptoms often seen in autism spectrum disorder and other developmental conditions

Date: January 12, 2018
Source: McLean Hospital

Summary: Neuroscientists have found that even a brief episode of immune system activation within days of birth can cause persistent changes in sleep patterns concurrent with increases in epilepsy-like brain activity -- a combination of symptoms common in autism spectrum disorder (ASD) and other developmental conditions.

FULL STORY

McLean Hospital neuroscientists have found that even a brief episode of immune system activation within days of birth can cause persistent changes in sleep patterns concurrent with increases in epilepsy-like brain activity -- a combination of symptoms common in autism spectrum disorder (ASD) and other developmental conditions. The detailed findings are available in the January 12, 2018, issue of Neuropsychopharmacology.

"A growing body of evidence suggests that immune system activation, such as that caused by bacterial and viral infections, can play important roles in many brain disorders," explained William Carlezon, PhD, chief of the Division of Basic Neuroscience at McLean Hospital, and senior author of the paper. "While previous research in laboratory animals has established that immune activation during critical prenatal (before birth) developmental periods can later produce the core features of ASD, including decreased social interaction, aberrant communication, and increased repetitive behavior, we wanted to evaluate whether postnatal (during infancy) immune activation could also produce other symptom clusters that are often seen in ASD and related conditions."

In humans, ASD is also frequently associated with certain co-occurring medical conditions, such as sleep disorders and seizures. To determine whether early postnatal immune system activation can produce these types of effects, McLean researchers treated mice with a lipopolysaccharide (LPS), a chemical that simulates a bacterial infection and causes a temporary (1-3 day) activation of the immune system. The LPS was given at a time point in mice (9 days after birth) that approximates the stage of brain development in humans at birth after full-term pregnancy. The mice were then implanted with micro-transmitters that enabled the researchers to collect an uninterrupted stream of data on sleep, muscle movement, and activity levels. Data collection continued through 12 weeks of age, a time point considered to represent adulthood in mice.

Carlezon, who is a professor of psychiatry at Harvard Medical School, and his team discovered that temporary immune system activation shortly after birth produced two main findings in the adult mice. First, immune-activated mice spent more time in slow-wave sleep, a sleep phase often associated with systemic inflammation. Second, the mice also showed dramatic increases in brief (lasting 2-3 seconds) bouts of abnormal brain wave activity. These events had the hallmark characteristics of spike-wave discharges (SWDs), a type of epilepsy-like brain activity that is not accompanied by full-body seizures. Although the SWDs occurred throughout the day, they were much more prevalent during periods when the mice were sleeping. When they occurred during wakefulness, they were accompanied by complete behavioral arrest -- a period of no movement throughout the body -- and immediately followed by recovery of normal brain activity and movement. Collectively, these findings demonstrate that even a brief period of immune system activation during critical periods of early development can leave a long-term signature upon the brain.

"The fact that immune system activation can produce these effects on its own, without any type of accompanying injury or trauma, provides new insight on the many paths that can lead to abnormal brain function" said Carlezon. "While there are clearly other factors that can cause these types of abnormalities, including genetic vulnerabilities, demonstrating that immune activation alone can produce these effects offers new hope for treatments that might reduce their severity, or prevent them altogether, in certain individuals."

While Carlezon's research focuses on animal models, his findings have implications for humans. The researchers believe that studying early developmental immune activation in mice may be valuable for diagnosing certain human illnesses and understanding how they develop. Persistent alterations in slow-wave sleep may represent a biomarker that could help differentiate immune-related neuropsychiatric conditions from those with other causes. Meanwhile, understanding epilepsy-like brain activity during both sleep and wakefulness may be useful in developing improved models of ASD. Studies in humans have shown that up to 60% of individuals with ASD experience SWDs during sleep, despite no diagnosis of clinical epilepsy, suggesting accuracy of the mouse model. The SWDs during wakefulness may resemble conditions such as "absence seizures" in humans, which are characterized by a brief loss of consciousness, a blank stare, and cessation of movement, and are often confused with inattention or intellectual disability.

"While more research needs to be conducted, these findings are a significant step forward in unlocking the mystery of ASD and other developmental disorders," said Carlezon.

Story Source:

Materials provided by **McLean Hospital**. Note: Content may be edited for style and length.

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McLean Hospital. "Newborn immune activation may have long-term negative impact on brain function: New research shows that triggering the immune system in infant mice produces symptoms often seen in autism spectrum disorder and other developmental conditions." ScienceDaily. ScienceDaily, 12 January 2018. <www.sciencedaily.com/releases/2018/01/180112095934.htm>.

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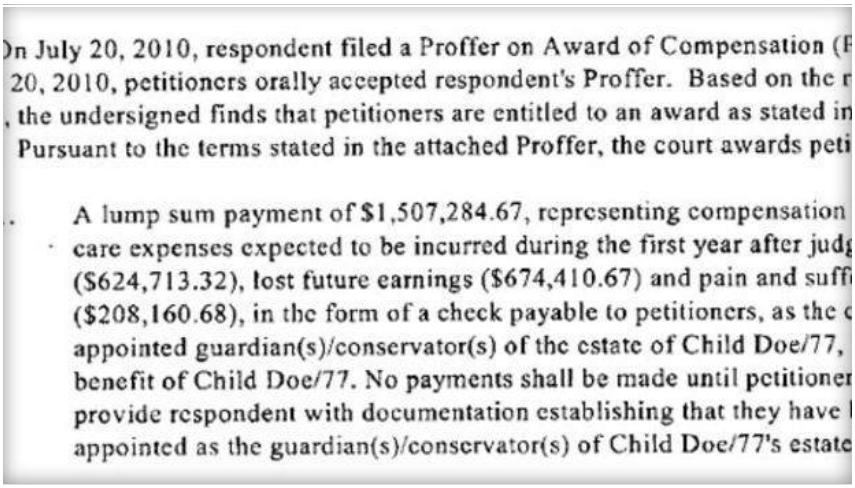
FROM AROUND THE WEB

By SHARYL ATTKISSON / CBS NEWS / September 10, 2010, 10:44 AM

Family to Receive $1.5M+ in First-Ever Vaccine-Autism Court Award



)n July 20, 2010, respondent filed a Proffer on Award of Compensation (F
20, 2010, petitioners orally accepted respondent's Proffer. Based on the r
, the undersigned finds that petitioners are entitled to an award as stated in
Pursuant to the terms stated in the attached Proffer, the court awards peti

A lump sum payment of $1,507,284.67, representing compensation
care expenses expected to be incurred during the first year after judg
($624,713.32), lost future earnings ($674,410.67) and pain and suff
($208,160.68), in the form of a check payable to petitioners, as the c
appointed guardian(s)/conservator(s) of the estate of Child Doe/77,
benefit of Child Doe/77. No payments shall be made until petitioner
provide respondent with documentation establishing that they have
appointed as the guardian(s)/conservator(s) of Child Doe/77's estate

Nine-year-old Hannah Poling is shown. (AP Photo/Atlanta Journal-Constitution, John Spink)

The first court award in a vaccine-autism claim is a big one. CBS News has learned the family of Hannah Poling will receive more than $1.5 million dollars for her life care; lost earnings; and pain and suffering for the first year alone.

In addition to the first year, the family will receive more than $500,000 per year to pay for Hannah's care. Those familiar with the case believe the compensation could easily amount to $20 million over the child's lifetime.

Hannah was described as normal, happy and precocious in her first 18 months.

Then, in July 2000, she was vaccinated against nine diseases in one doctor's visit: measles, mumps, rubella, polio, varicella, diphtheria, pertussis, tetanus, and Haemophilus influenzae.

Afterward, her health declined rapidly. She developed high fevers, stopped eating, didn't respond when spoken to, began showing signs of autism, and began having screaming fits. In 2002, Hannah's parents filed an autism claim in federal vaccine court. Five years later, the government settled the case before trial and had it sealed. It's taken more than two years for both sides to agree on how much Hannah will be compensated for her injuries.

Read Sharyl Attkisson's 2008 report on Hannah Poling

In acknowledging Hannah's injuries, the government said vaccines aggravated an unknown mitochondrial disorder Hannah had which didn't "cause" her autism, but "resulted" in it. It's unknown how many other children have similar undiagnosed mitochondrial disorder. All other autism "test cases" have been defeated at trial. Approximately 4,800 are awaiting disposition in federal vaccine court.

On July 20, 2010, respondent filed a Proffer on Award of Compensation (Proffer). On July 20, 2010, petitioners orally accepted respondent's Proffer. Based on the record a a whole, the undersigned finds that petitioners are entitled to an award as stated in the Proffer. Pursuant to the terms stated in the attached Proffer, the court awards petitioners:

1. A lump sum payment of $1,507,284.67, representing compensation for life care expenses expected to be incurred during the first year after judgment ($624,713.32), lost future earnings ($674,410.67) and pain and suffering ($208,160.68), in the form of a check payable to petitioners, as the court appointed guardian(s)/conservator(s) of the estate of Child Doe/77, for the benefit of Child Doe/77. No payments shall be made until petitioners provide respondent with documentation establishing that they have been appointed as the guardian(s)/conservator(s) of Child Doe/77's estate;

Time Magazine summed up the relevance of the Poling case in 2008: ...(T)here's no denying that the court's decision to award damages to the Poling family puts a chink -- a question mark -- in what had been an unqualified defense of vaccine safety with regard to autism. If Hannah Poling had an underlying condition that made her vulnerable to being harmed by vaccines, it stands to reason that other children might also have such vulnerabilities."

Then-director of the Centers for Disease Control Julie Gerberding (who is now President of Merck Vaccines) stated: "The government has made absolutely no statement indicating that vaccines are a cause of autism. This does not represent anything other than a very specific situation and a very sad situation as far as the family of the affected child."

Read the newly-released decision on Hannah Poling's compensation.

Sharyl Attkisson
ON TWITTER »
Sharyl Attkisson is a CBS News investigative correspondent based in Washington.

THE BLOG 05/10/2011 12:41 pm ET | Updated Jul 10, 2011

High Rates of Autism Found in Federal Vaccine Injury Program: Study Says More Answers Needed

By David Kirby

On Tuesday in Washington, members of the Elizabeth Birt Center for Autism Law and Advocacy (EBCALA), along with parents and children who received federal vaccine injury compensation, are having a press conference "to unveil an investigation linking vaccine injury to autism."

For the past two decades, according to the group, "the federal government has publicly denied a vaccine-autism link, while at the same time its Vaccine Injury Compensation Program (VICP) has been awarding damages for vaccine injury to children with brain damage, seizures and autism."

Their investigation, "based on public, verifiable government data, breaks new ground in the controversial vaccine-autism debate," and reports that "a substantial number of children compensated for vaccine injury also have autism — the evidence suggests that autism is at least three times more prevalent among vaccine-injured children than among children in the general population."

The following is a written Q&A conducted with EBCALA Directors:

Q) What is the Elizabeth Birt center, and who are the principal investigators on this project?

A) The Elizabeth Birt Center for Autism Law and Advocacy (EBCALA) is a nonprofit organization founded in 2008 to educate lawyers, advocates and parents about the legal challenges of autism (www.ebcala.org). The authors of this study are EBCALA board members. Mary Holland, Robert Krakow and Lisa Colin are attorneys and Louis Conte is a law enforcement officer who served as lead investigator.

Q) What were the main findings of this investigation?

A) The investigation found 83 cases of autism associated with compensated cases of vaccine-induced brain injury. It found that autism is at least three times more prevalent among vaccine injured children than among children in the general U.S. population today.

Q) How were the data compiled and analyzed?

We began collecting data over two years ago. We asked the federal government to provide us with this data through a Freedom Of Information Act request. We were told that our request would take four to five years, would cost $750,000, and would afford us incomplete information. We then assembled data about VICP decisions from legal databases and settlement information from publicly available docket reports. We found 21 published cases detailing autism spectrum disorders by name or description, which the study includes. We then interviewed families that we located through the docket reports. We trained interviewers to use a structured interview form for gathering information about the compensated cases. We also asked parents to complete standardized screening questionnaires for autism and to provide additional documentation. In these interviews, 62 families reported autism associated with vaccine injury.

Q) What evidence do you have that all these children actually received an ASD diagnosis?

A) In almost half the 83 cases, we have confirmation of autism beyond parental report, including medical and education records and completed standard autism screening questionnaires which are have a high degree of accuracy. The study calls for the complete medical review of all compensated cases of vaccine injury, including formal autism diagnosis, where appropriate.

Q) The government has conceded that vaccine injury can lead to brain disease (encephalopathy) and seizure disorders, but what scientific evidence is there to show that these injuries can result in autism symptoms?

A) This study is a review of decided and settled cases of vaccine-induced brain injury; it does not purport to be a scientific study. HHS or the Vaccine Injury Compensation Program compensated these cases based on the best available scientific information. Through interviewing the families of compensated claims, we have uncovered an association between vaccine-induced brain injury and autism. The article suggests that there is significant overlap between the definition of autism and the VICP's definitions of encephalopathy, seizure and sequela (resulting events).

Q) Don't these results simply suggest that children with ASD are more susceptible to vaccine injury than typical children? In others words, wasn't the injury an effect, rather than a cause of the ASD?

A) The parents interviewed in this study report that vaccines caused their children's autism as well as brain damage and seizures. The study notes a clear association between vaccine injury and autism in 83 compensated cases. The government has not previously brought this association to public attention. Whether this association between vaccine injury and autism is causal is one of the critical unanswered questions to which the study seeks answers. That is why the study calls on Congress to investigate further and to require full medical and scientific evaluation of all compensated claims of vaccine injury.

Q) Many critics say that it is easy to win a case in the VICP ("Vaccine Court") and that the legal standards of proof are much lower than in civil court. Dr. Paul Offit called it a "Kangaroo Court" after Hannah Poling won compensation for her autism and epilepsy (though he praised the court when it ruled against children with autism) — what is your response?

A) The VICP and HHS rely on the best science available in making compensation decisions. Proceedings are based largely on scientific and medical evidence in a field that the Court of Appeals for the Federal Circuit has described as "bereft of complete and direct proof of how vaccines affect the human body." Less than one in five claims in the VICP have received compensation. There is little question that those cases that have received compensation, including the 83 noted in our study, were the result of vaccine injury. Yet despite having received compensation, most of the families we interviewed were highly critical of the VICP, finding it to be exceptionally slow, parsimonious and hostile to petitioners.

Q) Critics also charge that these are merely legal decisions made by administrative judges, and not scientific conclusions based on rigorous analysis of all the existing data, and as such, they have no bearing on the debate about the causes of autism. Your reply?

A) We disagree. These compensation decisions are based on the best medical and scientific information available to the VICP and HHS. Many peer-reviewed scientific studies have used these compensated cases to elucidate the nature of vaccine injury. We have uncovered an association between vaccine injury and autism. Because we were only able to reach a fraction of the more than 2,500 individuals compensated for vaccine injury, we believe that we have identified the tip of the iceberg of this association. The study calls on Congress to investigate further and to ensure rigorous scientific analysis of all cases of compensated vaccine injury.

Q) Others contend that most of the seizure disorders reported in your paper were compensated following DTP vaccination, and that the government removed seizure disorders as an outcome of the DTP vaccine years ago after new evidence showed there was no association.

They contend that these cases should not have been compensated and do not provide evidence of an association between vaccines and autism, especially since many ASD children also suffer from seizure disorders. Your response?

A) Residual seizure disorder was removed as a presumption for vaccine injury from the VICP; that certainly does not mean that vaccines no longer cause seizure disorders in some children. In practice, the removal has meant that compensation for vaccine-induced seizure disorder is more difficult, but there have many compensated cases since that removal nonetheless. The study details compensation decisions before and after the removal of residual seizure disorder as a presumption for causation.

Q) How many of the cases you listed were for DTP vaccine, and what other vaccines were involved?

A) Diphtheria-petussis-tetanus (DPT) is the stated cause for 62 of the 83 cases; measles-mumps-rubella (MMR) makes up the next largest group, followed by cases caused by the diphtheria-acellular pertussis-tetanus (DpaT) vaccine.

Q) Many people will dismiss this paper as the act of desperate parents who willfully ignore all of the epidemiological studies done to date that show no link between vaccines and autism. Do they have a point? Again, why should anyone care about the legal proceedings of some obscure court when so much published science says otherwise?

A) Government officials in HHS or the VICP decided that the children in this study suffered vaccine injury based on science. We uncovered that these children also have autism. How can the government then continue to assert that there is no link between vaccines and autism? If in fact there is no link, why would there be even one case of vaccine-associated autism, let alone 83? The government itself is now calling for more research on vaccines and autism, including the VICP itself. Congress should investigate the vaccine-autism association in the VICP.

Q) In addition to being legal professionals and EBCALA board members, the authors are parents of children with an ASD diagnosis, and two of them have claims before the VICP. Does this bias the reporting and analysis of the study?

A) The two authors' pending claims on behalf of family members are disclosed; those claims are not the subject of this study in any way. The authors' experiences fuel their motivation in undertaking this investigation; they do not bias the study results which are based exclusively on government compensation decisions and structured interviews conducted by trained researchers. No attorney-authors conducted interviews with parents or caregivers; only trained non-lawyer researchers conducted interviews to avoid any possible conflict of interest.

Q) Where and when will this paper be published?

A) The article will be published on Tuesday, May 10 in the Pace Environmental Law Review at digitalcommons.pace.edu.

Q) What impact do you hope it will have?

The article calls on Congress to investigate the Vaccine Injury Compensation Program and to ensure that there is a medical review of all compensated cases of vaccine injury. We hope that the article leads to these results.

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What is regressive autism and why does it occur? Is it the consequence of multi-systemic dysfunction affecting the elimination of heavy metals and the ability to regulate neural temperature?

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Abstract

There is a compelling argument that the occurrence of regressive autism is attributable to genetic and chromosomal abnormalities, arising from the overuse of vaccines, which subsequently affects the stability and function of the autonomic nervous system and physiological systems. That sense perception is linked to the autonomic nervous system and the function of the physiological systems enables us to examine the significance of autistic symptoms from a systemic perspective. Failure of the excretory system influences elimination of heavy metals and facilitates their accumulation and subsequent manifestation as neurotoxins: the long-term consequences of which would lead to neurodegeneration, cognitive and developmental problems. It may also influence regulation of neural hyperthermia. This article explores the issues and concludes that sensory dysfunction and systemic failure, manifested as autism, is the inevitable consequence arising from subtle DNA alteration and consequently from the overuse of vaccines.

Keywords: autism, physiological systems, autonomic nervous system

Introduction

That the occurrence of autism has risen steadily in the last decades is not in dispute. Prior to the 1930's and the introduction of vaccinations autism was unknown. By 1968 in the UK, when Polio and DPT vaccines were given at 6 and 7 months autism was very rare. In 1988, when Polio and DPT was given at 3 months, DPT at 5 months and MMR at c13 months autism rates were still low. In 1996, when Polio and DPT/HIB injections were given at 2, 3 and 4 months, followed by MMR at c13 months autism rates began rising rapidly. By 2006 the occurrence of autism had reached pandemic proportions. In the period shortly before the 1980's the occurrence of autism was estimated to be circa 3-5 per 10,000; the majority having autism from birth[1]. Since the introduction of multiple vaccines the prevalence of autism has increased to an estimated 1 in 166 i.e. 60 per 10,000. Furthermore the trend is that of a continued increase. Some British teachers are claiming to see ASD in one in every 86 children[2]. This is supported by research which suggests that one in 100 British children may have some form of autism[3] and that ASDs are more prevalent than hitherto imagined[4] i.e. only severe cases of autism are recorded in the statistics. Such claims have been dismissed as mere speculation on the basis that there is not yet definitive proof of such claims however the perceived lack of evidence does not indicate that proof does not exist[5,6]. It may indicate that the understanding of the condition remains 'beyond the prevailing level of knowledge' (Table 1) [7].

By 1985 the incidence of regressive autism had equalled that from birth. By 1997 both types had increased although the regressive form was now >75% of the total occurrence. This suggests that an acquired condition was overtaking birth defects or purely genetic conditions. Autism affects four boys to every girl[10]. By contrast Autism appears not to occur in communities which do not use vaccines[11]. It occurs in immigrants from tropical climates who appear to have greater familial predisposition to autism[12] e.g. among Somali students in Minneapolis there was a rate of 1 in 28 (which compares with the local average of 1 in 56). This is more than five times the national rate of 1 in 150. Since the

1960's the number of vaccines given to a child before entering school has risen to c33. In children born to military families the occurrence of autism may now be as low as 1 in 67. In the vast majority of cases, the emergence of autistic indications appears to happen in children who had developed normally[10,13,14], and before three years[15,16]. The development of normal immune function appears to cease in the second year and is linked to the schedule of vaccines[17] and/or the MMR vaccine[18,19]. The consequences to society are estimated at c£2.4M in an autistic child's lifetime[20] which, if it continues to increase as many predict, will impose an unsustainable financial burden upon healthcare, education and social welfare systems.

The Systemic Nature of Physiology and Function

The body is a bio-dynamic, wholistic and systemic organism. It responds to sensory input which enables the autonomic nervous system thereby influencing behavior, the regulation of physiological systems, and function of the visceral organs (Fig. 1). The established association between visual perception, the autonomic nervous system, physiological systems, and biochemistry[21] raises issues which may be relevant to autism research.

- Different diseases are associated with differing colour perception[22] e.g. a yellow-blue deficit in diabetes[23], etc
- Different drugs are associated with altered color perception[24].
- Enzymes/Proteins are active in the visual spectrum[25,26].
- Suppressed immune function affects cognition[27]. In particular, t-cell deficiency (a common indicator of stress) is linked to cognitive dysfunction.

Any form of biochemical variation must therefore influence sense perception, sensory coordination and cognitive function. The existence of the physiological systems is not in doubt although there is not universal agreement on their structure. There is wide recognition that they regulate the function of organs (in each system), and that there are higher and lower levels for each system (homeostatic limits), however such systems remain an elusive and under-researched area of medicine. The Russian researcher I.G.Grakov[28,29] has mathematically modelled the consequences of cognition upon the autonomic nervous system and physiological systems. This included identifying and mapping the nature and structure of the physiological systems (Table 2).

Physiological Systems

Sleeping, Breathing, Digestion, Excretion, Osmotic Pressure, Blood Pressure, Blood Cell Content, Blood Volume, Blood Glucose , Sexual Function, pH, Temperature, Posture and Locomotion. See Table 2.

Such an explanation is highly inclusive and complete by comparison to the currently accepted but exclusive and limited explanation. The essential functions of temperature, sleeping and pH are now included; excretion is not limited to urination; whilst blood cell content (and other related systems) comprise what has hitherto been regarded as the immune system. Absorption of nutrients is influenced by system function including (but not limited to) blood pressure, blood volume, blood cell content, pH, temperature, etc. Elimination of toxins is similarly influenced by the complexities of system function.

The brain manages the autonomic nervous system and the function of the physiological systems. In addition, the brain waves are in a dynamic relationship with molecular biochemistry illustrating how drugs can be used to influence the body's biochemistry in order to act upon the symptoms of disease and how brain wave technologies such as neurofeedback can be used to alter the brain waves, physiological systems, organs, cells and molecular bio-chemistry.

Such systems regulate the function of the body's biochemistry e.g. (1) Most enzymatic reactions in the body are temperature dependent and catalysed by Magnesium. (2) The body requires maintenance of pH within a narrow operating range, and also the supply of minerals and vitamins/cofactors, to catalyse protein-substrate reactions in the body. (3) Appropriate blood volume, blood pressure, blood cell content and pH are required to ensure optimal absorption of minerals, vitamins, fatty acids from the intestines.

It is increasingly accepted that the synchronised activity of groups of neurons[30] in functionally coherent structures (the physiological systems), which exist in the brain and the body, synchronise their electrical impulses[31]. This may be evident when noting the evoked visual potentials, indicative of neural synchronisation, which are atypical in autism[32] and which may be part of the processes influencing sense perception (figure 1), sense coordination, memory[33], learning, etc. If so, this indicates that sensory input through the neurovisual pathways is integrated into actions, behaviour and movement and that learning requires synchronised activity between the brain, sensory

organs[34–36], and visceral organs. This is severely disrupted in the autistic[37]. Autism affects the function of all of the brain[38–40]. It is a neurobiologic, multi-systemic disorder i.e. affecting the function of every organ but not necessarily its structures[41]. It affects all aspects of the autonomic nervous system and hence influences all aspects of brain's function including that of neural networks involved in learning, memory, the function of the senses and the visceral organs.

The cerebellum, considered to be implicated in autistic spectrum disorders[42] comprises an estimated 50% of the brain's total processing capacity yet its role is not clear or understood[43]. It is involved in the accumulation of sensory data from the internal environment, including the organs in the body and those in the brain (including the sensory organs), thus distinguishing between sensory input from the external environment (a significant function of the cerebrum) and that of the biochemistry affecting the function of every organ (a significant function of the cerebellum), including the cerebellum. Such a role includes the processing, regulation and distribution of this data, through structures such as the Purkinje cells in the cerebellum which are attached by nervous structures to every part of the body. This includes the receipt of biosignals involved in the processes of movement, coordination and balance. Impaired flow of data to the brain via the cerebellum (and brainstem) may lead to functional problems affecting the body's fine control of e.g. balance, coordination, etc. Movement and balance involve the coordinated function of all body systems and organs and are coordinated by (1) sensory feedback from the external and internal environments and (2) the allocation of energy resources to and from each organ. They are dependent upon the precise nature, and timing, of data about each organ being provided to and by the cerebrum and cerebellum. This illustrates how the brain determines behaviour and actions appropriate to developing situations. It illustrates how changes at the organ, cell or molecular level influence brain function and vice-versa.

There are indications of cerebellar dysfunction in autism[44]. Inhibited flow of data to the cerebellum may be followed by developmental decay, cerebellar dysfunction[45,46], and reduced size of brain-stem. This is equivalent to the ‘use it or lose it’ phenomena affecting muscle tone and function.

Without cognitive input the brain cannot and does not function. Disease and drugs create cognitive dysfunction, altered sense perception, in particular affects visual perception. Accordingly, vaccines must also influence sense perception and coordination. Vaccines have a long-term influence and hence may have a more pervasive influence upon sense perception.

Our cognitive function depends upon the extent and coordination of sense perception i.e. between the eyes, ears, nose, mouth and skin. Genetic and/or environmental influences affect sense perception, the degree of sensory coordination and ultimately our connectedness with the surrounding world. Visual function is linked to the primary mechanism (rods, cones and pigments) but is also influenced at the biochemical level – noted by how pathology and drugs alter color perception[22,47] and affect the magnocellular and parvocellular neurovisual pathways which alter color perception and visual contrast. This influences the stability and function of the autonomic nervous system[48] and alters the processes of memory fixation, concentration, and behavior[49].

Anyone contracting disease e.g. measles, mumps, rubella, tetanus, etc; experiences altered visual perception therefore a weakened strain of the disease e.g. in vaccines, must also influence visual perception/cognition. Chronic disease is also accompanied by significant cognitive dysfunction and influences the coordination and processing of sense signals by the brain. The greater the number of illnesses, drugs or vaccines[50] the greater the alteration to the body's biochemistry therefore the greater its influence upon sense function and the degree of sensory distortion. It influences the autonomic nervous system and physiological systems and hence the coordination and function of every organ – visceral and sensory. This is a significant feature of autism[51,52].

Almost all diseases are linked to cognitive and behavioral disorders. Conversely, behavioral traits are influenced by biochemistry e.g. testosterone, oestrogen, cortisol, oxytocin, adrenaline, etc. Oxytocin influences the formation of social bonds influencing social engagement and attachment - which are dysfunctional in the autistic child[53–57].

Autonomic nervous system dysfunction?

In general problems with the stability of the autonomic nervous system[21,58] can be expected to be manifest as follows:

- Loss of Sense perception and Sensory Coordination
- System dysfunction (e.g. influencing breathing, blood pressure, heart rate, etc)
- Behavioural dysfunction (including learning problems, information feedback)

- Problems with Diet and Elimination (of toxins and wastes)
- Impaired and/or Delayed Neural Development
- Atypical brain waves

These are prevalent in autism.

Evidence of Systemic Dysfunction in Autism

Multi-systemic dysfunction is associated with a wide range of physiological disorders e.g. diabetes and obesity[59], cancer, cardiovascular disorders, pre-eclampsia, dyslexia[60], depression, etc. It affects the central[39] and autonomic nervous system in autistic children[61]. Systemic dysfunction in Autism includes that of temperature, blood cell content and immune function[62], blood pressure[63,64], digestion, excretion, posture and locomotion, sleep[65–67], pH, breathing; respiration rates, lower skin temperature. Each influences metabolic rate[68]. Autonomic dysfunction has also been linked to problems with appetite, swallowing food, nausea, recurrent vomiting, and abdominal bloating; constipation or diarrhoea; dry eyes, dilated pupils; dry skin, flushed skin following a meal, abnormal sweating, and unexplained high fevers; sleep apnoea, insomnia; bed-wetting, difficulty urinating, difficulty potty-training; altered perception of pain, sensory defensiveness, poor socialisation skills, anxiety, phobias, tics, emotional instability; and light intolerance. That autistic seizures are often linked to neural blood flow[69–71] is supported by fact that medications used to raise or lower blood pressure can alter the occurrence of seizures and improve sleep in the autistic child.

Autism affects sensory processing and sensory coordination[72] which is manifest in various ways e.g. tactile perception[73], vision[74], hearing[75], and smell. Autistic children may also display synaesthesia in which sensations become confused with one another[76]. Sounds may be experienced as touch or as visual stimulation e.g. autistic children may cover their eyes when they hear a loud sound. That autistic children have such sensory synaesthesia and sensitivity may indicate that their brains have extreme problems with sensory processing, regulation and coordination[77,78,60].

Vaccines and Vaccine Side-effects

Background The introduction of modified live viruses as vaccines enable the virus to attach its genetic material into the cell which replicates i.e. the host cell continues to function whilst producing the viral protein. This stimulates the production of antibodies. Under normal circumstances exposure to a viral disease would be countered (in vivo) at various levels enabling the body to steadily increase its immune response. By contrast, the injection of vaccines directly into the blood system overpowers the normal immune response leading to its rapid depletion. It is now suspected that long-term persistence of viruses and other proteins may produce chronic disease i.e. instead of producing a genuine immunity the vaccines are altering the body's systemic and biochemical stability, suppressing the production of differing types of white blood cells and hence immune function. Furthermore the introduction of many vaccines (up to 30 in a typical vaccination schedule) introduces a large number of foreign proteins which may be sufficient to ensure that immune function never returns to baseline and/or that immune biochemistry is fundamentally altered[62]. Consequently there now exists a growing concern which links immunizations to the huge increase in recent decades of auto-immune diseases[79] e.g., rheumatoid arthritis[80,81], multiple sclerosis, lupus erythematosus, lymphoma, leukemia, autoimmune demyelinative optic neuritis, diabetes mellitus, etc.

Vaccinations influence the balance of viral scavengers[82,83]. They suppress the production of b-cells, t-cells, etc. The synergistic action of these cells impairs antibody formation and becomes less effective in phagocytosis. This influences recognition of viral pathogens, leads to the progressive failure of immune function and hence to the increased incidence of auto-immune disease which we note as allergies[84–86] and immunodeficiency[87].

Some vaccinations have a greater effect than others e.g. Hib vaccine, pertussis vaccine[88–90], measles vaccine[91], etc. Indeed some articles indicate that the use of such vaccines can reliably induce asthma[92] by moderating adrenergic function[93].

Modified live viruses alter the structure and function of DNA. Each virus is a large molecule therefore its spatial arrangement must be influenced by its biochemistry which influences cross-helical structures and linkages within the DNA helix. Accordingly it is inevitable that the steady accumulation of such foreign proteins arising from an intensive vaccine programme will reach the stage where it significantly weakens DNA, gene, and chromosome structure and function. The prevailing reaction conditions - the consequence of protein expression which has been influenced by previous vaccines - will also affect the introduction of each modified live virus. Each will depress immune function. The

greater the number of viruses and foreign proteins (1) the greater the influence upon immune function and the time required for recovery from each vaccination; (2) the greater their influence upon DNA, gene and chromosome structure and function, the greater will be the risk of protein inhibition, system dysfunction, reproduction, etc.

The greater the amount of vaccines, introduction of foreign proteins and hence of alterations to the body's biochemistry the greater the risk that the body's immune function no longer recognizes or responds to existing vaccines or diseases[94] and/or that its immune response has been altered[95] and/or that sugar chains attached to an antibody alters its ability to bind to its receptors[96]. This may lead to mutated forms of disease[97–104] e.g. the reemergence of whooping cough[105], and a differentiated disease profile e.g. up to 30 per cent of individuals with a persistent cough are infected with B. pertussis[106]. Furthermore enhanced susceptibility to virus infection by vaccines is documented[107]. This could enable tougher strains to flourish[108].

Vaccines are not entirely safe. The currently used vaccines are merely less unsafe than previous vaccines[109,110] e.g.

- The Urabe strain of mumps vaccine in the MMR vaccine was replaced by the Jeryl Lynn mumps strain in response to reports from Japan linking the Urabe strain used, in the MMR vaccine, with high levels of meningoencephalitis.
- The Pluserix-MMR and Immramax-MMR vaccines were withdrawn because of reports of mild transient meningitis. The withdrawal of the smallpox vaccination led to a reduction in the incidence of TB.
- The Rubini vaccine continues to be used in some European territories although discredited[111].
- Leningrad-Zagreb strain is commonly used in developing countries, and may have superior efficacy when used during epidemics[112,113].
- Different strains of disease have different safety profiles[114]
- Different strengths of vaccine[115] carry risks which affect age groups or sexes differently.
- There are concerns over the use of whole-cell vaccines[116,117] although some argue that acellular vaccines are less effective[118].
- Sudden Infant Death Syndrome has been largely eradicated following withdrawal of the pertussis vaccine in Sweden and Japan.
- Side-effects arising from vaccination are associated with the onset of autoimmune disease[79,119], arthritis, diabetes mellitus, autoimmune demyelinative optic neuritis, etc.
- Sensory defects are a common side-effect of vaccines[120–122] e.g. sensori-neural hearing loss induced by the MMR vaccine.
- Drugs inhibit the effectiveness of vaccines (see 3.3.2). Systemic glucocorticoids (steroids) suppress the immune system and create risk of disseminated infection from live virus vaccines[123]. Vaccines may also be influenced by levels of immune function, dietary factors, and stress[124]. Many parents of autistic children and a number of medical experts believe the MMR vaccine is the culprit behind autism. In c15-20% of children it causes fever 7-12 days following immunization.

What are the risks from the diseases against which a vaccine is meant to protect?

Diphtheria, Polio, Tetanus, Meningitis, Pertussis Diptheria[125], Polio and Pertussis have largely been eradicated in the developed world although there may now be mutated forms of disease, a differentiated disease profile and/or an altered immune profile, which may be responsible for further outbreaks in vaccinated children and adults. Diphtheria is an upper respiratory tract infection characterized by sore throat and minor fever. It affects the central and peripheral nervous systems leading to deterioration of myelin sheaths, loss of motor control and sensation. Fatality rates are 5-10% although the rate of mortality may be higher for those under 5 years and over 40 years. It can be treated by antibiotics which prevent its transmission e.g. using erythromycin, procaine penicillin G, rifampin or clindamycin. Other minor complications including neck swelling, nausea, vomiting, listlessness, pallor, and a racing heart beat; lead to long term effects e.g low blood pressure, cardiac myopathy and peripheral neuropathy. Poliomyelitis is an infectious viral disease. Although c90% of polio infections are symptom-free, if the virus enters blood circulation this may lead to further complications. In c1% of cases, where the virus enters the central nervous system, it infects and/or destroys motor neurons thereby leading to muscle weakness and paralysis, usually involving the legs. Tetanus infection occurs through open wounds. It occurs commonly in hot, damp climates with soil rich in organic matter. It creates muscle spasms in the jaw, difficulty in swallowing, muscle stiffness and spasms throughout the body. The neonatal form of the disease is a

significant public health problem in the developing and/or agricultural economies. There are about one million cases of tetanus reported each year, mainly in the developing world, causing an estimated 300,000 to 500,000 deaths. In the United States, there are about five deaths from tetanus each year. Tetanus is the only disease that is infectious but not contagious. Pertussis is a highly contagious disease. There are 10–90 million pertussis cases and about 600,000 deaths per year. Sixty percent of all cases occur in the developing world. In children it is characterized initially by mild respiratory infection symptoms before developing into the characteristic 'whooping' cough. Other complications may include encephalitis, pneumonia, and secondary bacterial infections. Naturally-acquired disease caused by Hib (H. influenza) appears only to occur in humans with low natural immunity[126]. In infants and young children, H. influenza type b may cause pneumonia, and acute bacterial meningitis. Both H. influenza and S. pneumonia can be found in the upper respiratory system of humans i.e. both reside naturally in the body. Alterations in the immune response; attributed to poor nutrition, stress or transmission; enable their proliferation with potentially serious outcomes.

Measles, Mumps and Rubella Measles is largely a consequence of compromised immunity arising from poor diet and is linked to high levels of mortality[127] in the developing world. In developed countries, most children are immunized against measles by the age of 18 months, generally as part of the triple vaccine treating measles, mumps and rubella (children younger than 18 months usually retain measles antibodies (Immunoglobulins (Ig)) transmitted from the mother during pregnancy). The rate of mortality from measles is typically 0.3% however in the developing world this may be as high as 28%. The classical symptoms of measles are typically fever (up to 40C), cough, coryza and conjunctivitis. Complications include mild diarrhoea, pneumonia, encephalitis, SSPC, and corneal ulceration or scarring. They are usually more severe amongst adults. Permanent hearing loss or damage to vision is recognized complications of measles. Measles has been known to occur in children with congenital rubella syndrome, and has been implicated in the etiology of inflammatory bowel diseases (IBDs). The more common symptoms of mumps are parotitis, fever (typically 38.3C), headache and orchitis[128] Other symptoms of mumps include sore face and/or ears, and loss of voice. Known complications of mumps include infection of other organ systems, sterility in older men, mild forms of meningitis, encephalitis, sensorineural hearing loss, pancreatitis, inflammation of the ovaries, and risk of spontaneous abortion during pregnancy. Rubella is a mild disease which often passes unnoticed[129]. The primary reason for the introduction of a vaccine is to prevent infection during pregnancy. The common symptoms of rubella are the appearance of a rash on the face, trunk and limbs (after an incubation period of 14-21 days) which usually fades after several days. Other symptoms include fever (typically 38C), swollen glands (post cervical lymphadenopathy), joint pains, headache and conjunctivitis. Rubella is generally a mild disease, rare in infants or those over the age of 40. The older the person the more severe the symptoms e.g. some women experience arthritis type symptoms. Children exposed to rubella in the womb may show developmental delay, inhibited growth, hearing disabilities, diabetes, glaucoma, schizophrenia, etc. If infected during the first 12 week period of pregnancy this may lead to congenital rubella syndrome (CRS), which is manifest as a series of complications including spontaneous abortion and, in the neonate: cardiac, cerebral, ophthalmic and auditory side-effects. Known complications include prematurity, low birth weight, and neonatal thrombocytopenia, anemia and hepatitis. CRS is the main reason a vaccine for rubella was developed. It increases the risk of miscarriage or still birth in mothers who contract rubella shortly before or early in pregnancy. If the baby survives, it may have heart disorders, blindness, deafness, etc. CRS is manifest as sensorineural deafness, eye problems, heart disease. Other complications include low birth weight, mental retardation, problems with the spleen, liver and bone marrow, etc. Hepatitis B is difficult to catch and comes from blood or sexual contact with an infected carrier. Further, vaccine-derived immunity is thought to be short-lived. Hpv , an infection transmitted during sexual intercourse, clears naturally after several months/years. Mumps and Rubella may occur without the patient being aware that they have the disease.

Some diseases may confer natural immunity e.g. the mumps virus may confer a degree of immunity against ovarian cancer[130–133].

In summary, disease side-effects reflect the effect of the disease upon the body's functional systems i.e. upon temperature, digestion, excretion, etc. Typical viral fevers are circa 1-2C above the body's normal body temperature. Measles is particularly noteworthy because fever may reach 40C (or higher), some 3-4C above normal body temperature and just 1C below the point where proteins denature and at which brain death commences.

What are the risks from the Vaccine? Typical vaccine side-effects There is evidence that BCG and measles vaccinations administered singly reduce child mortality[134] but that this is unrelated to the incidence of measles or measles deaths[135,136]. By contrast the pertussis vaccine is associated with a negative effect[137].

Dtap: Recorded common side-effects with the DtaP vaccine include fever, tiredness, poor appetite, vomiting and inflammation. Less common and more severe side-effects include distress (crying), seizures, lowered consciousness or coma, brain damage.

MMR: Recorded common side-effects with the MMR vaccine include fever, swelling of the lymph glands, tiredness, poor appetite, and abhorrence of bright lights. More severe problems include low platelet count, pain and stiffness in the joints/inflammation. Less common and more severe side-effects include distress (crying), seizures, deafness, lowered consciousness or coma, brain damage.

Tdap: Recorded common side-effects with the Tdap vaccine include pain, chills, fever, headache, tiredness, poor appetite, stomach ache, vomiting, diarrhoea and inflammation

The above listed vaccine side-effects are indicative of systemic instability affecting most physiological systems – temperature (chills and fever), excretion (inflammation of the lymph glands), blood cell content (low platelet count), excretion (diarrhoea), digestion (poor appetite, vomiting), sleep (coma), and metabolic rate (tiredness, lowered levels of consciousness). In addition there is evidence of altered sense perception, indicative of problems with the autonomic nervous system, which affects hearing, visual perception (abhorrence of bright lights), smell and touch.

Significant vaccine side-effects have been linked to swine flu vaccine (Guillain-Barre paralysis); in RSV vaccine[138]; in the measles, mumps and MMR vaccines[139]; hepatitis A and B vaccine[140]; tetanus vaccine; smallpox vaccine; polio vaccine; pertussis vaccine[141], etc. The incidence of vaccine side-effects may now be sufficiently great to question the claims that the risks from the disease exceed that of vaccines[109].

The MMR vaccine has been linked to autism, Crohn's disease, inflammatory bowel disease[142,143] and other serious chronic stomach problems[144], epilepsy, brain damage including meningitis[145,146], cerebral palsy, pancreatitis[147] and diabetes mellitus[148–150], encephalopathy, encephalitis[151,152], hearing and vision problems, arthritis, behavioural and learning problems, chronic fatigue syndrome, diabetes, Guillain-Barre syndrome, idiopathic thrombocytopaenic purpura, subacute sclerosing panencephalitis (SSPE), leukaemia, multiple sclerosis, and death.

There is evidence that in cases of immune deficiency that viruses continue to persist in the body[143,153–155]. The measles virus is known to persist in patients with subacute sclerosing panencephalitis (SSPE), measles inclusion body encephalitis (MIBE)[156] and multiple sclerosis[157]. Since the introduction of measles vaccines, vaccine-associated SSPE has increased in the USA. Furthermore patients with B or T-cell immunodeficiencies have cognitive side-effects[27] and are advised against vaccination due to the risk of severe and/or fatal infection (Merck). That viruses persist in the body and are linked to autoimmune disorders is a feature of rubella virus[158–160], anthrax vaccination[161], hepatitis B[162], etc. There is a reported increased risk of death with combined vaccination DPT and polio[134].

In summary, vaccine's side-effects reflect the vaccine's influence upon the body's functional systems i.e. upon temperature, digestion, excretion, blood cell content, etc.

The Cumulative Effect of Vaccines There is concern that the cumulative effect of vaccines upon the body's function has not been properly assessed[137]. Unvaccinated children appear to have less exposure to disease[84,85], delaying vaccination reduces exposure to disease[163], contracting the disease naturally leads to less disease in future[164], and that excessive vaccination is considered ineffective and dangerous[165].

Vaccine-vaccine and Vaccine-drug interactions In general, vaccines may be influenced by antibiotics[166], immunoglobulins, immunosuppressants, monoclonal antibodies, anticoagulants and corticosteroids. The interaction between a vaccine and a drug has been reported only with influenza vaccine and four drugs (aminopyrine, phenytoin sodium, theophylline, and warfarin sodium), and with BCG vaccine and theophylline. The clinical significance of vaccine-drug interactions is not fully determined[167]. There is further evidence of interactions involving most vaccines e.g. HPV Vaccine: (http://hpv.emedtv.com/hpv-vaccine/drug-interactions-with-the-hpv-vaccine.html); Shingles Vaccine: An Introduction: (http://senior-health.emedtv.com/shingles-vaccine/drug-interactions-with-the-shingles-vaccine.html); yellow fever vaccine; polio vaccine (neomycin, streptomycin, phenoxy ethanol, formaldehyde), rotavirus vaccine, etc.

Vaccines are not subject to double blind clinical trials despite the evidence of vaccine-drug interactions and perhaps also of vaccine-vaccine interactions.

Effectiveness of Vaccines/Vaccines are not 100% effective Whooping cough is becoming increasingly prevalent[168–170]. Although claimed to be 88 per cent effective among children of 7-18 months, during a nationwide epidemic of whooping cough in 1993, a group of researchers discovered that 82 per cent had completed their full complement of DPT vaccines[171]. Others have commented that the whooping cough vaccine is only to be 36% effective[109].

Many studies show that the measles vaccine isn't completely effective[172–175] and that a significant proportion of those infected in measles outbreaks (>60%) had been vaccinated. There is also a lack of consensus concerning the effectiveness of whole or acellular vaccines, each having their own side-effects and effectiveness[176] e.g. vaccine efficacy was estimated at 75.4% for an acellular 5 component vaccine, 42.4% for an acellular two component vaccine and 28% for a whole cell DTP vaccine[177]. The whole-cell vaccine was associated with different levels of side-effects including significantly higher rates of crying, cyanosis, fever, and local reactions than the other three vaccines.

There is evidence of declining vaccine immunity[178] illustrated by transmission of mumps[179], measles[180,181], rubella[182], polio[183], Hib[184,185], Hepatitis B[186,187], smallpox, diphtheria, varicella[188], whooping cough[189], etc.

Effect upon Learning One in 14 children i.e. up to half of all children starting school, have problems with speech, language and communication[190]. Is this significant bearing in mind[4] that the occurrence of autism may be more widely spread than has hitherto been considered possible i.e. that only the most severe and chronic cases of autism are recorded? Learning problems are a significant problem in autism[191]. It affects the body's processing of data from the external and internal environments. This affects, in the autistic, the ability of the autonomic nervous system to regulate organ function and hence influences their ability to make sense of the external world. The problem may be part of a spectrum of biochemical disorders[60] influencing all aspects of the learning process e.g. including memory, concentration, sense perception and sense coordination.

Biochemical Evidence

Biochemical Instability Indications of almost complete physiological instability are manifest in the autistic as a proliferation of biochemical deficiencies e.g. (1) Fatty acid deficiency[192]; (2) a distinctly different immune response[62] including reduced natural killer cell activity[193], decreased immunoglobulins and T cells and altered lymphocyte functions[194,195–197], (3) Vitamin D deficiency[198]. Vitamin D regulates the levels of glutathione which may explain the link between heavy metals and autism. Depleted levels of glutathione increase oxidative stress, suppress the detoxifying effect of liver enzymes e.g. P450, reduce the elimination of heavy metals, and increase the neurodegenerative effects of heavy metals. Mercury inhibits the enzyme methionine synthase which converts homocysteine into methionine. Accordingly, levels of cysteine, glutathione and metallothionine are low. This illustrates that the methionine pathway may be faulty in many with autism and supports earlier suggestions that redox imbalances[199–200] and detoxification are impaired. (4) Vitamin A deficiency[201–202] is a commonly observed symptom of measles. The severity of complications have been linked to the degree of Vitamin A deficiency; (5) Carnitine deficiency[203]; (6) increased norepinephrine levels and decreased dopamine-hydroxylase activity[204]; (7) demonstration of inter- and intra- species differences in serotonin binding sites by antibodies from an autistic child[205]; (8) the levels of gut flora[206]; (9) Enterocolitis in Children with Developmental Disorders[207]; (10) Adenosine Deaminase Activity Decreased in Autism[208,209]; (11) Small intestinal enteropathy with epithelial, IgG and complement deposition in children with regressive autism[210]; (12) Mitochondrial disorder[211]. Findings suggest that mitochondrial dysfunction, including abnormal enzyme function, mitochondrial structure, and mitochondrial DNA integrity, may be present in children with autism[212].

Other biochemical deficiencies/chromosomal abnormalities include:

Phosphoribosylpyrophosphate (PRPP) synthetase superactivity, Adenylosuccinate lyase deficiency, Histidinemia, Lesch-Nyhan disease, Fragile X syndrome, Rett Syndrome, Dihydropyrimidine dehydrogenase (DPD) deficiency, Tuberous sclerosis, Superactivity of pyrimidine 5'-nucleotidase (P5N), etc.

The use of Drugs Biochemical instability is a feature of autism. Accordingly, drugs are used to mitigate autistic symptoms e.g. (1) Lofexidine[213] has been shown to improve prefrontal cortical function in nonhuman primates. This is consistent with the view that the prefrontal cortex regulates executive/system function. (2) An open trial[214] suggested that methylphenidate use in autistic hyperactive children may ameliorate hyperactivity, and impulsivity in autistic children. (3) Neuroleptics e.g. haloperidol, are mildly effective in reducing hyperactivity, impulsivity, and inattention in children with autistic disorder[215]; clonidine is used in the treatment of tic disorders and ADHD[216]. Other drugs used include Tianeptine[217]; Galanthamine[218]; Immunoglobulins[219]; melatonin[220]; and beta-blockers[221].

The Cause of Autism The occurrence of autism is due to a significant genetic insult[222] but it is not considered to be an inheritable condition. How and when this occurs can be debated however, for a young child with a developing immune system, there are few factors which could be held responsible other than vaccines and/or the related and damaging effect of exposure to high levels of mercury. No other factor or explanation has been offered as a viable alternative explanation for the occurrence of regressive autism. The evidence indicates there is alteration to

chromosome structure and/or function. It indicates the influence of external stressor(s) influencing mitochondrial structure and DNA, chromosomal instability and translocation, which ultimately influences protein expression. The combined effect influences system stability, organ function, the prevailing levels of biochemistry, sense perception, behavior, etc. It influences protein expression and the rate and completeness of subsequent protein-substrate reactions leading to lowered immune function, reduced absorption of nutrients, slowed metabolism, impaired development[262], etc; i.e. the body's biochemical processes do not proceed as they should.

Is this an indication of chromosomal damage?

Viruses are able to infiltrate cells, inserting their genetic material into them. As outlined earlier (see 4.1) there are biochemical markers of vaccine damage. That it affects four boys to every girl[10] illustrates that the condition is largely due to a defect with the X-chromosome and leads to consideration of the factors which could influence at the genetic/chromosomal level. In general, chromosomal damage is linked to radiation e.g. due to adverse nuclear events which leads ultimately to birth defects. The prevailing evidence appears to suggest the influence of e.g. proteolytic enzymes or temperature[223,224] which may alter chromosome structure. Little evidence has been offered for the 1 in 5 occurrence experienced by girls although this appears likely to be the consequence of a chromosomal stressor.

It is widely recognised that genetic predisposition and protein expression can be influenced by environment influences[7], and that genetic damage can be the result of exposure to radiation, however the evidence being offered appears to suggest a subtle form of genetic alteration - associated with the wider use of vaccines[17] - which may not necessarily be inherited but is responsible for altered system stability and function and consequently of altered biochemistry and function. There is evidence that system function is intact but dysfunctional i.e. that homeostasis is severely compromised. Such findings are supported by research into Gulf-War Syndrome (GWS) in which[225] untypical RNA was found in the blood of sick GW veterans. This illustrates that the viral encephalopathies originated from RNA-viruses and hence from vaccines. That immunosuppression, shown to be a factor in GWS[226] and autism, is associated with the concentrated use of vaccines[227] is further supported by the fact that French soldiers who were not vaccinated yet who served in the gulf war did not get GWS however American and British soldiers[228], irrespective of whether they served in Iraq or not, reported a significantly greater incidence of autistic-spectrum disorders and GWS.

The Effect of Heavy Metals

Heavy Metals and Mercury in particular, affects the function of the CNS and are extensively documented and associated with autism[229]. Amongst a variety of side-effects mercury decreases lymphocyte viability, and in the brain: dysfunction in the amygdala, hippocampus, basal ganglia, and cerebral cortex; destruction of neurons in the cerebellum; and brainstem abnormalities. Demyelination is evident in such conditions. The brain's electrical patterns are similarly abnormal.

A note on the following paragraph: Mercury was removed from vaccines except for multidose flu vaccines. Subsequently, the use of aluminum as an adjuvant in vaccines, began to increase. The mechanism of aluminum neurotoxicity is similar to that of mercury.

The most significant contributors to the increased mercury burden are: Mercury in vaccines (e.g. DTP (at typically 25 micrograms of mercury per dose), Tetanus, Hepatitis B & (most) influenza vaccines), contamination of fish[230], wild/bush fires; and emissions from power stations[231] and industrial chimneys including incinerators, waste-burning cement works, crematoria, etc. The characteristics of autism and mercury poisoning are extremely similar which suggests that autism arises from mercury poisoning[232,233]. Children with autism have greater amounts of mercury and other heavy metals in their system[234]. For these children the exposure route is considered to be predominately via childhood vaccines, most of which contain thimerosal. Vaccinated children of circa 10-20 kgs are exposed to an adult overdose of mercury, over 62.5 micrograms of mercury within the first three months, which significantly increases a child's risk of developing some form of neuro-developmental disorder such as impaired development, speech and language, autism, stuttering and attention deficit disorder.

Children living downstream of coal-fired power stations have a greater incidence of autistic spectrum disorders[231]. This indicates that the innate physiological processes, which the body uses to eliminate heavy metals, are being overcome by overexposure.

Mercury poisoning is an insidious process. In general the symptoms do not appear immediately upon exposure, although they may in especially sensitive individuals or in cases of excessive exposure. The initial preclinical stage is followed by the development of symptoms of mercury poisoning over a period which may last from weeks, months, and years[235–237]. Consequently, mercury given in vaccines to very young children would not be expected to lead to a recognizable disorder, except for subtle signs, before age 6-12 months, and might not emerge for several years[233].

In autistic children, the initial signs occur shortly after the first injections, and consist of abnormalities in motor behavior and in the sensory systems, particularly touch sensitivity, vision, and numbness in the mouth[15,238]. These signs are followed by parental reports of speech and hearing abnormalities appearing before the child's second birthday[10]. Finally, there is the development of autistic-like traits and a continuing regression or lack of development in subsequent years. These symptoms change[239] depending upon the circumstances surrounding each child.

Most autistic children have impaired liver detoxification. Many have low levels of metallothionine, conceivably the consequence of a deficiency of Zinc, which is indicative of a lowered capacity to chelate mercury and other heavy metals. Mercury is a powerful oxidant which depletes cellular antioxidants, especially glutathione. The P450 detoxifying enzymes of the liver rely heavily on adequate availability of glutathione. EthylMercury the active component in thimerosal causes apoptosis of the t-cells[240–242].

Although the withdrawal of mercury from vaccines has not resulted in an overall decline in the occurrence of autism this does not mean that the problem does not lie with thimerosal[243,263]. It may indicate that the problem is associated with the elimination of mercury[244] i.e. affecting function of the lymphatic system and excretion[245]. This is supported by noting evidence of urea cycle dysfunction. Problems with the urea cycle, conceivably the consequence of mercury poisoning, have been linked to autism. A child with ornithine transcarbamylase (OTC) deficiency is likely to be lacking in energy, have appetite problems, poorly-controlled breathing rate and/or body temperature, and slow development. Significantly, OTC deficiency is an X-linked recessive disorder (http://www.merck.com/mmpe/sec13/ch164/ch164a.html) one of a number of primary immunodeficiencies associated with vaccine use.

As in autism, onset of Hg toxicity symptoms is gradual in some cases, sudden in others[232,233]. In the case of poisoning, the first signs to emerge are abnormal sensation and motor disturbances. As exposure increases, these signs are followed by speech problems, and hearing deficits[246]. Upon removal of the mercury the symptoms tend to recede except in instances of severe poisoning, which may lead to death[232]. As in autism, epilepsy arising from Hg exposure is also associated with a poor prognosis[247]. Mercury acts upon the catecholamines and influences the function of the autonomic nervous system[245]. This affects cognitive performance[248], spatial vision[249], etc.

Other metals have been implicated in adverse neurodevelopmental outcomes in children e.g. lead and mercury[250,251], with exposure to cadmium, arsenic, antimony and chromium also a concern. Studies have found adverse effects of prenatal lead exposure on growth and development, but little research has examined an association with autism. Whilst Mercury is of concern, because of evidence for neurotoxic effects and the fact that it has become so prevalent in the wider environment[250], Aluminum also shares common mechanisms with mercury e.g. it interferes with cellular and metabolic processes in the nervous system. Children given the recommended vaccinations are injected with nearly 5 mg of aluminum by the time they are just 1.5 years old, almost 6 times the safe level. Furthermore the nature of the Aluminium affects the prevailing blood levels and is also increasingly implicated, through their use as vaccine adjuvants, in autism[252].

Current Therapeutic Approaches used to Treat Autism

There is evidence that autism is a treatable disease and that some therapies can mitigate the effects of autism[253,254]. Although there is no recognised method of treatment, or of significant and/or proven outcomes, autistic children appear to respond to therapies which enhance the function of the breathing , to enhance oxygen levels[255], and excretory system e.g. by osteopathy[256]. Moreover a commonly observed side-effect with autistic children is that when a child has an elevated temperature, perhaps resulting from a fever, the autistic symptoms appear to recede and the child behaves normally[41]. Autistic children suffer from adverse sleep patterns. In the US autistic children are often treated by chelation therapy and biofeedback[257–259].

Dysfunction of the Excretory or lymphatic system leads to long-term exposure to mercury which under normal circumstances would have been rapidly eliminated from the body. This may also lead to higher neural temperatures which will inevitably influence brain function.

Further evidence of biochemical deficits[260] and of the benefit of biochemical based supplements e.g. vitamin B6 and magnesium; melatonin; methylcobalamin; vitamin A, C & D supplements; dimethylglycine (DMG) and trimethylglycine (TMG). DMG provides building blocks that are required for purine nucleotide synthesis. DMG comes from TMG when TMG methylates homocysteine. Significantly, absorption of Vitamin A Palmitate requires an intact gut mucosa at the appropriate pH and in the presence of bile for metabolism. Many autistic children have damaged mucosal surfaces therefore they have impaired capacity to absorb vitamin A[261].

That some children can become normal when their temperature increases above normal levels e.g. due to a viral infection,[41] may illustrate that the levels of the homeostatic mechanism affecting the physiological systems have been reset at what can be considered to be abnormal levels[47]. This may indicate that autism is treatable - perhaps to a greater degree than has hitherto been considered possible.

Discussion

The mass of scientific evidence compiled by researchers clearly indicates that the incidence of autism occurs following vaccination and is most closely associated with the schedule of vaccines culminating in the MMR vaccine. That vaccines suppress natural immune function is not in dispute e.g. those with naturally low levels of immune function (immigrants from tropical climates) show greater predisposition to autistic spectrum disorders.

The immediate effect arising from vaccination influences gene function and protein expression. This leads to lower levels of white blood cells including e.g. lymphocytes, immunoglobulins, t-cells, b-cells and/or neutrophils, and disturbs their synergistic action and hence their ability to memorize and respond to immune responses when challenged. This impairs the ability to kill pathogens thereby predisposing to further infections. The short and long-term outcome is to the neural mechanisms regulating system function affecting e.g. pH, the excretory system, temperature, and the elimination of toxins and heavy metals. This explains why the discontinuation of thimerosal in vaccines was followed by a steady increase in the incidence of autism and hence that researchers did not find a correlation between the incidence of autism and the use of thimerosal-containing vaccines[263]. This may also explain the effect of multiple vaccines, in particular the MMR vaccine, and the greater predisposition to autistic spectrum disorders in military families.

In most autistic children brain structures are initially unaffected but become steadily underdeveloped as a consequence of exposure to mercury and other heavy metals. This evolves into a neurodevelopmental problem leading to chromosomal abnormalities, affecting myelination, the subsequent degeneration of the cerebellum, etc.

The MMR triple vaccine may inhibit normal immune function which, directly or indirectly, ultimately leads to chromosomal and/or genetic damage and/or dysfunction. The occurrence of GWS in adults, a condition with many features which are common with autism, indicates the problem may be due to the number and/or intense schedule of vaccinations however this does not excuse the measles or MMR vaccine from suspicion. The combined vaccine raises body temperature whilst lowering immune and system function. This may make a mild measles vaccine more virulent which may increase fever to an abnormally high level. It suggests (1) single vaccines may pose less risk than triple vaccines; (2) some vaccines pose a greater risk than others e.g. pertussis and measles; and (3) the way in which vaccines are administered will be accompanied by different side-effects e.g. if pertussis is followed by measles or vice-versa, if BCG gives a beneficial effect to be followed by pertussis, if vaccines are given in combination, etc. Increased disease loading is the inevitable consequence of multiple vaccine or lots of single vaccines or triple vaccines e.g. of asthma, autoimmune disease, etc. It suggests that adherence to the vaccine schedule is the problem – too many vaccines, too quickly.

Vaccines cause an inflammatory response in some e.g. for those with an inadequately developed or artificially lowered immune system, for those genetically predisposed, or perhaps due to viral or bacterial infection. This creates genetic damage and/or dysfunction and hence influences the brain's ability to regulate the physiological systems, and especially to the lymphatic system and its ability to excrete mercury and heavy metals, would lead to long-term damage and problems processing sensory/cognitive input. This would inevitably affect the brain's ability to maintain a regulated temperature below that which affects brain damage (41° C). This inevitably influences the autonomic nervous system and the stability of all related physiological systems including temperature, blood pressure, blood cell content, blood glucose, digestion, excretion, sleeping, etc.

Further evidence of multi-level dysfunction is evident from unusual brain-wave stability, aberrant sleep patterns, loss of sense perception and coordination, mirror neuron dysfunction, lower pain thresholds, mental and physical deterioration, short periods of concentration, etc. That it is a problem of systemic dysfunction is further supported by noting how it can be treated using sensory therapies which may facilitate the re-establishment of some degree of physiological stability.

Where is the proof that vaccines are safe? The argument has never been that they are completely safe but that the consequences are less than having the disease. Now it is illustrated that the consequences of intensive vaccination schedules pose a greater risk than could ever have been imagined. This leads to the evolution of new viral strains, an unsurprising development when the environment to which it is exposed is being altered by new proteins, structural variants and altered DNA.

Vaccines are an essential component of preventative healthcare however it may be necessary to review the ways in which vaccines are used, administered and regulated[141,264] i.e.

- As drugs are tested in the clinical environment to assess their interaction with other drugs, the cumulative use of vaccines including that of multiple vaccines should be researched and shown, through double-blind placebo controlled clinical trials, to be free from any such interactions i.e. of one single vaccine with another single or multiple vaccine or drug. It has been considered unethical to select a control group of children which would otherwise not be vaccinated yet such is the levels of conscientious objectors in the industrialized world and through circumstances of impoverishment in the underdeveloped countries that such statistics must currently exist.
- Measures to assess the suitability of children for vaccination i.e. how to assess whether a child has a greater predisposition to an adverse vaccine reaction and the subsequent development of autism?[265]
- The time when vaccinations should be given and the time between vaccinations e.g. giving mumps and rubella vaccinations later in childhood.
- Are some vaccines necessary in the industrialized world e.g. mumps, rubella, Hib, Hpv, etc? With more than 200 other vaccines under development this must be an issue of review.

The risks from disease and vaccinations differ upon location. In the developed world, there is an estimated 0.1-0.3% risk of mortality from measles which compares with a 0.6% risk and rising (with some estimates at 1-2%) of autism. This excludes the cost of treating the wide range of side-effects which must clearly be attributed to the use of vaccines. The cost of treating vaccine-related side-effects may now be far greater than the diseases against which the vaccine(s) were designed to protect. Furthermore, in the developed world there is a highly developed social structure which is able to assist parents to deal with the condition. By comparison, what are the implications for an autistic child in the developing world where there is absence of resources to deal with the condition?

Statement of Interest

Graham and Elena Ewing (Dr) are Directors of Montague Healthcare a company devoted to the commercialisation of Virtual Scanning and hence to the diagnostic and therapeutic use of Virtual Scanning. They are co-authors of the book ‘Virtual Scanning – a new generation of healthcare – beyond biomedicine?’ ISBN 978-0-9556213-0-7 published by Montague Healthcare books.

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Full text links

ELSEVIER FULL-TEXT ARTICLE

J Inorg Biochem. 2018 Apr;181:132-138. doi: 10.1016/j.jinorgbio.2017.09.019. Epub 2017 Oct 6.

Cognitive dysfunction associated with aluminum hydroxide-induced macrophagic myofasciitis: A reappraisal of neuropsychological profile.

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Author information

Abstract

Patients with macrophagic myofasciitis (MMF) present with diffuse arthromyalgias, chronic fatigue, and cognitive disorder. Representative features of MMF-associated cognitive dysfunction include attentional dysfunction, dysexecutive syndrome, visual memory deficit and left ear extinction. Our study aims to reevaluate the neuropsychological profile of MMF. 105 unselected consecutive MMF patients were subjected to a neuropsychological battery of screen short term and long-term memory, executive functions, attentional abilities, instrumental functions and dichotic listening. From these results, patients were classified in four different groups: Subsymptomatic patients (n=41) with performance above pathological threshold (-1.65 SD) in all tests; Fronto-subcortical patients (n=31) who showed pathological results at executive functions and selective attention tests; Papezian patients (n=24) who showed pathological results in storage, recognition and consolidation functions for episodic verbal memory, in addition to fronto-subcortical dysfunction; and Extinction patients (n=9) who had a left ear extinction at dichotic listening test in association to fronto-subcortical and papezian dysfunction. In addition, inter-test analysis showed that patients with apparently normal cognitive functions (Subsymptomatic group) performed significantly worse to attention tests compared to others. In conclusion, our study shows that (i) most patients have specific cognitive deficits; (ii) all patients with cognitive deficit have impairment of executive functions and selective attention; (iii) patients without measurable cognitive deficits display significant weakness in attention; (iv) episodic memory impairment affects verbal, but not visual, memory; (v) none of the patients show an instrumental dysfunction.

KEYWORDS: Aluminum; Attention; Dichotic listening; Dysexecutive syndrome; Episodic memory; Macrophagic myofasciitis

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The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry.

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Author information

Abstract

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a recently identified condition in which the exposure to an adjuvant leads to an aberrant autoimmune response. We aimed to summarize the results obtained from the ASIA syndrome registry up to December 2016, in a descriptive analysis of 300 cases of ASIA syndrome, with a focus on the adjuvants, the clinical manifestations, and the relationship with other autoimmune diseases. A Web-based registry, based on a multicenter international study, collected clinical and laboratory data in a form of a questionnaire applied to patients with ASIA syndrome. Experts in the disease validated all cases independently. A comparison study regarding type of adjuvants and differences in clinical and laboratory findings was performed. Three hundred patients were analyzed. The mean age at disease onset was 37 years, and the mean duration of time latency between adjuvant stimuli and development of autoimmune conditions was 16.8 months, ranging between 3 days to 5 years. Arthralgia, myalgia, and chronic fatigue were the most frequently reported symptoms. Eighty-nine percent of patients were also diagnosed with another defined rheumatic/autoimmune condition. The most frequent autoimmune disease related to ASIA syndrome was undifferentiated connective tissue disease (UCTD). ASIA syndrome is associated with a high incidence of UCTD and positive anti-nuclear antibodies (ANA) test. Clinical and laboratory features differ from the type of adjuvant used. These findings may contribute to an increased awareness of ASIA syndrome and help physicians to identify patients at a greater risk of autoimmune diseases following the exposure to vaccines and other adjuvants. The ASIA syndrome registry provides a useful tool to systematize this rare condition.

KEYWORDS: ANA; Adjuvants; Autoantibodies; Autoimmune diseases; Chronic fatigue syndrome (CFS); Fibromyalgia; Silicone; Systemic lupus erythematosus; Vaccines

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Adjuvants- and vaccines-induced autoimmunity: animal models.

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Author information

Abstract

The emergence of autoimmunity after vaccination has been described in many case reports and series. Everyday there is more evidence that this relationship is more than casual. In humans, adjuvants can induce non-specific constitutional, musculoskeletal or neurological clinical manifestations and in certain cases can lead to the appearance or acceleration of an autoimmune disease in a subject with genetic susceptibility. The fact that vaccines and adjuvants can trigger a pathogenic autoimmune response is corroborated by animal models. The use of animal models has enabled the study of the effects of application of adjuvants in a homogeneous population with certain genetic backgrounds. In some cases, adjuvants may trigger generalized autoimmune response, resulting in multiple auto-antibodies, but sometimes they can reproduce human autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, autoimmune thyroiditis and antiphospholipid syndrome and may provide insights about the potential adverse effects of adjuvants. Likewise, they give information about the clinical, immunological and histologic characteristics of autoimmune diseases in many organs, especially secondary lymphoid tissue. Through the description of the physiopathological characteristics of autoimmune diseases reproduced in animal models, new treatment targets can be described and maybe in the future, we will be able to recognize some high-risk population in whom the avoidance of certain adjuvants can reduce the incidence of autoimmune diseases, which typically results in high morbidity and mortality in young people. Herein, we describe the main animal models that can reproduce human autoimmune diseases with emphasis in how they are similar to human conditions.

KEYWORDS: Adjuvants; Alum; Autoimmunity; Pristane; Squalene; Vaccines

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MeSH terms, Substances

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HPV vaccination syndrome. A questionnaire-based study.

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Author information

Abstract

Isolated cases and small series have described the development of complex regional pain syndrome, postural orthostatic tachycardia, and fibromyalgia after human papillomavirus (HPV) vaccination. These illnesses are difficult to diagnose and have overlapping clinical features. Small fiber neuropathy and dysautonomia may play a major role in the pathogenesis of these entities. We used the following validated questionnaires to appraise the chronic illness that might appear after HPV vaccination: The 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria, COMPASS 31 dysautonomia questionnaire, and S-LANSS neuropathic pain form. These questionnaires and a "present illness" survey were e-mailed to persons who had the onset of a chronic ailment soon after HPV vaccination. Forty-five filled questionnaires from individuals living in 13 different countries were collected in a month's period. Mean (±SD) age at vaccination time was 14 ± 5 years. Twenty-nine percent of the cases had immediate (within 24 h) post-vaccination illness onset. The most common presenting complaints were musculoskeletal pain (66%), fatigue (57%), headache (57%), dizziness/vertigo (43%), and paresthesias/allodynia (36%). Fifty-three percent of affected individuals fulfill the fibromyalgia criteria. COMPASS-31 score was 43 ± 21, implying advanced autonomic dysfunction. Eighty-three percent of the patients who had ongoing pain displayed S-LANSS values >12, suggesting a neuropathic component in their pain experience. After a mean period of 4.2 ± 2.5 years post-vaccination, 93% of patients continue to have incapacitating symptoms and remain unable to attend school or work. In conclusion, a disabling syndrome of chronic neuropathic pain, fatigue, and autonomic dysfunction may appear after HPV vaccination.

KEYWORDS: Complex regional pain syndrome; Dysautonomia; Fibromyalgia; Gulf War Illness; HPV vaccine; Myalgic encephalomyelitis; Small fiber neuropathy

Comment in

Re: Proposed HPV vaccination syndrome is unsubstantiated. [Clin Rheumatol. 2016]

Proposed HPV vaccination syndrome is unsubstantiated. [Clin Rheumatol. 2016]

PMID: 26354426 DOI: 10.1007/s10067-015-3070-3

[Indexed for MEDLINE]

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Full text links

Immunol Res. 2014 Dec;60(2-3):376-83. doi: 10.1007/s12026-014-8604-2.

Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA).

Agmon-Levin N[1], Zafrir Y, Kivity S, Balofsky A, Amital H, Shoenfeld Y.

Author information

Abstract

The objectives of this study were to gather information regarding demographic and clinical characteristics of patients diagnosed with either fibromyalgia (FM) or chronic fatigue (CFS) following hepatitis B vaccination (HBVv) and furthermore to apply the recently suggested criteria of autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), in the aim of identifying common characteristics that may suggest an association between fibromyalgia, chronic fatigue and HBV vaccination. Medical records of 19 patients with CFS and/or fibromyalgia following HBVv immunization were analyzed. All of which were immunized during 1990-2008 in different centers in the USA. All medical records were evaluated for demographics, medical history, the number of vaccine doses, as well as immediate and long term post-immunization adverse events and clinical manifestations. In addition, available blood tests, imaging results, treatments and outcomes were analyzed. ASIA criteria were applied to all patients. The mean age of patients was 28.6 ± 11 years, of which 68.4 % were females. 21.05 % had either personal or familial background of autoimmune disease. The mean latency period from the last dose of HBVv to onset of symptoms was 38.6 ± 79.4 days, ranging from days to a year. Eight (42.1 %) patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neurological manifestations (84.2 %), musculoskeletal (78.9 %), psychiatric (63.1 %), fatigue (63.1 %), gastrointestinal complains (58 %) and mucocutaneous manifestations (36.8 %). Autoantibodies were detected in 71 % of patients tested. All patients fulfilled the ASIA criteria. This study suggests that in some cases CFS and FM can be temporally related to immunization, as part of ASIA syndrome. The appearance of adverse event during immunization, the presence of autoimmune susceptibility and higher titers of autoantibodies all can be suggested as risk factors. ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM.

PMID: 25427994 DOI: 10.1007/s12026-014-8604-2

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MeSH terms, Substances

LinkOut - more resources

Format: Abstract

Immunol Res. 2014 Dec;60(2-3):219-25. doi: 10.1007/s12026-014-8574-4.

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination.

Le Houézec D[1].

Author information

Abstract

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data and also from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of the Hill's criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.

Comment in

Comment on: Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination. [Immunol Res. 2015]

PMID: 25395338 PMCID: PMC4266455 DOI: 10.1007/s12026-014-8574-4

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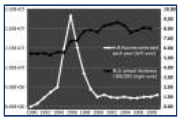
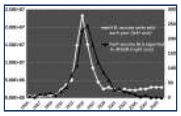

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Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review

Lucija Tomljenovic, PhD[1,2], Serena Colafrancesco, MD[1,3], Carlo Perricone, MD[1,3], and Yehuda Shoenfeld, MD, FRCP (Hon), MaACR[1,4]

Abstract

We report the case of a 14-year-old girl who developed postural orthostatic tachycardia syndrome (POTS) with chronic fatigue 2 months following Gardasil vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. The psychiatric evaluation ruled out the possibility that her symptoms were psychogenic or related to anxiety disorders. Furthermore, the patient tested positive for ANA (1:1280), lupus anticoagulant, and antiphospholipid. On clinical examination she presented livedo reticularis and was diagnosed with Raynaud's syndrome. This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA). Because human papillomavirus vaccination is universally recommended to teenagers and because POTS frequently results in long-term disabilities (as was the case in our patient), a thorough follow-up of patients who present with relevant complaints after vaccination is strongly recommended.

Keywords

Postural orthostatic tachycardia, chronic fatigue, HPV vaccine, Gardasil, ASIA syndrome, vaccine adjuvants, autoimmunity, autoantibodies

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous disorder of the autonomic nervous system in which a change from the supine position to an upright position causes an abnormally large increase in heart rate or tachycardia (30 bpm within 10 minutes of standing or head-up tilt).[1] The tachycardic response in POTS is frequently accompanied by a decrease in blood flow to the brain and hence a spectrum of symptoms associated with cerebral hypoperfusion (Table 1).[1-3] Due to the wide heterogeneity of symptoms and its frequent co-occurrence with other systemic autoimmune diseases, POTS is difficult to diagnose. Moreover, because many of POTS-related symptoms are also observed in chronic anxiety and panic disorders, POTS is frequently underdiagnosed and misdiagnosed.[2]

POTS predominantly affects women of the childbearing age with a 5:1 female–male ratio.[2] The estimated prevalence of POTS is at least 170/100 000. This estimate was based on the finding that 40% of patients with chronic fatigue syndrome (CFS) also suffer from POTS.[4] Indeed, CFS is a frequent and major comorbidity in POTS.[5,6] The 2 conditions frequently appear together, and research shows that there is a clinically identifiable subgroup of patients with CFS and orthostatic intolerance that differs from control subjects and from those with CFS without orthostatic intolerance.[4] In agreement with these observations, Okamoto et al[7] recently found that the majority of patients with POTS also fulfilled the criteria for CFS and that severe fatigue and CFS-defining

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Table 1. Symptoms Associated With Postural Orthostatic Tachycardia Syndrome (POTS).[2,3]

Symptom Category	Present in Current Case
Orthostatic symptoms associated with general hypoperfusion	
Light headedness/dizziness	+
Presyncope and syncope	+
Palpitations	+
Exacerbation by exercise/exercise intolerance	+
Sense of weakness	+
Tremulousness	–
Dyspnea	+
Ventricular fibrillation	–
Myocardial infarction	–
Cold extremities	+
Chest pain	–
Exacerbation associated with menses	Not reported
Hyperhidrosis	Not reported
Loss of sweating	Not reported
Tinnitus	–
Visual disturbances	+
Nonorthostatic symptoms	
Nausea	+
Bloating	–
Diarrhea	–
Constipation	–
Abdominal pain	+
Bladder symptoms	–
Other associated symptoms	
Fatigue	+
Sleep disturbances	+
Migraines	+
Neuropathic type pain	+
Cognitive disturbances	+
Flu-like symptoms	+

symptoms were also common in POTS patients who did not meet all the criteria for CFS. Such typical CFS symptoms that are overrepresented in POTS patients include migraine, incapacitating fatigue, fibromyalgia, unrefreshing sleep, and impaired memory or concentration. Flu-like symptoms associated with CFS such as joint pains, tender lymph nodes, and sore throat are also present in POTS albeit with lesser prevalence.[7] These and other similar observations indicate that POTS with CFS is not a separate clinical entity entirely distinct from POTS but rather a more severe form of this condition.[7,8] Much like POTS, CFS affects predominantly women and can be severely disabling, profoundly impairing patients' ability to function on a daily basis.[6,9]

Genetic as well as nongenetic factors such as trauma, bacterial or viral infection, and pregnancy may predispose to POTS.[1] In addition, it is becoming increasingly recognized that POTS and CFS can also be triggered by various medications (ie, antihypertensive drugs, antipsychotics)[1] and vaccines.[10-15] Herein we describe a case of a 14-year-old girl who presented with POTS/CFS of an autoimmune origin approximately 2 months after receiving her second injection of the quadrivalent human papillomavirus (qHPV) vaccine Gardasil.

Case Report

A 14-year-old previously healthy girl presented with flu-like symptoms, sore throat, low-grade fever, fatigue, swollen glands, and intense headaches in February 2009, approximately 2 months after her second qHPV vaccine injection. Over the course of 1 week, the headache intensified and the patient further presented with photophobia, phonophobia, altered sense of taste, diminished appetite, gait disturbances, leg weakness, and inability to walk without assistance. By March 2009, her condition worsened and she quit regular school attendance due to progressively disabling symptoms. At that time she developed syncope and incapacitating chronic fatigue. Although the patient subsequently resumed attending school (by the end of 2009), her attendance was limited to 2 hours per day due to fatigue, diminished ability to focus, weakness, and severely impaired balance and coordination. She attended school in a wheel-chair and was exhausted after the 2-hour period. Her illness continue to progress, and by the end of 2010, she had the following symptoms: persistent incapacitating headaches, dizziness, recurrent syncope, lower extremity weakness, poor motor coordination, fatigue, neck pain, joint pains, numbness in the legs, blurred vision, photophobia, phonophobia, cognitive impairment, insomnia, tachycardia, dyspnea, impaired thermoregulation, cold extremities, blush discoloration of toes, excessive hair loss, gastrointestinal (GI) disturbances, altered sense of taste, diminished appetite, and weight loss (20 pounds within 3 months of symptoms onset). The psychiatric evaluation in September 2009 ruled out the possibility that the patient's symptom were of psychosomatic origin, and the subsequent evaluation in 2010 found no evident signs of panic and anxiety disorders.

Serological evaluations revealed a number of abnormalities, including an elevated ANA at 1:1280, a positive lupus anticoagulant, and a weakly positive antiphospholipid of 7.3 in October 2009. On clinical examination, the patient presented livedo reticularis. She was then diagnosed with an undifferentiated connective tissue disease and Raynaud's syndrome. Serology results for Epstein–Barr virus, Lyme, Babesia, and Ehrlichia were negative. Titers to *Streptococcus pneumoniae* indicated previous exposure but were however within a normal range, thus ruling out recent exposure.

Over the course of her illness, the patient experienced a complete loss of consciousness with syncope approximately 12 times. These problems were never present prior to the onset of the illness in February 2009. On further testing, the patient was diagnosed with orthostatic intolerance. In

Table 2. The Suggested Criteria of ASIA[29,30] in the Current Case of Post-HPV Vaccine POTS/CFS.

Major Criteria	Present in Current Case
1. Exposure to an external stimuli (infection, vaccine, and/or immune adjuvants) prior to clinical manifestations	+
2. The appearance of "typical" clinical manifestations	
Myalgia, muscle weakness	+
Arthralgia and/joint pain	+
Chronic fatigue, unrefreshing sleep or sleep disturbances	+
Neurological manifestations	+
Cognitive impairment, memory loss	+
Pyrexia	−
3. Removal of inciting agent induces improvement	NA
4. Typical biopsy of involved organs	Not assessed
Minor Criteria	**Present in Current Case**
1. The appearance of autoantibodies	+
2. Other clinical manifestations (gastrointestinal disturbances, livedo reticularis)	+
3. Specific HLA (eg, HLA DRB1, HLA DQB1)	Not assessed
4. Evolvement of an autoimmune disease (undifferentiated connective tissue disease/ Raynaud's, probable secondary antiphospholipid syndrome)	+

particular, on the standing test the patient's lowest heart rate supine was 47 bpm with a blood pressure 103/56 mm Hg. On standing, the patient's heart rate increased immediately to 82 bpm and continued to increase to a maximum of 98 bpm after 9 minutes. According to the electrophysiologist, the patient's recurrent syncope was thus consistent with neurally mediated hypotension, and in December 2009, she was finally diagnosed with vasovagal syncope and associated postural orthostatic tachycardia syndrome. In addition, her illness met the criteria for CSF given her persisting fatigue of over 6 months, new-onset disabling headaches, postexertional worsening of the fatigue, myalgias, cognitive dysfunction, and unrefreshing sleep (Table 1). The patient's relevant medical history includes a family history of Raynaud's (patient's mother) and a personal history of headaches, dizziness, photophobia, and phonophobia in 2007, all of which however resolved completely in the same year.

Discussion

Autoimmune Origin of POTS and CFS

Herein we described a case that clearly fulfilled the criteria for POTS/CFS (Table 1) secondary to qHPV vaccine booster injection. An autoimmune mechanism has been suggested as a causal mechanism in both POTS and CFS due to frequent findings of autoantibodies (including ANA) in POTS/CFS patients.[16,17] Other reported abnormalities in CFS also point to an underlying autoimmune mechanism (ie, increased levels of pro-inflammatory cytokines interleukin-1, tumor necrosis factor-α, and increased levels of nuclear factor-κB).[18] It is estimated that up to 60% of CFS patients suffer from autoimmune responses[18] and that both POTS and CFS frequently co-occur with systemic autoimmune disorders including multiple sclerosis,[19] Sjorgen's syndrome,[20] lupus,[1,21] and Raynaud's.[22] Similarly, our case was diagnosed with Raynaud's, CFS, and neurally mediated hypotension or more specifically, POTS.

Our patient's symptoms began manifesting approximately 2 months following vaccination. An interval of 6 weeks between exposure and outcome is often used as evidence of a plausible causal association; however, immune and autoimmune diseases are chronic diseases that more often than not have a long incubation time.[23] For example, it was reported by Arbuckle et al that systemic lupus erythematosus (SLE) evolves slowly and progressively over many years and only when enough autoantibodies are present.[24] In particular, autoantibodies were found in 88% of SLE patients up to 9.4 years before the clinical diagnosis of the syndrome (mean = 3.3 years).[24] Thus, long-term persistence of elevated titers of autoantibodies was necessary for the emergence of clinically overt signs and symptoms for the diagnosis of SLE. Notably, the accumulation of autoantibodies occurred while patients were still asymptomatic.

Similarly, postvaccination adverse immune phenomena can have long latency periods (ie, month to years following immunization).[25-27] As early as 1982, compelling evidence from epidemiological, clinical, and animal research has emerged to show that autoimmune neuropathies can occur 4 to 10 months following vaccination.[28] In such cases the disease would first manifest with vague symptoms (ie, arthralgia, myalgia, paraesthesia, weakness—note also that these are typical ASIA symptoms; Table 2), which were frequently deemed as insignificant and thus ignored. These symptoms, otherwise known as "bridging symptoms" and consistent with a mild subclinical disease, would progress slowly and insidiously until exposure to a secondary immune stimulus. The latter would then trigger the rapid and acute clinical

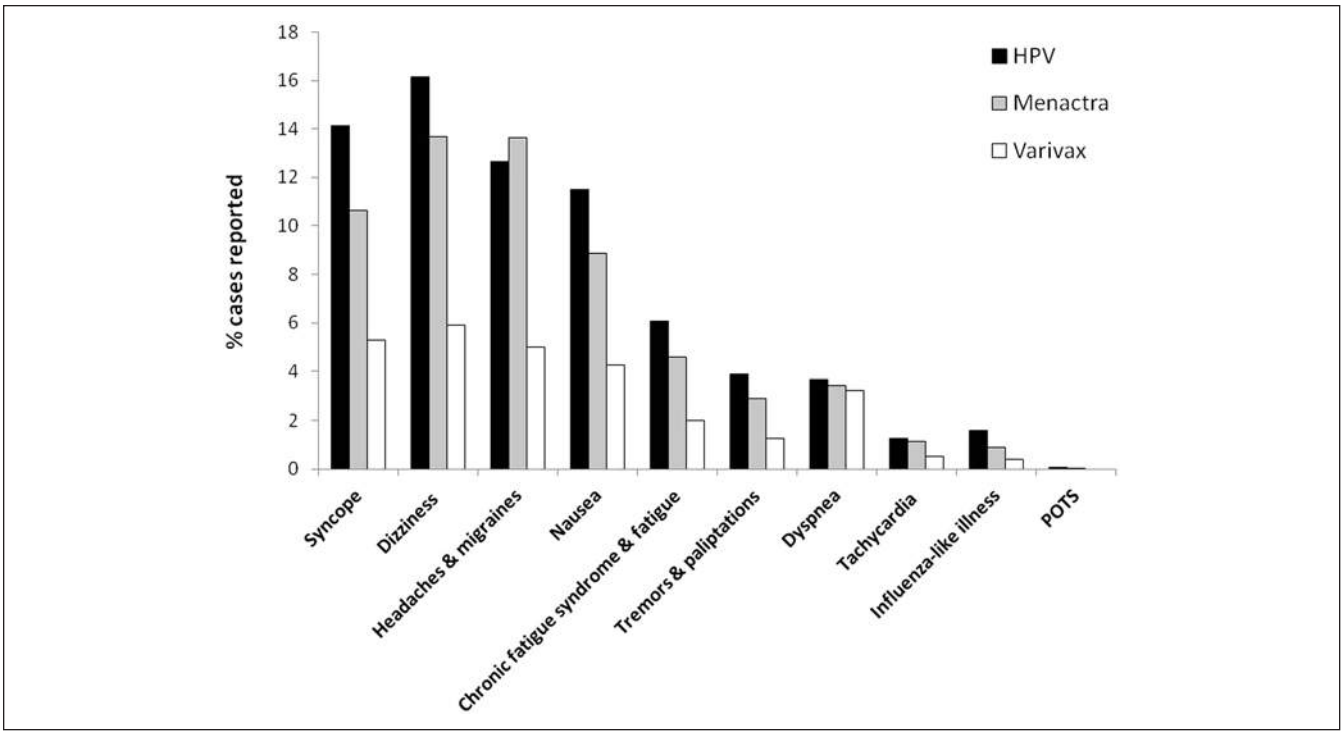

Figure 1. Number of adverse event reports related to POTS/CFS following HPV, Menactra meningococcal polysaccharide diphtheria toxoid conjugate, and Varivax Varicella vaccines in the US Vaccine Adverse Event Reporting System (VAERS) as of February 13, 2013. The VAERS database[33] was searched using the following criteria: (1) Symptoms: syncope (general, exertional, postural); headaches (including migraines); nausea; chronic fatigue syndrome (including general fatigue); tremors and palpitations; dyspnea (general, exertional, at rest); tachycardia (including tachyarrhythmia, tachycardia paroxysomal, heart rate abnormal, heart rate increased, heart rate irregular); influenza-like illness (including viremia, viral infection); POTS; (2) Vaccine products: HPV, HPV2 (human papilloma virus bivalent), HPV4 (human papilloma virus types 6, 11, 16,1 8); MNQ (Meningococcal vaccine Menactra); Varcel (Varivax-Varicella virus live); (3) Gender (all genders); (4) Age (6 to 29 years; target age group for HPV, Menactra and Varivax vaccines); (5) Territory (the United States); (6) Date vaccinated (2007-2013; HPV vaccine postlicensure period).[34] Adverse events related to a particular symptom are reported as percentages of the total number of events reported for the particular vaccine (ie, 14% syncope refers to the 2354 reports of syncope out of a total of 16 644 adverse events associated with the HPV vaccine; the total number of adverse events reported for Varivax and Menactra was 9136 and 8790, respectively).

manifestation of the disease.[28] In other words, it was the secondary anamnestic response that would bring about the acute overt manifestation of an already present subclinical long-term persisting disease.

Consistent with these observations, we recently described several cases of autoimmunity (systemic lupus) following Gardasil where the nonspecific ASIA-related manifestations eventually progressed over time to a full-blown immune disease following subsequent vaccine reexposure.[31] Moreover, in all of our cases, several common features were observed, namely, a personal or familial susceptibility to autoimmunity and an adverse response to a prior dose of the vaccine, both of which were associated with a higher risk of postvaccination full-blown autoimmunity.[31]

POTS and Vaccinations

Ours is the seventh case of POTS associated with the qHPV vaccine Gardasil reported in the literature. In addition, POTS following administration of the novel H1N1 influenza vaccine was reported recently.[13] Recently, Blitshteyn[12] reported six cases of POTS following HPV vaccination. In this case series, all six previously healthy young women (aged 12 to 22 years) developed symptoms of POTS within 6 days to 2 months after vaccination with the Gardasil HPV vaccine. Of further relevance to our case, two out of six cases reported by Blitshteyn also showed a positive ANA and, in all six cases the symptoms were disabling. In particular, three of the patients were not capable of attending school full time and one of them became wheel-chair bound like the patient described in our report. The course of POTS following HPV vaccination was similar in all six patients, with all of them improving in 2 to 3 years' time frame with the use of standard pharmacotherapy for POTS. It is possible as emphasized by Blitshteyn[12] that some patients with POTS are simply undiagnosed or misdiagnosed with anxiety and panic-related disorders, which leads to underreporting and a paucity of data on the incidence of POTS and other autonomic system disorders following vaccination. The analysis of the US VAERS database substantiates this concern. In particular, although the majority of POTS-related symptoms were reported in 4% to 16% of HPV vaccine recipients, POTS was only reported in 0.07% of cases (Figure 1). The highest number of both POTS- and CFS-related symptom reports was associated

with HPV vaccines when compared with 2 other vaccines (Menactra and Varivax), routinely given to adolescents in the United States. On average, the number of VAERS reports related to POTS/CFS symptoms was 3 to 5 times greater for the HPV compared with the Varivax vaccine. A relatively high percentage of POTS/CFS symptom reports was also associated with the Menactra vaccine. If these symptoms were psychogenic and not related to a specific vaccine but rather a reaction to the injection procedure itself, one would expect a more even distribution of reports with different vaccines. In particular, the percentage of POTS/CFS reports for Varivax should be more or less the same as for Menactra especially considering the fact that the total number of VAERS reports associated with these 2 vaccines was roughly the same (9136 and 8790, respectively). As shown in Figure 1, this is not the case. Consistent with our findings, Slade et al[32] found a disproportional reporting of syncope following HPV compared with other vaccines in their 2009 postlicensure analysis of adverse events reported to VAERS and published in JAMA. We are in further agreement with Slade et al[32] who also noted that although VAERS shares inherent limitations of all passive surveillance systems, it is national in scope and can thus provide important signals that may require further attention. Indeed, because both POTS and CFS are frequently severely disabling,[1,6,9,10,13,15] a more thorough follow-up of patients who present with relevant complaints postvaccination seems warranted in order to determine the true incidence of these syndromes with particular vaccines.

Another possible reason for the frequent misdiagnosis of POTS is that patients with this syndrome typically present with complaints that partially overlap with those seen in panic disorders or chronic anxiety.[2] Notably, such symptoms (syncope, hyperventilation, limb jerking, numbness or tingling, palpitations, and tremors) appear to be among the most frequently reported adverse reactions following vaccination with HPV vaccines and may be mistakenly labeled as "psychogenic events."[35] From our patient's medical history, it is evident however that the post-qHPV vaccination phenomena were neither temporary nor psychogenic. Indeed, the psychiatrist's evaluation specifically excluded the latter in addition of finding no relevant signs of anxiety or panic disorders. The highly positive ANA further excludes a psychosomatic origin of the patient's illness; rather, it suggest an immune-/auto-immune-mediated underlying pathology.

Although in our case the patient had a previous history of relevant symptoms (headaches, dizziness, photophobia, and phonophobia) 2 years prior to qHPV vaccination, all of these symptoms resolved in the same year and did not cause long-term disability of the patient. Indeed, at the time of first vaccination the patient was in good general health. Moreover, during the course of her illness, the patient experienced a wide spectrum of new-onset adverse conditions, including recurrent episodes of syncope with complete loss of consciousness, disabling fatigue, neck pain, joint pains, numbness in the legs, cognitive disturbances, blurred vision, unrefreshing sleep, tachycardia, dyspnea, impaired thermoregulation, cold extremities, blush discoloration of toes, excessive hair loss, GI disturbances, diminished appetite, altered sense of taste, and significant weight loss. She also tested positive for ANA, lupus anticoagulant, and antiphospholipid and was subsequently diagnosed with undifferentiated connective tissue disease/Raynaud's. Notably, none of these manifestations were present prior to the onset of her illness in February 2009 following Gardasil vaccination, indicating that the vaccine may have been the triggering, or at the very least, the exacerbating factor.

Although a viral illness cannot be completely excluded as the primary trigger of POTS/CFS in our case, it should be noted that symptoms mimicking viral illness (commonly referred to as flu-like symptoms) are in fact one of the well-recognized symptom categories in CFS.[10,36] Moreover, both flu-like symptoms and CFS are associated with the use of certain vaccines, and more specifically, aluminum and other vaccine adjuvants.[14,15,37] Indeed, because vaccines induce an immune response similarly to infections, they may also just like infections trigger autoimmune diseases.[38] However, unlike infectious agents, vaccines frequently contain adjuvants that further enhance their immune stimulation, above the levels of natural infections.[39] These observations suggest that vaccines may provoke more exaggerated, anarchic immune responses than infections. The latter point is specially relevant in view of the fact that vaccines (including HPV) are typically repeatedly administered over relatively short periods of times (ie, weeks or months). Moreover, vaccines have been reported to precede CFS mainly following exposure to multiple vaccinations and/or as an adverse response to the vaccine adjuvant.[14,15,39,40]

POTS, CFS, and the ASIA Syndrome

It is of further relevance to note that the safety trials for Gardasil (which is an aluminum-adjuvanted vaccine) did not include a true inactive placebo but rather an aluminum-adjuvant-containing placebo,[41] despite much data showing that aluminum in vaccine-relevant exposures can be toxic to humans.[42,43] In the last decade, studies on animal models have repeatedly demonstrated the ability of aluminum adjuvants to inflict immune-mediated diseases by themselves.[44,45] This research culminated in delineation of ASIA (autoimmune/inflammatory syndrome induced by adjuvants), which encompasses several medical conditions with similar set of signs and symptoms and a common exposure to an immune adjuvant.[10,29] Shoenfeld and colleagues proposed 4 major and 4 minor criteria for ASIA (Table 2), and in order to diagnose ASIA, fulfillment of either 2 major or 1 major and 2 minor criteria is required.[29] The criteria for ASIA enable the inclusion of patients with well-defined autoimmune diseases (ie, multiple sclerosis, lupus) as well as those with ill-defined and nonspecific yet clinically relevant conditions (ie, myalgia, chronic fatigue, and cognitive disturbances) under the spectrum of vaccine adjuvant-associated conditions.[30] The

inclusion of the latter category of manifestations under ASIA is of special importance as these nonspecific manifestations are all too easily ignored or disregarded as irrelevant and nonvaccine related not only by patients and physicians but also by scientists involved in design of vaccine trials.[46,47] Nonetheless, many ill-defined medical conditions that fall under the ASIA spectrum are frequently disabling and thus of significant clinical relevance. For example, CFS and cognitive dysfunction associated with the aluminum vaccine adjuvant-induced macrophagic myofasciitis (MMF) syndrome are disabling in 87% and 53% of cases, respectively,[9] and impair both professional activities as well as numerous aspects of daily life.[9,42] Similarly in our case, the patient was unable to attend regular school due to progressive and disabling POTS/CFS symptoms. In addition, some of the nonspecific ASIA manifestations have the potential to progress over time to a full-blown autoimmune disease, especially following subsequent vaccine re-exposure.[31] Of note, our patient fulfilled the first 2 major criteria for ASIA (due to a prior exposure to the HPV vaccine and the obvious appearance of "typical" manifestations) as well as 3 minor criteria, owing to the positive ANA, lupus anticoagulant, and antiphospholipid and the concurrent diagnosis of Raynaud's (Table 2).

In years following licensure, numerous case reports of serious adverse reactions of the autoimmune origin associated with the qHPV vaccine Gardasil have raised concerns about the safety of the vaccine.[12,31,48-52] Postlicensure data from vaccine safety surveillance databases worldwide appear to substantiate these concerns. For example, in the United States, compared with all other vaccines Gardasil alone is associated with >60% of all serious adverse reactions (including 63.8% of all deaths and 81.2% cases of permanent disability) in females younger than 30 years of age.[34] These observations suggest that HPV vaccine risks may not have been fully identified during prelicensure trials.[34,41,53] The unusual frequency of adverse reactions following HPV vaccination cannot solely attributed to the aluminum adjuvant, as many other vaccines also contain aluminum (ie, tetanus, diphtheria, etc) but are not associated with as many adverse reactions. However, it is the aluminum that evokes the enhanced immune reaction necessary for inducing the production of the elevated titers of antibodies. The antigen on its own is not capable of evoking this strong immune response. Because of this, any adverse effect arising from the antigen (or other constituents in the vaccine) is ultimately linked to the action of the adjuvant. For example, Zivkovic et al[54] showed that induction of the antiphospholipid syndrome (APS) syndrome and associated decreased fecundity by tetanus toxoid (TTd) hyperimmunization in C57BL/6 mice critically depends on the aluminum adjuvant. In particular, Zivkovic et al[54] investigated reproductive pathology induced in C57BL/6 mice by TTd hyperimmunization using a combination of different pretreatments (complete Freund's adjuvant or glycerol) and adjuvants (aluminum-hydrogel or glycerol). A decrease in fecundity was recorded in only C57BL/6 mice immunized with aluminum-hydrogel adjuvant, irrespective of the kind of applied pretreatment.

In conclusion, herein we described a case of disabling CFS/POTS secondary to qHPV Gardasil vaccination with symptom onset at 2 months following the second vaccine booster. With the concurrent detection of elevated ANA, lupus anticoagulant, antiphospholipid, and subsequent diagnosis of Raynaud's, this case fully meets the criteria for the recently identified ASIA syndrome (Table 2). Moreover, the case presented here is consistent with other literature supporting an immune-mediated etiology of POTS and CFS.[1,12,13,15-17] To the best of our knowledge, this is the second case of post-HPV vaccine associated POTS described in the literature to date. Due to the wide heterogeneity of symptoms and its frequent co-occurrence with other systemic autoimmune diseases, POTS is difficult to diagnose and hence many cases remain unreported. The relatively high prevalence of POTS/CFS-related symptoms in young women vaccinated with HPV vaccines (Figure 1) should alert physicians to a closer monitoring of post-HPV-related manifestations fitting the POTS/CFS criteria. We also recommend further studies to ascertain whether or not the association between HPV vaccination and POTS is causal.

Authors' Note

An informed consent has been received from the patient to present her case.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Y. Shoenfeld is currently providing expert testimony in cases involving adverse reactions to the HPV and other vaccines in the US National Vaccine Injury Compensation Program (including this case). LT, SC, and CP declared no potential conflicts of interest.

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Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.

Perricone C[1], Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y.

Author information

Abstract

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post-vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hypothesized to be involved in the onset of adjuvant-induced autoimmunity; a genetic favorable background plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

KEYWORDS: Adjuvant; Autoantibodies; Autoimmune/Inflammatory syndrome induced by adjuvants; Autoimmunity; Saccharomyces cerevisiae; Vaccine

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Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)--animal models as a proof of concept.

Cruz-Tapias P[1], Agmon-Levin N, Israeli E, Anaya JM, Shoenfeld Y.

Author information

Abstract

ASIA syndrome, "Autoimmune (Auto-inflammatory) Syndromes Induced by Adjuvants" includes at least four conditions which share a similar complex of signs and symptoms and have been defined by hyperactive immune responses: siliconosis, macrophagic myofasciitis syndrome, Gulf war syndrome and post-vaccination phenomena. Exposure to adjuvants has been documented in these four medical conditions, suggesting that the common denominator to these syndromes is a trigger entailing adjuvant activity. An important role of animal models in proving the ASIA concept has been established. Experimentally animal models of autoimmune diseases induced by adjuvants are currently widely used to understand the mechanisms and etiology and pathogenesis of these diseases and might thus promote the development of new diagnostic, predictive and therapeutic methods. In the current review we wish to unveil the variety of ASIA animal models associated with systemic and organ specific autoimmune diseases induced by adjuvants. We included in this review animal models for rheumatoid arthritis-like disease, for systemic lupus erythematosus-like disease, autoimmune thyroid disease-like disease, antiphospholipid syndrome, myocarditis and others. All these models support the concept of ASIA, as the Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants.

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Macrophagic myofasciitis: characterization and pathophysiology

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Summary

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Aluminium oxyhydroxide (alum), a nano-crystaline compound forming agglomerates, has been introduced in vaccine for its immunologic adjuvant effect in 1927. Alum is the most commonly used adjuvant in human and veterinary vaccines but mechanisms by which it stimulates immune responses remains incompletely understood. Although generally well tolerated, alum may occasionally cause disabling health problems in presumably susceptible individuals. A small proportion of vaccinated people present with delayed onset of diffuse myalgia, chronic fatigue and cognitive dysfunction, and exhibit very long-term persistence of alum-loaded macrophages at site of previous intra-muscular (i.m.) immunization, forming a granulomatous lesion called macrophagic myofasciitis (MMF). Clinical symptoms associated with MMF are paradigmatic of the recently delineated “autoimmune/inflammatory syndrome induced by adjuvants” (ASIA). The stereotyped cognitive dysfunction is reminiscent of cognitive deficits described in foundry workers exposed to inhaled Al particles. Alum safety concerns will largely depend on whether the compound remains localized at site of injection or may diffuse and accumulate in distant organs. Animal experiments indicate that biopersistent nanomaterials taken-up by monocytes-lineage cells in tissues, e.g. fluorescent alum surrogates, can first translocate to draining lymph nodes, and thereafter circulate in blood within phagocytes and reach the spleen, and, eventually, slowly accumulate in brain.

Keywords: Adjuvants, Immunologic; adverse effects; Alum Compounds; adverse effects; Animals; Fasciitis; chemically induced; immunology; pathology; physiopathology; Humans; Myositis; chemically induced; immunology; pathology; physiopathology; Nanostructures; Phagocytes; metabolism; Syndrome

Introduction

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In 1998, a consortium of French myopathologists described an emerging condition of unknown cause characterized by a pathognomonic lesion at muscle biopsy we called macrophagic myofasciitis (MMF).[1] MMF was detected in middle-aged adult patients with diffuse myalgias and fatigue.[1] Macrophages was the major cell type in the lesion, and enclosed agglomerates of nanocrystals in their cytoplasm.[1] Subsequently, these inclusions proved to be a key finding as they were constantly present at electron microscopy, and conspicuously contained aluminium as shown by ionic or X-ray microanalysis.[2] MMF was typically detected in the deltoid muscle, and could be differentiated both clinically and pathologically from Whipple’s disease and other infectious histiocytoses, and from diffuse dysimmune fasciitis and panniculitis. [3] The crystalline rather than amorphous ultrastructural appearance of the inclusions was suggestive of aluminium hydroxide. Patients had normal renal function and had no peculiar exposure to aluminium other than previous immunization against hepatitis B (HBV), hepatitis A (HAV) or tetanus toxoid (TT) vaccines (100%), thus strongly suggesting that MMF inclusions correspond to aluminium oxyhydroxide (alum), an adjuvant incorporated in these vaccines to boost immunologic responses.[2] It is now clear that rapid emergence of MMF in France resulted from the specific combination of 3 factors : (1) replacement of the subcutaneous route by the i.m. route of vaccination in the early 1990s; (2) widespread extension of HBV primovaccination to the French adult population in the same time; and (3) the choice of the deltoid muscle (also used for i.m. vaccination) for routine muscle biopsy in France whereas biceps brachialis and quadriceps femoris muscles are preferred in most other countries. MMF lesion is now universally recognized to assess long-term persistence of alum at site of previous intramuscular (i.m.) immunization.[4] However, alum has been generally

considered as safe on the basis of short-term surveys, and exact significance of longstanding MMF detection in a given patient remains uncertain because of (i) apparently "poorly specific" clinical manifestations, which of course does not mean non-disabling ones, and (ii) lack of self-evident link between persistence of alum agglomerates into macrophages at site of immunization and delayed onset of systemic and neurologic manifestations. Formal delineation of "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA),[5] and novel insights into the biodistribution of slowly biodegradable particles taken-up by monocyte-lineage cells in peripheral tissues provide settlement for a better understanding of this rare adverse effect of alum.

MMF histopathology

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Deltoid muscle biopsy findings are stereotyped,[1–4] consisting of focal infiltration of the epimysium, perimysium and perifascicular endomysium by well-circumscribed and cohesive sheets of large mononuleated cells of the monocyte and macrophage lineage, usually intermingled with a minor lymphocytic population. The maximum observed section size of the lesion is 1cm. Aluminium salts are positively stained by hematoxylin and, consistently, the cytoplasm of macrophages is basophilic (dark blue) on hematoxylin-eosin stained cryostat sections. Probably due to specific chemical reactions, this is not observed on formalin fixed material in which macrophages exhibit a finely granular grey/beige content. In both cryostat and paraffin sections, macrophages are strongly periodic Acid Schiff $(PAS)^+$. They express CD68 and major histocompatibility complex (MHC) class 1 and MHC class 2 antigens. $CD3^+$ T-cells, mainly $CD8^+$, forming perivascular cuffs are constantly found. Occasional $CD19^+$ B cells, rarely forming lymphoid follicles, and $CD138^+$ plasma cells may be detected. Giant multinucleated cells are not detected except when another foreign material, e.g. coton wool, is present. In rare instances (about 1%) the granuloma may be encircled by thick fibrotic tissue and centered by a large necrotic area, forming a lesion reminiscent of a rheumatoid nodule. Myofibers remote from the infiltrate are typically intact, but MMF may be occasionnaly associated with typical dermatomyositis or autoimmine necrotizing myopathy. At electron microscopy, macrophages appear heavily loaded with submicron/micron-sized agglomerates of spiculated osmiophilic structures surrounded by discontinuous lysosomal membranes. In routine, inclusions can be visualized by the Morin stain for aluminium. Micro-organisms are not detected by appropriate stainings or electron microscopy.

Similar MMF lesions can be detected in the quadriceps muscle in babies and children because this muscle is used for i.m. vaccine administration in young individuals. MMF can be experimentally reproduced by i.m. vaccination in mice, rats and monkeys,[2,6,7] progressively shrinking with time.[6] It is, therefore, important to determine if the MMF lesion is unusually persistent in biopsied patients by precisely recapitulating history of previous vaccinations. In practice we consider MMF to be so when the time elapsed from last vaccine shot to MMF detection is >18 months. This point is particularly important in small children who receive numerous alum-containing vaccine shots in the first year of life, increasing risk of chance associations between MMF lesions and unrelated conditions, e.g. congenital myopathies and muscular dystrophies.[8] The risk also exists in adults but accounts for no more than 5–10% of MMF^+ biopsies, including fully asymptomatic patients and patients investigated for hereditary disorders.

In contrast to i.m. injections, alum-containing vaccines administered by the s.c. route may elicit chronic lesions that are somewhat different from MMF, so-called cutaneous pseudo-lymphoma, associated with a rim of alum-containing macrophages.[9]

From MMF-associated syndrome to ASIA

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According to the patient association, about 1000 patients with documented MMF have been identified in France. Occasional cases have been reported in many other countries.[8,10–15] The structure of symptoms was strikingly similar in independent cohorts of French adult patients.[4] We recently reviewed the files of 457 adult MMF patients collected from 1994 to 2011 in our centre. Patients were either investigated and biopsied (n=270) at the Neuromuscular Centre of Créteil (Neuromuscular Reference Centre Garches-Necker-Mondor-Hendaye), or were referred for follow-up or complementary investigation after MMF detection in other French hospitals by one of the myopathologists that had described the lesion (n=187). Most patients were females (70%) and at the middle age at time of biopsy (median 45 years, range 12–83). They had received 1 to 17 i.m. alum-containing vaccine administrations (mean 5.3) in the 10 years before MMF detection, and these included HBV vaccination in 85%. Patients mainly complained of chronic diffuse myalgias >6mois (89%) with or without arthralgias, disabling chronique fatigue >6 months (77%), overt cognitive alterations affecting memory and attention (51%), and dyspnea 50%. As previously reported, onset of these clinical symptoms was always posterior to, and delayed from, immunization, median time elapsed from last vaccine administration being 7 months (range 0.5–84) for initial systemic symptoms, and 11 months (range 0–72) for first myalgia.[4] Time elapsed from last vaccine administration to biopsy was 65 months (range 3–219). Compared to our previous reports, this delay has progressively increased (36 months in the initial series of 2001, 53 months in series of 2003), [4] indicating that MMF patients are chronically diseased and, though mainly vaccinated in the late nineties or early 2000', frequently looked for diagnosis long after onset of symptoms.

Myalgias and fatigue may not be synchronous. Myalgia may follow an exercise of unusual intensity and often begin in lower limbs,[4] and almost never at site of previous vaccine injection. Myalgia progressively extend upward to affect paravertebral muscles and become diffuse at time of biopsy.[4] Muscle weakness is rare. Myopathic electromyogram and CK elevation are found in less than one half of patients. Some fibromyalgic tender points are detected in a minority of patients, but the 1990 ACR criteria for fibromyalgia are rarely fulfilled.[4] Interestingly, ^{67}Gallium scintigrams has shown the presence of subtle radionuclide uptake predominating in the painful areas along the lower limb muscle fascias and in para-articular tissues in all tested patients.[17] This was not found in fibromyalgic controls.

Fatigue, sleep disturbances with unrereshing sleep, and sometimes headaches may be very disabling and often deeply impacts professional and personal life. A case-control study conducted by AFSSAPS pointed out chronic fatigue as more frequent and more pronounced in patients with than without MMF in deltoid muscle (http://afssaps.sante.fr/htm/10/myofasci/etude.pdf). In fact, a majority of patients fulfil international criteria of chronic fatigue syndrome.[18] Consequently, history of exposure to alum-containing vaccines should be checked carefully in patients with CFS, and muscle biopsy searching persistent MMF at site of injection should be considered when chronology is consistent, even many years after onset of symptoms.

CNS involvement is assessed by cognitive dysfunction. Patients complain of subjective memory impairment, difficulties in sustaining attention, and mood disturbancies. Although often disabling, cognitive dysfunction is often underestimated or remains undetected by routine examination. A comprehensive battery of neuropsychological tests in unselected MMF patients without MS showed alterations in all individuals, consistent with mild cognitive impairment (MCI) but including at least one test reaching the dementia threshold in 96%.[19] Compared to arthritis controls matched for pain severity and duration, depression and educational level, MMF patients displayed distinctive impairment of visual memory, working memory and dichotic listening, a pattern suggestive of cortico-subcortical organic damage involving fronto-parieto-thalamo-striatal areas, with deep white matter alterations.[19] Very similar cognitive alterations have been documented workers exposed to inhaled Al fumes or powder.[20–22] These alterations are also reminiscent of those described in HIV- or HCV-infected individuals.[19]

In addition to CFS, 15–20% of patients with MMF concurrently develop an autoimmune disease, the most frequent of which being multiple sclerosis (MS)-like demyelinating disorders [12–23, 23,24] Hashimoto's thyroiditis, and diffuse dysimmune neuromuscular diseases, such as dermatomyositis, necrotizing autoimmune myopathy, myasthenia gravis, and inclusion body myositis. Even in the absence of overt autoimmune disease, low titers of various autoantibodies, increased inflammatory biomarkers, and abnormal iron status are commonly detected.[4]

Taken individually, none of the clinical manifestations commonly associated with persistent MMF is specific of a given cause. Combination of chronic myalgias, fatigue, and cognitive dysfunction is consistent with CFS,[18] a poorly understood condition also known as myalgic encephalomyelitis,[25] which may be triggered by various infectious and non-infectious agents. We previously noted the closely similar structure of symptoms in individuals with MMF and with the so-called Gulf war syndrome[4] which is increasingly recognized as linked to multiple vaccinations,[26,27] with special emphasis put on anthrax vaccine, an alum-adjuvanted vaccine administered in 6 shots, that was recently shown to also induce MMF.[13] On these grounds, we proposed to consider MMF-associated symptoms as an adjuvant-induced syndrome.[28] Therefore, we fully support the term ASIA (autoimmune/inflammatory syndrome induced by adjuvants) coined by Pr Shoenfeld to designate these symptoms, regardless of the nature of the involved immunologic adjuvant (alum, silicone gel, viral components, etc).[5]

Handling and transport of poorly soluble nanomaterials by phagocytes : a possible clue for understanding MMF and ASIA

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For decades, aluminium oxyhydroxide, is the most commonly used adjuvant in human and veterinary vaccines. The mechanism by which it stimulates the immune response remains incompletely understood. [29]

Imbalance between the huge number of alum-vaccine receivers and the small number of biopsy-proven MMF cases strongly suggest that individual susceptibility factors play a crucial role in intolerance to alum. In rats, the genetic background strongly influences the size of lesions induced by i.m. injection of alum.[6] Adverse response to alum injection may also depend on susceptibility genes, such as HLA-DRB1*01, that may favour the development of autoimmune diseases.[30] Thus, aluminium likely represents one environmental factor able to trigger adverse effects in individuals with as yet largely unknown susceptibility genes. In keeping with this view, several closely related conditions have been shown to be associated with Al overload, including MMF,[14] idiopathic CFS,[31] and MS.[32] Moreover, strong suspicion of a possible link between Gulf war syndrome and alum administration has been experimentally supported.[33] Quite logically, questions are currently burgeoning about the exact safety level of aluminium adjuvants.[34]

However, if biopersistence of the adjuvant in the body is a priori undesirable, the exact significance of MMF remains uncertain since a conceptual link is still a missing between the observed persistence of particle-loaded MPs at site of previous immunization and the systemic, especially neurologic, clinical manifestations. Alum is potentially highly neurotoxic,[33] but it is used at concentrations viewed as an acceptable compromise between adjuvanticity and toxicity by industry and regulatory agencies. In fact, the potential toxicity of alum will be influenced by whether the bioactive nanomaterial remains localized at injection points or rather scatters and accumulates in distant organs and tissues. Characterization of the fate of i.m. injected particles is therefore crucial for understanding pathophysiology of MMF and related disorders.

A reference study based on isotopic ^{26}Al showed poor ^{26}Al clearance in the urine after i.m. injection of isotopic alum to rabbits (6% at d28 endpoint), and detected ^{26}Al, in an unknown form, in lymph nodes, spleen, liver, and brain.[35] However, as for other slowly biodegradable nanomaterials, the biodistribution of alum particles following injection into muscle is currently unknown.

Aluminium oxyhydroxide is composed of micron/submicron-sized aggregates of nano-sized (ca 13 nm) particles and these aggregates were initially believed to remain extracellular until their complete solubilisation in interstitial fluids.[35] We now know that quite the reverse is the case and that APCs avidly take up alum particles,[36] and, in so-doing, become long-lived cells,[37] and impede alum solubilization.[2] Inflammatory monocytes (MOs) are attracted into muscle by danger signals, becoming macrophages and MO-derived dendritic cells (DCs), before migrating to the draining lymph nodes (DLNs).[38] Since one function of migratory DCs is to transfer antigenic material to a large network of distant resident APCs, we examined if fluorescent nanomaterials injected into muscle could translocate to distant organs as part of a general mechanism linked to phagocytosis.

Preliminary results have substantiated this view.[39,40] We observed that fluorescent surrogates of alum particles injected into mouse muscle were rapidly taken up by macrophages to form a MMF-like granuloma. An important proportion of particles escaped the injected muscle, mainly within immune cells, gaining access to the regional lymph nodes. Then particle-loaded cells exited the lymphatic system to reach the blood stream (presumably through the thoracic duct, a terminal lymphatic vessel plugged to the subclavian vein), allowing them to gain access to distant organs such as spleen, liver and, eventually, the brain. Using lymph node ablation and genetically manipulated animals, we documented that systemic biodistribution of particles injected into muscle necessitates early cell loading in muscle or lymph nodes, and crucially depend on the presence of attracting signals for monocytes (namely the MCP-1/CCL2 chemokine) in tissues. Thus, immune cells loaded with alum-like particles circulate after the i.m. injection and can reach distant tissues such as brain, especially if they produce attracting signals for inflammatory cells or exhibit weak blood brain barrier (BBB).[39,40] This may also apply to other poorly degradable nanomaterials such as silicone, another compound suspected to cause ASIA.[5] Of course, lot remains to be done to determine if, in what conditions, and to what extent alum and other mineral particles gaining access to the brain by a Trojan horse mechanism, as HIV and HCV particles do, can cause significant inflammatory and neurotoxic damage.

In conclusion, MMF revealed an almost complete lack of knowledge on the fate, systemic diffusion, and long-term safety of alum particles. On the grounds of our clinical and experimental data, we believe that increased attention should be paid to possible long-term neurologic effects of continuously escalating doses of alum-containing vaccines administered to the general population. Special emphasis should be put on individuals with immature/altered BBB or inflammatory states.

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ELSEVIER FULL-TEXT ARTICLE

Infect Dis Clin North Am. 2011 Dec;25(4):851-63. doi: 10.1016/j.idc.2011.07.012. Epub 2011 Sep 9.

The common immunogenic etiology of chronic fatigue syndrome: from infections to vaccines via adjuvants to the ASIA syndrome.

Rosenblum H[1], Shoenfeld Y, Amital H.

Author information

Abstract

Chronic fatigue syndrome (CFS) is characterized by unexplained fatigue that lasts for at least 6 months with a constellation of other symptoms. Most cases start suddenly, and are usually accompanied by a flu-like illness. It is a symptom-based diagnosis of exclusion, the pathogenesis of which is unknown. Studies have examined and hypothesized about the possible biomedical and epidemiologic characteristics of the disease, including genetic predisposition, infections, endocrine abnormalities, and immune dysfunction and psychological and psychosocial factors. Recently, the AISA (autoimmune/inflammatory syndrome induced by adjuvants) syndrome was recognized, indicating the possible contribution of adjuvants and vaccines to the development of autoimmunity.

PMID: 22054760 DOI: 10.1016/j.idc.2011.07.012

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

PubMed

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Full text links

Clin Rev Allergy Immunol. 2011 Oct;41(2):163-8. doi: 10.1007/s12016-010-8212-4.

Macrophagic myofaciitis a vaccine (alum) autoimmune-related disease.

Israeli E[1], Agmon-Levin N, Blank M, Shoenfeld Y.

Author information

Abstract

Macrophagic myofasciitis (MMF) is an immune-mediated condition first reported in 1998. MMF is characterized by post-vaccination systemic manifestations as well as local-stereotyped and immunologically active lesion in the site of inoculation (deltoid muscle). MMF systemic symptoms included myalgias, arthralgias, marked asthenia, muscle weakness, chronic fatigue, and fever. Recently, studies demonstrated that the local lesion is due to persistence for years at site of injection of an aluminum (Al(OH)3) adjuvant commonly used in human vaccines. Time elapsed from last immunization with an Al(OH)3-containing vaccine to muscle biopsy range from 3 months to 8 years; in rare cases, MMF may be diagnosed even 10 years post-vaccination. The discrepancy between the wide applications of aluminum hydroxide-containing vaccines and the very limited number of MMF cases reported may be resolved by observations suggesting that aluminum-containing vaccinations may trigger MMF in genetically susceptible subjects carrying the HLA-DRB1*01. Thus, MMF may be defined as an emerging novel condition that may be triggered by exposure to alum-containing vaccines, in patients with a specific genetic background, and this temporal association may be exhibited from a few months up to 10 years.

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Publication type, MeSH terms, Substances, Supplementary concept

LinkOut - more resources

ASIA OR SHOENFELD'S SYNDROME: HIGHLIGHTING DIFFERENT PERSPECTIVES FOR DIFFUSE CHRONIC PAIN

Jozélio Freire Carvalho*, Solange Murta Barros**, Jaime C. Branco***, João Eurico Fonseca****

Is the Gulf War Syndrome (GWS) and the silicone related scleroderma –like syndrome spectres of the same disease? What do they have in common with a rare aluminium induced myopathic syndrome described for the first time in France in 1998? The logic answer was suggested by an elegant integration of the existing evidence into the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) proposed recently by Shoenfeld in a paper published in *Journal of Autoimmunity*[1]. A mosaic of environmental factors can be classified as adjuvants. In fact, we know for decades a variety of compounds that are able to induce autoimmunity in animal models and used in clinical practice to increase the immunogenicity of vaccines, but also known to be able, in genetic susceptible individuals, to induce autoimmune diseases[2,3]. In this vast group of substances bacterial antigens, hormones, aluminium, silicone and several other molecules have been included[4].

The GWS was described in veterans that were suffering from atypical rheumatic symptoms, such as arthralgia, myalgia, lymphadenopaty, chronic fatigue syndrome, malar rash and autoimmune thyroiditis[5].

A cohort study performed 10 years ago compared the titter of anti squalene antibodies of 144 Golf War immunized veterans or medical employees, 48 blood donors, 40 systemic lupus erythematosus patients, 34 silicone breast implant recipients and 30 chronic fatigue syndrome patients. The majority (95%) of overtly ill deployed GWS patients had antibodies to squalene. All (100%) GWS patients immunized for service in Desert Shield/ /Desert Storm who were not in the fighting front had antibodies to squalen. In contrast, none (0%) of the veterans that were in the fighting zone and were not showing signs and symptoms of GWS have antibodies to squalen. Neither patients with idiopathic autoimmune disease nor healthy controls had detectable serum antibodies to squalene. The majority of symptomatic GWS patients had serum antibodies to squalene[6]. The authors proposed that GWS was not a result of the exposition to weapons but rather induced by the intense vaccination program that they were submitted to. It is ironic that more solders were ill due to an oil adjuvant injected in their organisms than fighting against the hostile environment and the armed enemies.

Silicon was considered an inert material and thus unable to induce immune reactions. Recent metanalysis have supported this view, as the risk of silicon exposed individuals for developing a diffuse connective tissue disease is only 0.8%, not significantly higher than the risk of the general population. However, that is not the case for more unspecific symptoms such as arthralgia and myalgia and even some diffuse neurologic manifestations that appear to be more common in individuals exposed to silicon implants[7]. The possible association between chronic fatigue syndrome, fibromyalgia, and previous silicone mammoplasty was proposed almost two decades ago[8].

The post vaccination muscle disease described by Gehardi *et al.* in 1987 is of particular interest as it is based in well defined histologic features[9]. It is a miofasceitis that has the presence of macrophages with aluminum inclusions, which occurs associated with vaccination. Clinically the disease is expressed by systemic symptoms such as fatigue, myalgia, arthalgia, fever and, in some cases, by a demyelinating condition similar to Guillain-Barré, with electromyographic changes. Elevated acute

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Table I. Criteria suggested by Shoenfeld for ASIA diagnosis

Major Criteria

- Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
- The appearance of 'typical' clinical manifestations:
  - Myalgia, myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease

For ASIA's diagnosis: at least 2 major criteria or 2 minor and 1 major.

phase proteins and creatine quinase also occur. The same group determined that the disease occurs only in HLA DRB1*01 positive individuals[9]. On top of that, it was shown that aluminum can persist in the local of injection, up to 10 years after vaccine administration, which can explain the persistence of this condition in some individuals[10].

These conditions and other observations, regarding for instance de H1N1 vaccination, have motivated the definition of the ASIA syndrome, with the criteria proposed by Shoenfeld listed in Table I[1]. These criteria, if properly validated, are of great clinical relevance, as they raise a major clinical doubt on the classification of some patients with chronic pain syndromes, as chronic fatigue syndrome, or even fibromyalgia. In fact, if we compare the cardinal symptoms of the Shoenfeld's ASIA syndrome with the typical clinical manifestations of patients with diffuse chronic pain we came quickly to the conclusion that reviewing the recent exposition to adjuvants and other potential exogenous stimulus seems to be a wise attitude. This is also in line with the characteristic symptoms of fibromyalgia and chronic fatigue syndrome that frequently occur in patients with well-defined Lyme disease, even after adequate treatment. Lyme disease is caused by an infection due to *Borrelia burgdorferi* spirochete and most of the clinical symptoms are in fact a consequence of an immune response to this infectious agent. Although a biological relationship between Lyme disease and diffuse pain syndromes has not been established, in fact this can be encompassed by the ASIA syndrome[11]. In addition, recent studies have detected the presence of retroviral sequences like xenotropic murine leukemia virus-related virus (XMRV) and polytropic murine leukemia virus related--virus (PMLV) in chronic fatigue syndrome patients, expanding, in fact, the need for thinking on alternative diagnosis in patients classified into these conditions[12]. Consequently, countries such as Australia, Canada, New Zealand and the UK elaborated restrictive guidelines for "blood donors with a history of current diagnosis of CFS". If upcoming research will confirm these observations and validate the ASIA/Shoenfeld criteria, a major paradigm shift will have to occur in the way rheumatologists perceive some cases of diffuse chronic pain. Interestingly, in this issue of Acta Reumatologica Portuguesa 2 case reports related to the ASIA/Shoenfeld are reported[13,14].

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CONCISE COMMUNICATIONS

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Chronic fatigue syndrome in patients with macrophagic myofasciitis

Macrophagic myofasciitis (MMF), a condition first reported in France in 1998, is defined by the presence of a stereotyped and immunologically active lesion at deltoid muscle biopsy (1,2). It was recently demonstrated that this lesion is an indicator of long-term persistence of the immunologic adjuvant aluminum hydroxide within the cytoplasm of macrophages at the site of previous intramuscular (IM) injection (2). MMF is typically detected in patients with diffuse arthromyalgias that have appeared subsequent to aluminum hydroxide administration in the absence of a clearly defined anatomic substratum (2). Patients also report unexplained chronic fatigue (1). These manifestations are reminiscent of the so-called chronic fatigue syndrome (CFS), a poorly understood condition manifesting as disabling fatigue, musculoskeletal pain, sleep disturbance, impaired concentration, and headaches (3). The present study was conducted to determine the proportion of MMF patients fulfilling international criteria for CFS.

Thirty unselected consecutive patients with biopsy-proven MMF identified in Créteil and Bordeaux were retrospectively included, regardless of symptoms that led to indication of muscle biopsy. As previously described (2), MMF was assessed by 1) well-circumscribed sheets of densely-packed, large, nonepithelioid macrophages with a finely granular, periodic acid–Schiff–positive content, in the connective structures of deltoid muscle; 2) lymphocytic infiltrates intermingled with macrophages and forming microvascular cuffs; and 3) absence of significant muscle fiber injury (see Figure 1). In each patient, we determined, through both chart review and either direct patient questioning or telephone interview, 1) the presence of chronic fatigue of >6 months' duration, 2) the alleged severity of fatigue, and 3) the presence of CFS according to Centers for Disease Control and Prevention (CDC) criteria (1994) (4) or Oxford criteria (1991) (5). In addition, in 20 patients, we retrospectively evaluated history of immunization as well as prevalence of fever and neurologic features suggestive of central nervous system demyelinating disease; laboratory findings, including erythrocyte sedimentation rate, creatine kinase levels, and ^{67}Ga scintigraphy; and responsiveness to steroids.

The male:female ratio was 1:2. The mean age of patients was 52 years (range 12–78 years). Chronic fatigue was found in 28 of 30 patients (93%) and was considered disabling in 26 of 30 patients (87%). Sixteen patients (53%) fulfilled CFS criteria from either the CDC (14 of 30 patients, 47%) or Oxford (12 of 30 patients, 40%), 11 of 30 patients (37%) fulfilled both CDC and Oxford criteria. Other symptoms, laboratory findings, and steroid responsiveness are detailed in Table 1. ^{67}Ga scintigraphy was performed in 5 patients and showed increased levels of ^{67}Ga uptake in muscle and paraarticular areas, mainly in lower limbs. A history of vaccination was available for 19 of 20 patients. All 19 patients had received IM administration of aluminum-containing vaccine prior to the onset of CFS symptoms, and the delay from the last vaccination to the first manifestations ranged from 1 month to 72 months (median 12 months).

We have previously determined that myalgias are a major symptom in patients with MMF. The prevalence of myalgias was much higher in such patients than in other patients who had undergone deltoid muscle biopsies at the same time in the same centers (85% versus 45%; $P < 0.0001$ by Fisher's exact test) (2). We show now that chronic disabling fatigue is a symptom as frequent as diffuse myalgias in patients with MMF (87%), a finding also noted in the French Institut de Veille Sanitaire exploratory investigation report (6). More than half of the patients also reported other manifestations of CFS. Therefore, MMF should be alternatively considered as a cause of CFS or as an additional exclusion criterion, along with rheumatoid arthritis, lupus, and other diseases, for the diagnosis of idiopathic CFS (4). Consequently, we suggest that patients with CFS should be carefully checked for a history of IM administration of aluminum hydroxide, and, if there is consistent chronology, a muscle biopsy to search for MMF at the site of injection should be considered, even many years after onset of symptoms.

Pathophysiology of CFS is still fiercely debated by psychologists, neuroendocrinologists, and immunologists. Chronic immune stimulation that fails to switch off has been previously reported as a possible cause of CFS (7–9), and such a situation may very well result from persistence of the immunologic adjuvant aluminum hydroxide within antigen-presenting cells (2,10). Therefore, MMF may well represent a paradigm for CFS of immunologic origin. We believe that clarification of MMF pathophysiology would significantly contribute to the understanding of the whole spectrum of chronic fatigue and its syndromes.

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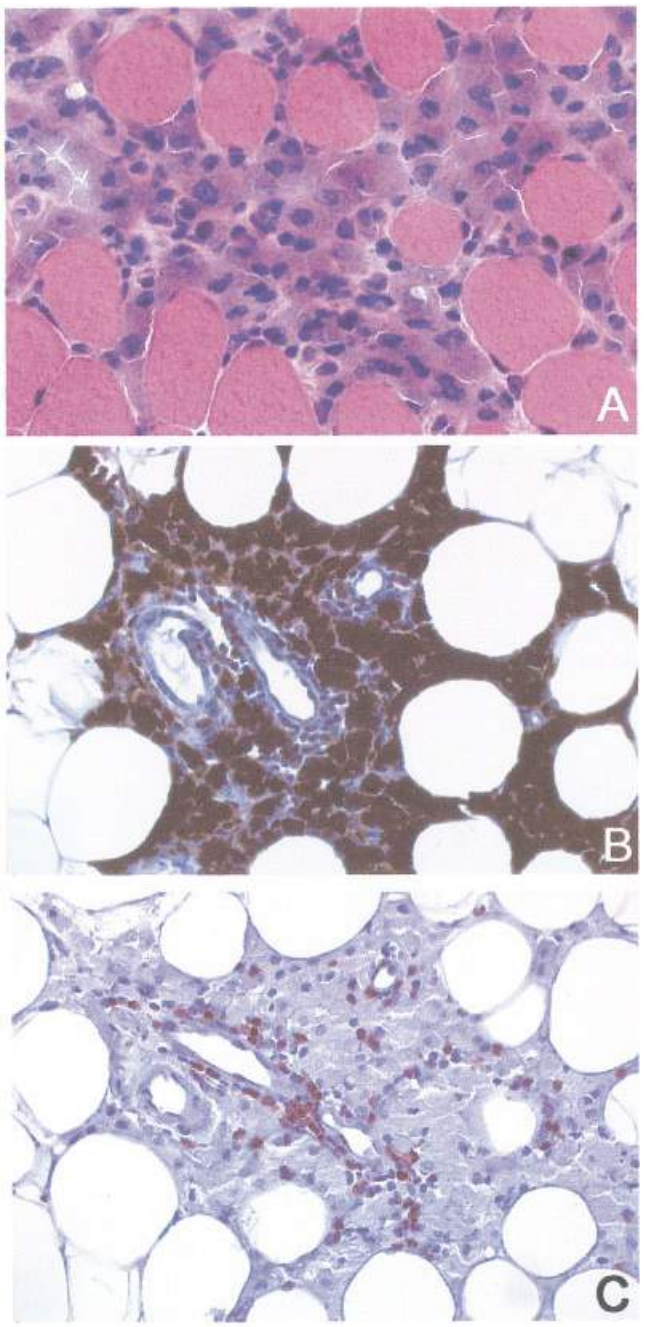

Figure 1. Deltoid muscle biopsy samples from patients with macrophagic myofasciitis (MMF). **A,** Tightly packed, large, basophilic macrophages intermingled with lymphocytes in perifascicular endomysium (frozen section, hematoxylin and eosin stained; original magnification ×400). **B,** MMF lesion in perimuscular adipose tissue showing immunolocalization of the macrophage marker CD68 (paraffin section, immunoperoxidase procedure; original magnification ×400). **C,** Adjacent section of the same biopsy sample showing immunolocalization of the T cell marker CD3 (paraffin section, immunoperoxidase procedure; original magnification ×400).

Table 1. Clinical and laboratory findings in patients with macrophagic myofasciitis*

Chronic fatigue†	28/30 (93)
Severe and disabling	26/30 (87)
Of new onset	25/30 (83)
Leading to substantial reduction in previous levels of activity	24/30 (80)
Present for >50% of the time	19/30 (63)
Not a result of ongoing exertion	18/30 (60)
Affecting both physical and mental functioning	16/30 (53)
Not substantially alleviated by rest	13/30 (43)
Other symptoms†	
Muscle pain	26/30 (87)
Joint pain	17/30 (57)
Sleep disturbance	16/30 (53)
Mood disturbance	16/30 (53)
Subjective memory impairment	15/30 (50)
Headache	14/30 (47)
Unrefreshing sleep	14/30 (47)
CFS criteria fulfilled	16/30 (53)
CDC (1994) (see ref. 4)	14/30 (47)
Oxford (1991) (see ref. 5)	12/30 (40)
Neurologic features suggestive of CNS demyelinating disease	2/20 (10)
Fever	2/20 (10)
Abnormal laboratory findings	
ESR >40 mm/hour	2/14 (14)
CK level >200 IU/liter	4/14 (29)
^{67}Ga scintigraphy	5/5 (100)
Responsive to steroids‡	10/10 (100)

* Values are the number (%) of patients. CFS = chronic fatigue syndrome; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; ESR = erythrocyte sedimentation rate; CK = creatine kinase.
† Part of diagnostic criteria for CFS.
‡ Improvement of both fatigue and myalgias. One patient received intravenous methylprednisolone without significant effect.

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CASE REPORT

Identical Twins With Macrophagic Myofasciitis: Genetic Susceptibility and Triggering by Aluminic Vaccine Adjuvants?

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Introduction

Macrophagic myofasciitis (MMF) is an inflammatory myopathy, recently described (1,2). Clinical symptoms include myalgias, arthralgias, muscle weakness, asthenia, and fever. Diagnosis is based on deltoid muscle biopsy that usually shows specific histologic abnormalities including infiltration of connective tissue structures by densely packed large and grossly rounded CD68+ histiocytes. These cells are characterized by central, round, and often nucleolated nuclei, and clear, slightly basophilic cytoplasms with fine PAS-positive granules (1). Aluminic vaccine adjuvants (3) as well as *Tropheryma whippelii* infection (4,5) have been recently suggested as possible etiopathogenic agents of MMF. We report 2 cases of MMF observed after hepatitis B vaccination in twin sisters. This observation illustrates the importance of the genetic background in MMF, and its possible triggering by aluminic vaccines.

Case report

Two 64-year-old identical twin sisters were referred to our department for possible rheumatoid arthritis. They had no family history of inflammatory disease. The first sister's medical history was unremarkable until December 1993, 6 months after she received a third and final injection of hepatitis B vaccine (Engerix B vaccination, containing aluminic hydroxide, vaccination in April, May, and July, 1993) in the left deltoid. At this time, she began complaining of arthritis. On physical examination, arthritis involving both wrists and the proximal and distal interphalangeal joints of the hands and feet were noted. Arthritis was associated with myalgias and upper limb muscle weakness. She complained of dry eyes and mouth and of oral aphthae. Treatment with oral prednisone (5 mg/day) and methotrexate (20 mg weekly) proved ineffective. Neurologic examination revealed distal paresthesias and cramps affecting the 4 limbs, slight weakness of hand muscles, no pyramidal syndrome, and partial visual acuity loss. Sicca syndrome was confirmed by Schirmer's test. Salivary gland biopsy showed Chisholm 3 grade, consistent with the diagnosis of Gougerot-Sjögren's syndrome. Erythrocyte sedimentation rate (ESR) was 20 mm/hour, C-reactive protein was 30 mg/l. Serum creatine kinase and cerebrospinal fluid were normal. Antinuclear antibodies (ANA) were weakly positive (200 UI/ml) with spotted pattern. Anti-DNA, anti-SSA, anti-SSB, rheumatoid factor, and anticardiolipin antibodies were not detected. Serologic tests for hepatitis A, B, C, and parvovirus B 19 were negative. The patient typed as HLA–A01, A02, B13, B35, DRB1*01, DRB1*07. Electromyography showed a slight myogenic aspect. Radiographs of the hands, shoulders, wrists, ankles, and feet were normal. Technetium bone scan showed symmetric increased uptake of the main joints. Upper right limb muscle magnetic resonance imaging (MRI) showed general muscle atrophy. The morphology and chronology of the visual-, auditory-, motor-, and somaesthesic-evoked responses were normal, and cerebral MRI was normal. Esophago-gastro-duodenoscopy was normal with no evidence of PAS+ cells on duodenal biopsies, the culture for *Tropheryma whippelii* in duodenal biopsies was negative. Diagnosis of MMF was obtained by histologic examination of biopsy sample of the left deltoid muscle, which showed stereotypical epi-, peri- and endomysial infiltrates of densely packed CD68+ macrophages twice associated T and B cells (Figure 1). Electron microscopic examination was not performed on this biopsy.

The twin sister had a similar clinical presentation with bilateral arthritis of wrists, shoulders, temporomandibular joints, hands, and ankles. She received prednisone (15

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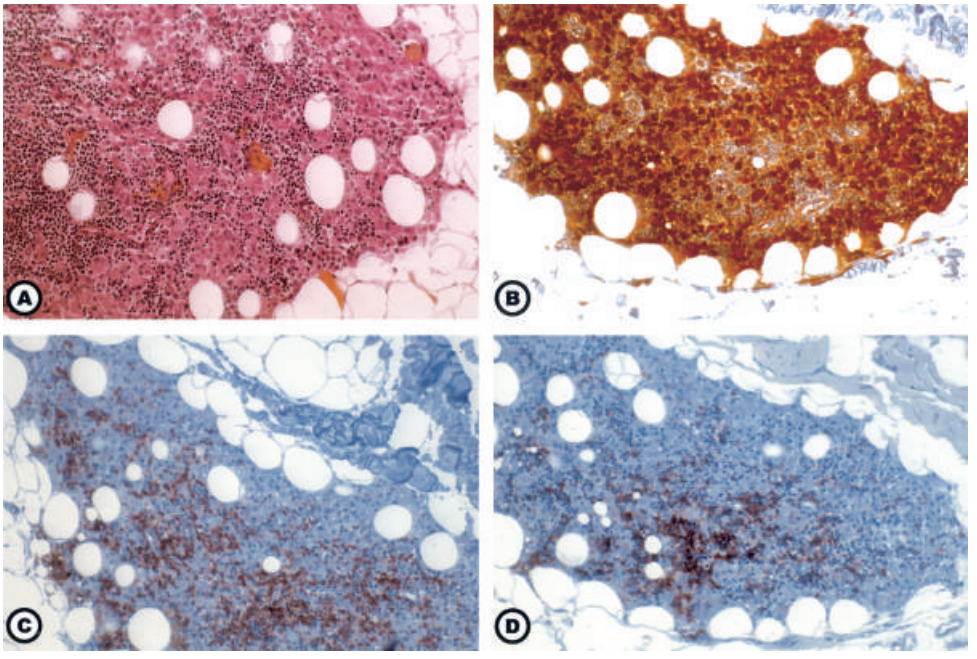

Figure 1. Deltoid muscle biopsy (light microscopy, serial sections, original magnification × 125) demonstrating macrophagic myofasciitis in patient 1. **A,** inflammatory infiltrates of adipose tissue of fascia (fasciitis) by macrophages notably large in size and lymphocytes (Hematoxylin and eosin stained). **B,** immunoreactivity of CD68+ showing large predominance of macrophages. **C,** immunoreactivity of CD3+ mononucleated cells corresponding to T cells. **D,** immunoreactivity of DBB42 antibody showing B cells.

mg/day), hydroxychloroquine (400 mg/day), and methotrexate (20 mg/week). Her medical history was unremarkable except for mild asthma and high blood pressure. On admission, she reported peripheral arthritis with myalgias. Neurologic examination showed distal paresthesias and cramps of the 4 limbs, severe weakness of the hand muscles, hyperreflexia of the right upper limb, right Hoffmann's sign, and normal plantar reflexes urgency of micturition. The symptoms had started 7 months after intramuscular hepatitis B vaccination in the left deltoid (Engerix B containing aluminic hydroxide, vaccination in December 1995, February, and July 1997). ESR was 30 mm at one hour. Serum creatine kinase was normal. ANA, anti-DNA, anti-SSA, anti-SSB, rheumatoid factor, and anticardiolipin antibodies were negative. Serologic tests for hepatitis A, C and parvovirus B 19 were negative. Hepatitis B serology confirmed the vaccination status, specifically the absence of hepatitis B surface, anti-hepatitis B core and anti-hepatitis B e antigens, and the presence of anti-hepatitis B surface antibodies. The patient typed as HLA–A01, A02, B13, B35, DRB1*01, DRB1*07. Schirmer's test was positive. Electromyography showed myogenic aspect. Radiographs of the hands, shoulders, wrists, ankles, and feet were normal. MRI of the superior right limb muscles showed a diffuse muscle atrophy. Evoked potentials and brain MRI were normal. Esophago-gastro-duodenoscopy was normal and cultures for *Tropheryma whippelii* in duodenal biopsies were negative. Once again, muscle biopsy of the left deltoid muscle confirmed the diagnosis of MMF.

Discussion

We report cases of MMF affecting twin sisters, which occurred 6–7 months after hepatitis B vaccination. In both cases, clinical symptoms were remarkable because of the importance of arthritis associated with muscle involvement. Laboratory tests showed slight inflammation, and normal muscle enzyme levels. Remarkably, although both twin sisters had had complete hepatitis B vaccination, only the second had developed antibodies to the hepatitis B surface antigen. Indeed, the HLA–DRB1*07 allele, which both twins expressed, is associated with poor humoral responses to hepatitis B vaccination (6). Thus, antibody responses to hepatitis B surface antigen may not be crucial to the development of MMF.

Conversely, the role of vaccines containing aluminum hydroxide in the pathogenesis of MMF has been recently suggested (3). Despite the fact that histologic abnormalities are present only at the site of vaccination, systemic symptoms are generally observed. However, there is a discrepancy between the wide usage of aluminum hydroxide-containing vaccines (especially anti hepatitis B vaccines) and the very limited number of MMF cases reported so far. We did not perform electron microscopy on muscle biopsies to check for aluminium inclusions in macrophages. This report suggests that additional factors, perhaps genetic, may influence the occurrence of MMF. Aluminum hydroxyde may trigger unusual muscle inflammatory infiltrates in patients with increased susceptibility to inflammatory disease or decrease macrophages' capacity for aluminum hydroxyde digestion. The nature of the predis-

posing genetic factor is unknown. HLA–DRB1*01, which was found in both sisters (identical twins) could be a potential candidate. Thus, our observation suggests that aluminic vaccinations may trigger MMF on the HLA–DRB1*01 genetic background.

REFERENCES

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3. Gherardi RK, Coquet M, Belec L, Chariot P, Moretto P, Figarella-Branger D, et al. Macrophagic myofasciitis: a reaction to intramuscular injections of aluminum-containing vaccines [abstract]. J Neurol 1999;246 Suppl 1:I19.
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6. McDermott AB, Zuckermann JN, Sabin CA, Marsh SG, Madrigal JA. Contribution of human leukocyte antigens to the antibody response to hepatitis B vaccination. Tissue Antigens 1997;50:8–14.

PubMed

Format: Abstract

Full text links

SAGE journals

Pediatr Dev Pathol. 2002 Mar-Apr;5(2):151-8.

Aluminum phagocytosis in quadriceps muscle following vaccination in children: relationship to macrophagic myofasciitis.

Lacson AG[1], D'Cruz CA, Gilbert-Barness E, Sharer L, Jacinto S, Cuenca R.

Author information

Abstract

Macrophagic myofasciitis (MMF) is a rare, seemingly emerging entity among adult patients in France. We encountered two children with the first two cases of MMF in North America. A 5-year-old male with chronic intestinal pseudo-obstruction required nighttime parenteral nutrition. Abnormal pupillary reflexes and urinary retention suggested a diffuse dysautonomia, which prompted a neurological diagnostic work-up. A 3-year-old child had developmental delay and hypotonia. Both children received age-appropriate immunizations. Quadriceps muscle biopsy from each child showed the typical patchy, cohesive centripetal infiltration of alpha-1-antitrypsin+, alpha-1-antichymotrypsin+, CD68+, PAS+, CD1a-, S-100-, factor XIII- granular macrophages with adjacent myofiber atrophy, dilated blood vessels, and mild endomysial and perimysial fibrosis. No myonecrosis was observed and no discrete granulomas were seen. A single aluminum peak was demonstrated on energy dispersive X-ray microanalysis. The etiology of the clinical symptoms in these cases and in cases reported as MMF remains intriguing. Despite numerous stains to demonstrate organisms, most infectious causes leading to macrophage activation were ruled out. These cases are being reported to increase awareness of this condition and to encourage a systematic epidemiologic and clinicopathologic study in North America.

PMID: 11910509 DOI: 10.1007/s10024-001-0137-8

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

PubMed

Format: Abstract

J Rheumatol. 1998 Sep;25(9):1687-93.

The development of rheumatoid arthritis after recombinant hepatitis B vaccination.

Pope JE[1], Stevens A, Howson W, Bell DA.

Author information

Abstract

OBJECTIVE: Hepatitis B vaccination has been associated with reactive arthritis and rarely rheumatoid arthritis (RA). We defined the clinical, serologic, and immunogenetic background of patients developing RA, soon after recombinant hepatitis B vaccination.

METHODS: The clinical, serologic, and HLA antigens of a cluster of firefighters who developed arthritis after prophylactic recombinant hepatitis B vaccination (5 subjects), as well as a second group of sporadic cases of arthritis (6 patients) after hepatitis B vaccination are described.

RESULTS: Ten of 11 patients fulfilled revised American College of Rheumatology criteria for RA. All cases had persistent arthritis for more than 6 months; at 48 months followup 2 cases no longer had inflammatory arthritis. Nine patients required disease modifying antirheumatic drugs. Five subjects were HLA-DR4 positive. HLA class II genes expressing the RA shared motif were identified in 9/11 patients genotyped for HLA-DRbeta1 and DQbeta1 alleles (0401, 0101, or 0404). All the firefighters shared the HLA-DRbeta1 allele 0301 and the DQbeta1 allele 0201, with which it is in linkage disequilibrium.

CONCLUSION: These polymorphic residues in the binding site of the MHC class II molecules of the affected patients appear capable of binding some peptide sequences of the recombinant vaccine peptides they received and may be responsible for hepatitis B vaccine triggering development of RA in these cases. Recombinant hepatitis B vaccine may trigger the development of RA in MHC class II genetically susceptible individuals.

Comment in

Rheumatoid epitopes and CD4+ immunodominant regions of recombinant hepatitis B surface antigen. [J Rheumatol. 1999]

PMID: 9733447

[Indexed for MEDLINE]

MeSH terms, Substances

LinkOut - more resources

Lupus. 2009 Nov;18(13):1198-204. doi: 10.1177/0961203309345730.

Transverse myelitis and vaccines: a multi-analysis.

Agmon-Levin N[1], Kivity S, Szyper-Kravitz M, Shoenfeld Y.

Author information

Abstract

Transverse myelitis is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord. The pathogenesis of transverse myelitis is mostly of an autoimmune nature, triggered by various environmental factors, including vaccination. Our aim here was to search for and analyze reported cases of transverse myelitis following vaccination. A systematic review of PubMed, EMBASE and DynaMed for all English-language journals published between 1970 and 2009 was preformed, utilizing the key words transverse myelitis, myelitis, vaccines, post-vaccination, vaccination and autoimmunity. We have disclosed 37 reported cases of transverse myelitis associated with different vaccines including those against hepatitis B virus, measles-mumps-rubella, diphtheria-tetanus-pertussis and others, given to infants, children and adults. In most of these reported cases the temporal association was between several days and 3 months, although a longer time frame of up to several years was also suggested. Although vaccines harbor a major contribution to public health in the modern era, in rare cases they may be associated with autoimmune phenomena such as transverse myelitis. The associations of different vaccines with a single autoimmune phenomenon allude to the idea that a common denominator of these vaccines, such as an adjuvant, might trigger this syndrome.

PMID: 19880568 DOI: 10.1177/0961203309345730

[Indexed for MEDLINE]

Autoimmun Rev. 2014 Mar;13(3):215-24.

The spectrum of post-vaccination inflammatory CNS demyelinating syndromes.

Karussis D, Petrou P.

Abstract

A wide variety of inflammatory diseases temporally associated with the administration of various vaccines, has been reported in the literature. A PubMed search from 1979 to 2013 revealed seventy one (71) documented cases. The most commonly reported vaccinations that were associated with CNS demyelinating diseases included influenza (21 cases), human papilloma virus (HPV) (9 cases), hepatitis A or B (8 cases), rabies (5 cases), measles (5 cases), rubella (5 cases), yellow fever (3 cases), anthrax (2 cases),meningococcus (2 cases) and tetanus (2 cases). The vast majority of post-vaccination CNS demyelinating syndromes, are related to influenza vaccination and this could be attributed to the high percentage of the population that received the vaccine during the HI1N1 epidemia from 2009 to 2012. Usually the symptoms of the CNS demyelinating syndrome appear few days following the immunization (mean: 14.2 days) but there are cases where the clinical presentation was delayed (more than 3 weeks or even up to 5 months post-vaccination) (approximately a third of all the reported cases). In terms of the clinical presentation and the affected CNS areas, there is a great diversity among the reported cases of post-vaccination acute demyelinating syndromes. Optic neuritis was the prominent clinical presentation in 38 cases, multifocal disseminated demyelination in 30, myelitis in 24 and encephalitis in 17. Interestingly in a rather high proportion of the patients (and especially following influenza and human papiloma virus vaccination-HPV) the dominant localizations of demyelination were the optic nerves and the myelon, presenting as optic neuritis and myelitis (with or without additional manifestations of ADEM), reminiscent to neuromyelitic optica (or, more generally, the NMO-spectrum of diseases). Seven patients suffered an NMO-like disease following HPV and we had two similar cases in our Center. One patient with post-vaccination ADEM, subsequently developed NMO. Overall, the risk of a demyelinating CNS disease following vaccination, although non-negligible, is relatively low. The risk of onset or relapse of CNS demyelination following infections against which the vaccines are aimed to protect, is substantially higher and the benefits of vaccinations surpass the potential risks of CNS inflammation. This does not in any way exempt us from“learning” the lessons taught by the reported cases and searching new and safer ways to improve vaccination techniques and increase their safety profile.

PMID: 24514081 DOI: 10.1016/j.autrev.2013.10.003

[Indexed for MEDLINE]

Format: Abstract

Neurology. 2009 Mar 10;72(10):873-80. doi: 10.1212/01.wnl.0000335762.42177.07. Epub 2008 Oct 8.

Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood.

Mikaeloff Y[1], Caridade G, Suissa S, Tardieu M.

Author information

Abstract

BACKGROUND: The risk of CNS inflammatory demyelination associated with hepatitis B (HB) vaccine is debated, with studies reporting conflicting findings.

METHODS: We conducted a population-based case-control study where the cases were children with a first episode of acute CNS inflammatory demyelination in France (1994-2003). Each case was matched on age, sex, and geographic location to up to 12 controls, randomly selected from the general population. Information on vaccinations was confirmed by a copy of the vaccination certificate. The odds ratios (ORs) of CNS inflammatory demyelination associated with HB vaccination were estimated using conditional logistic regression.

RESULTS: The rates of HB vaccination in the 3 years before the index date were 24.4% for the 349 cases and 27.3% for their 2,941 matched controls. HB vaccination within this period was not associated with an increase in the rate of CNS inflammatory demyelination (adjusted OR, 0.74; 0.54-1.02), neither >3 years nor as a function of the number of injections or brand type. When the analysis was restricted to subjects compliant with vaccination, HB vaccine exposure >3 years before index date was associated with an increased trend (1.50; 0.93-2.43), essentially from the Engerix B vaccine (1.74; 1.03-2.95). The OR was particularly elevated for this brand in patients with confirmed multiple sclerosis (2.77; 1.23-6.24).

CONCLUSIONS: Hepatitis B vaccination does not generally increase the risk of CNS inflammatory demyelination in childhood. However, the Engerix B vaccine appears to increase this risk, particularly for confirmed multiple sclerosis, in the longer term. Our results require confirmation in future studies.

Comment in

Hepatitis vaccines and pediatric multiple sclerosis: does timing or type matter? [Neurology. 2009]
Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. [Neurology. 2009]
Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. [Neurology. 2009]

PMID: 18843097 DOI: 10.1212/01.wnl.0000335762.42177.07

[Indexed for MEDLINE]

Publication type, MeSH terms, Substance

LinkOut - more resources

Format: Abstract

Immunol Res. 2014 Dec;60(2-3):219-25. doi: 10.1007/s12026-014-8574-4.

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination.

Le Houézec D[1].

Author information

Abstract

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data and also from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of the Hill's criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.

Comment in

Comment on: Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination. [Immunol Res. 2015]

PMID: 25395338 PMCID: PMC4266455 DOI: 10.1007/s12026-014-8574-4

[Indexed for MEDLINE] **Free PMC Article**

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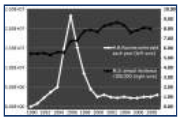
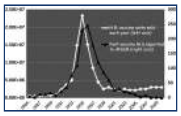

Publication type, MeSH terms, Substance

LinkOut - more resources

Format: Abstract

Full text links
PEDIATRICS FINAL VERSION

Pediatrics. 2010 Jul;126(1):e1-8. doi: 10.1542/peds.2010-0665. Epub 2010 Jun 29.

Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.

Klein NP[1], Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E; Vaccine Safety Datalink.

Author information

Abstract

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000-2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83,107) were compared with recipients of MMR + varicella vaccines (376,354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43-2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10,000 doses (95% confidence interval: 2.6-5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines.

Comment in

Measles-mumps-rubella-varicella combination vaccine increases risk of febrile seizure. [J Pediatr. 2011]

PMID: 20587679 DOI: 10.1542/peds.2010-0665

[Indexed for MEDLINE]

Publication types, MeSH terms, Substances

LinkOut - more resources

PubMed

Format: Abstract

Full text links

Am J Reprod Immunol. 2013 Oct;70(4):309-16. doi: 10.1111/aji.12151. Epub 2013 Jul 31.

Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants.

Colafrancesco S[1], Perricone C, Tomljenovic L, Shoenfeld Y.

Author information

Abstract

PROBLEM: Post-vaccination autoimmune phenomena are a major facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and different vaccines, including HPV, have been identified as possible causes.

METHOD OF STUDY: The medical history of three young women who presented with secondary amenorrhea following HPV vaccination was collected. Data regarding type of vaccine, number of vaccination, personal, clinical and serological features, as well as response to treatments were analyzed.

RESULTS: All three patients developed secondary amenorrhea following HPV vaccinations, which did not resolve upon treatment with hormone replacement therapies. In all three cases sexual development was normal and genetic screen revealed no pertinent abnormalities (i.e., Turner's syndrome, Fragile X test were all negative). Serological evaluations showed low levels of estradiol and increased FSH and LH and in two cases, specific auto-antibodies were detected (antiovarian and anti thyroid), suggesting that the HPV vaccine triggered an autoimmune response. Pelvic ultrasound did not reveal any abnormalities in any of the three cases. All three patients experienced a range of common non-specific post-vaccine symptoms including nausea, headache, sleep disturbances, arthralgia and a range of cognitive and psychiatric disturbances. According to these clinical features, a diagnosis of primary ovarian failure (POF) was determined which also fulfilled the required criteria for the ASIA syndrome.

CONCLUSION: We documented here the evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition. The increasing number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term clinical benefits of HPV vaccination are a matter of public health that warrants further rigorous inquiry.

KEYWORDS: Autoantibodies; autoimmune/inflammatory syndrome induced by adjuvants; autoimmunity; human papilloma virus; primary ovarian failure

Comment in

Authors' reply: Human papillomavirus vaccine and primary ovarian failure. [Am J Reprod Immunol. 2014]
Authors' reply: Human papilloma virus vaccine and primary ovarian failure. [Am J Reprod Immunol. 2014]
On the association between human papillomavirus vaccine and primary ovarian failure. [Am J Reprod Immunol. 2014]
RE: Human papillomavirus vaccine and primary ovarian failure paper. [Am J Reprod Immunol. 2014]

PMID: 23902317 DOI: 10.1111/aji.12151

[Indexed for MEDLINE]

Publication types, MeSH terms, Substances

LinkOut - more resources

Format: Abstract

J Toxicol Environ Health A. 2018;81(14):661-674. doi: 10.1080/15287394.2018.1477640. Epub 2018 Jun 11.

A lowered probability of pregnancy in females in the USA aged 25-29 who received a human papillomavirus vaccine injection.

DeLong G[1].

Author information

Abstract

Birth rates in the United States have recently fallen. Birth rates per 1000 females aged 25-29 fell from 118 in 2007 to 105 in 2015. One factor may involve the vaccination against the human papillomavirus (HPV). Shortly after the vaccine was licensed, several reports of recipients experiencing primary ovarian failure emerged. This study analyzed information gathered in National Health and Nutrition Examination Survey, which represented 8 million 25-to-29-year-old women residing in the United States between 2007 and 2014. Approximately 60% of women who did not receive the HPV vaccine had been pregnant at least once, whereas only 35% of women who were exposed to the vaccine had conceived. For married women, 75% who did not receive the shot were found to conceive, while only 50% who received the vaccine had ever been pregnant. Using logistic regression to analyze the data, the probability of having been pregnant was estimated for females who received an HPV vaccine compared with females who did not receive the shot. Results suggest that females who received the HPV shot were less likely to have ever been pregnant than women in the same age group who did not receive the shot. If 100% of females in this study had received the HPV vaccine, data suggest the number of women having ever conceived would have fallen by 2 million. Further study into the influence of HPV vaccine on fertility is thus warranted.

PMID: 29889622 DOI: 10.1080/15287394.2018.1477640

Vaccine. 2017 Sep 25;35(40):5314-5322. doi: 10.1016/j.vaccine.2017.06.069.

Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12.

Donahue JG[1], Kieke BA[2], King JP[3], DeStefano F[4], Mascola MA[5], Irving SA[6], Cheetham TC[7], Glanz JM[8], Jackson LA[9], Klein NP[10], Naleway AL[11], Weintraub E[12], Belongia EA[13].

Author information

Abstract

INTRODUCTION: Inactivated influenza vaccine is recommended in any stage of pregnancy, but evidence of safety in early pregnancy is limited, including for vaccines containing A/H1N1pdm2009 (pH1N1) antigen. We sought to determine if receipt of vaccine containing pH1N1 was associated with spontaneous abortion (SAB).

METHODS: We conducted a case-control study over two influenza seasons (2010-11, 2011-12) in the Vaccine Safety Datalink. Cases had SAB and controls had live births or stillbirths and were matched on site, date of last menstrual period, and age. Of 919 potential cases identified using diagnosis codes, 485 were eligible and confirmed by medical record review. Exposure was defined as vaccination with inactivated influenza vaccine before the SAB date; the primary exposure window was the 1-28days before the SAB.

RESULTS: The overall adjusted odds ratio (aOR) was 2.0 (95% CI, 1.1-3.6) for vaccine receipt in the 28-day exposure window; there was no association in other exposure windows. In season-specific analyses, the aOR in the 1-28days was 3.7 (95% CI 1.4-9.4) in 2010-11 and 1.4 (95% CI 0.6-3.3) in 2011-12. The association was modified by influenza vaccination in the prior season (post hoc analysis). Among women who received pH1N1-containing vaccine in the previous influenza season, the aOR in the 1-28days was 7.7 (95% CI 2.2-27.3); the aOR was 1.3 (95% CI 0.7-2.7) among women not vaccinated in the previous season. This effect modification was observed in each season.

CONCLUSION: SAB was associated with influenza vaccination in the preceding 28days. The association was significant only among women vaccinated in the previous influenza season with pH1N1-containing vaccine. This study does not and cannot establish a causal relationship between repeated influenza vaccination and SAB, but further research is warranted.

KEYWORDS: Influenza; Influenza vaccine; Pregnancy; Spontaneous abortion

Comment in

Commentary on: "Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12". [Vaccine. 2017]

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[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

LinkOut - more resources

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Genetic Basis for Adverse Events Following Smallpox Vaccination

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Abstract

Background—Although vaccinia immunization is highly effective in preventing smallpox, post-vaccination reactions are common. Identifying genetic factors associated with AEs might allow screening before vaccinia administration and provide a rational basis for the development of improved vaccine candidates.

Methods—Two independent clinical trials in healthy, vaccinia-naïve adult volunteers were conducted with the Aventis Pasteur smallpox vaccine (APSV). Volunteers were assessed repeatedly for local and systemic AEs to vaccine and were genotyped using the same panel of 1442 single-nucleotide polymorphisms (SNPs).

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Results—In the first study, thirty-six SNPs in 26 genes were associated with systemic AEs (p-value ≤ 0.05). In the second study, only those SNPs associated with AEs in the first sample were tested. In the final analysis, three SNPs were associated consistently with AEs in both studies. A nonsynonymous SNP in methylenetetrahydrofolate reductase (*MTHFR*) was associated with AE risk in both trials (odds ratio [OR]; 95% confidence interval [CI]); p-value [p]): (OR=2.3; CI=1.1–5.2; p=0.04) and (OR=4.1; CI=1.4–11.4; p<0.01). Two SNPs in the interferon regulatory factor 1 (*IRF1*) gene were associated with AE risk in both sample sets: (OR=3.2; CI=1.1–9.8; p=0.03) and (OR=3.0; CI=1.1–8.3; p=0.03).

Conclusions—Genetic polymorphisms in an enzyme previously associated with adverse reactions to a variety of pharmacologic agents (*MTHFR*) and an immunological transcription factor (*IRF1*) were associated with AEs after smallpox vaccination in two independent study samples. These findings highlight common genetic variants with promising clinical significance that merit further investigation.

Keywords

adverse events; vaccination; smallpox; genetics; epidemiology

INTRODUCTION

Although reactions following inoculation with vaccinia virus were common in the recent population-wide vaccination programs [1], the biological basis for these adverse events (AEs) is not well understood. The performance of two independent clinical studies of a single vaccinia vaccine at our study site afforded us the unique opportunity to assess genetic factors that might predict systemic AEs. All of the vaccinia-naïve subjects enrolled developed pock formation at the vaccination site, and a subset experienced systemic reactions including fever, rash or regional lymphadenopathy. Since poxviruses have evolved multiple mechanisms to evade host immune responses, such as targeting of primary innate immunity and manipulating intracellular signal transduction pathways [2], we questioned whether subjects encountering AEs exhibited unique genetic polymorphisms in these pathways that made them more susceptible to these reactions.

In earlier studies, we characterized humoral and cellular immune responses and outlined patterns of systemic cytokine expression following smallpox vaccination [3–8]. In the current report, we utilized data collected during two independent studies to identify stable genetic factors associated with AEs. Since many genetic association studies fail to replicate during subsequent studies, we sought to repeat the assessment on an additional study group [9,10]. Independent replication of the results of our first study with the second strengthens the plausibility of these genetic associations. An identical panel of candidate single-nucleotide polymorphisms (SNPs) was evaluated in each of the studies. Subjects with systemic AEs including fever, lymphadenopathy, or generalized acneiform rash, were compared with those who did not experience these reactions. For both studies, the data were genotypes at 1442 SNPs across at least 386 candidate genes. This investigation provides important preliminary findings in two independent data sets addressing the contribution of common genetic variants to a complex clinical phenotype, which also bears substantial importance with respect to public health.

METHODS

Study Subjects

Vaccines, study subjects, and study design for both of the clinical trials have been described previously in detail. Both trials were conducted at Vanderbilt University in the NIH-funded

Vaccine and Treatment Evaluation Unit (VTEU) [4,8,11]. The first study [7] enrolled 85 healthy vaccinia-naïve adults in genotyping studies and the second study [11] also enrolled 46 healthy vaccinia-naïve adults. In both studies, individuals were asked to self-identify ethnic background. Both studies complied with the Internal Review Board policies of Vanderbilt and the NIH, and written consent was obtained for all individuals.

Clinical Assessments

For both studies, the same team of trained physicians and nurses used the same forms to obtain medical history and to record local and systemic AEs after vaccination. Subjects were examined at regular intervals (days 3–5, 6–8, 9–11, 12–15, and 26–30 after vaccination). Local and systemic AEs were recorded. Subjects with an oral temperature of greater than 38.3 °C anytime during the study, generalized skin eruptions on non-contiguous areas to the site of vaccination [11], or enlarged or tender regional lymph nodes associated with vaccination were defined as those experiencing systemic AEs.

Identification of Genetic Polymorphisms

We used a previously described custom SNP panel based on the NCI SNP500 Cancer project [12]; specifically, this panel targets investigation of soluble factor mediators and signaling pathways, many of which have known immunological significance [13]. There is a heavy weighting towards non-synonymous SNPs in this panel (*i.e.*, those that result in an amino acid substitution). Genotyping for single nucleotide polymorphisms (SNPs) was performed using DNA amplified directly from EBV-transformed B cells generated from peripheral blood samples collected from each subject. Genotyping was performed at the Core Genotyping Facility of the National Cancer Institute (NCI) in Gaithersburg, MD. Genotypes were generated using the Illumina™ GoldenGate assay technology. Of the 1536 SNPs assayed, a total of 1442 genotypes passed quality control filters for both the first and second sample sets. A complete list of the SNPs examined in this study is found in Supplemental Table 1.

Statistical Analysis

Demographic characteristics including age, gender, and race were compared between the first and second study using Student's t-test (for age) and two-sample tests of proportions (for AE status, gender, and race). Allele frequencies were estimated from the total number of copies of individual alleles divided by the number of all alleles in the sample, and compared between the two studies using a two-sample test of proportions. Deviations in the fitness for Hardy-Weinberg proportion were evaluated using the exact test described in Wigginton *et al* [14].

We chose a two-stage design for identifying and replicating genetic associations in the independent clinical trials. This study design was selected with the goal of minimizing Type I errors (false positives). For comparison, we also performed the genetic association analysis in a single pooled sample. In the first study, potential associations were tested between each of the 1442 SNPs passing quality control filters and the occurrence of AEs using logistic regression. For each SNP in the first sample set, we recorded the odds ratio estimate and p-value of the likelihood ratio test for a univariate logistic model. No correction for multiple comparisons was made in our first set, because we reserved the second study sample set for determination of probable true positives. In the second sample set, we tested only those SNPs having an AE-associated p-value ≤ 0.05 in the first study. We considered a significant SNP association in the first study to have replicated if it met the following criteria in the second study: an odds ratio that consistently associated AE risk with the same genotypes and a p-value ≤ 0.05. To obtain an empirical probability of meeting our replication criteria purely by chance, we generated 1,000 simulated data sets from both study sample sets by permuting case-control labels. An additional association with p-value 0.06 is discussed below because of its high biologic plausibility.

Patterns of linkage disequilibrium (LD) between replicated SNPs on the same chromosome were assessed using Haploview [15]. Haplotypes were inferred for SNPs in high LD using the iterative approach described in Lake *et al* [16]. The resulting haplotypes were tested for association with AEs using univariate logistic models. Statistical analyses and simulations were performed using R version 2.5.1, Stata version 9 (Stata Corp, College Station, TX), and Haploview version 3.32 [15,17,18].

RESULTS

Demographic Characteristics of Subjects Included in Genetic Analysis

In both studies, all participants were invited to donate genetic samples. In the first study, of the 148 vaccinia-naïve participants enrolled in the clinical trial, a total of 96 individuals gave consent for the genetic substudy. Of those 96 subjects with genetic data, 16 experienced *systemic* AEs following immunization. An additional 11 genotyped subjects who reported only a localized rash near the inoculation site were removed from the analysis to focus only on systemic AEs. The other 69 reporting no AEs were used as controls. Thus the first study included analysis of 85 subjects. In the second study, which included 48 vaccinia-naïve healthy adults, 46 gave consent for genotyping and were enrolled. Of the 46 individuals, 24 experienced systemic AEs.

Table 1 summarizes age, race, gender, and AE status decompositions of both studies. Table 1 also describes the results of the demographic comparisons between the first and second studies. As the table indicates, there was no statistical difference in age, gender, or race between the two study populations. In the first study, 40 (47%) individuals were male, 84 (99%) were white and 1 (1%) was Asian. In the second study, 27 (59%) individuals were male, 44 (96%) were white, 1 (2%) was black, and 1 (2%) was Asian.

Genetic Associations with Adverse Events

A total of 36 SNPs (within 26 genes) that showed significant associations in the first study were tested for potential associations in the second study. Three variant genotypes were confirmed to be associated with AEs in the second study. These included one SNP in *MTHFR* ($p < 0.01$) and two SNPs in *IRF1* ($p = 0.03$). The strong significance of the association in the replication study suggested a high level of plausibility that the gene products were involved in the pathogenesis of the AEs. The results of our simulation study indicated that the probability of meeting our replication criteria (an odds ratio that consistently associated AE risk with the same genotypes and a p-value ≤ 0.05) entirely by chance was $p < 0.001$. It is important to note that we also reanalyzed the data as a single pooled sample and found the same pattern of statistically significant associations. The statistical results that replicated in the second study are shown alongside those from the first study in Table 2.

Three SNPs in a third gene, *IL4*, had p-values equal to 0.06 in the second study. While not significant using a strict requirement for $p \leq 0.05$, we thought this association of great interest because of the prior biologic studies showing a central role for this cytokine in poxvirus biology [19–21]. Considering the reduced size of the second sample and the fact that the AE risk associated with variant genotypes was consistent across studies, these *IL4* SNPs warrant further study, because additional variants in linkage disequilibrium could also be associated with AE outcomes (Table 3).

The SNPs located in *IRF1* and *IL4* are located in the same chromosomal region (5q31.1), suggesting an indirect association with one or more functional variants in that region. Because of the close physical proximity of the associated variants in the two genes, Haploview [15] software was used to examine the patterns of LD among those variants in each sample. Figure

1 shows that the LD plots for SNPs in the two genes follow the same pattern in each study sample. While there is strong LD between SNPs within the two genes, there is little evidence for LD between the two genes, indicating that the associations for each gene are statistically separate signals.

This region of chromosome 5q31 contains discrete haplotype blocks [22]. Accordingly, haplotypes were inferred for AE-associated SNPs in *IRF1* (rs839 and rs9282763) and *IL4* (rs2070874, rs2243268, rs2243290). In both studies, two *IRF1* haplotypes accounted for all subjects. The common *IRF1* haplotype listed in Table 4 represented 71% of the first sample set and 63% of the second sample set. The rare *IRF1* haplotype was significantly associated with AEs in both studies ($p = 0.03$). Across both studies, two different three-SNP haplotypes in *IL4* accounted for 99% of subjects. The common *IL4* haplotype listed in Table 4 represented 78% of the first set and 87% of the second set. The rare *IL4* haplotype was significantly associated with risk of AEs in the first study ($p = 0.05$); the association was similar in the second study ($p = 0.06$).

DISCUSSION

The candidate genes identified with the strongest association with AEs in both studies include a metabolism gene previously associated with adverse reactions to a variety of pharmacologic agents (*MTHFR*) and an immunological transcription factor (*IRF1*). The statistical results from these studies have strong biological plausibility and are in agreement with previous work on the immune response to poxviruses.

MTHFR

A SNP in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene (rs1801133) was associated strongly with AE risk in both studies. This non-synonymous SNP in exon 5 causes an amino acid change from alanine to valine, and functional characterization of this SNP demonstrated that it is thermolabile and affects both the quantity and activity of the MTHFR enzyme [23]. The enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a co-substrate for homocysteine remethylation to methionine. *MTHFR* function provides pools of methyl groups that are crucial for the control of DNA synthesis and repair mechanisms [24]. *MTHFR* is a key enzyme in homocysteine metabolism, which plays a major role in regulating endothelial function. It may be of interest in the future to examine the association of genetic variation in this gene with the rare cardiac events that occur after vaccination.

Genetic variation of *MTHFR* has been associated with a range of clinical outcomes, including altered cardiovascular function, organ transplantation, toxicity of immunosuppressive drugs, and systemic inflammation [25–28]. Elevated plasma homocysteine levels stimulate endothelial inflammatory responses, which could contribute to systemic AEs. Alternatively, since vaccination elicits immune responses involving the rapid proliferation of cells, demand for DNA synthesis metabolites would be elevated, and alterations in the level or activity of *MTHFR* enzyme may exert significant influence over this process.

Interferon regulatory factor-1

The interferon regulatory factor-1 (*IRF1*) gene is part of the immunological gene cluster on chromosome 5q31. We found two SNPs in *IRF1* that are significantly associated with AEs in both study samples. The *IRF1* gene encodes an important member of the interferon regulatory transcription factor (IRF) family. The IRF family regulates interferons and interferon-inducible genes. *IRF1* activates transcription of the Type I interferons α and β as well as genes induced

by the Type II interferon γ [29]. Many viruses target IRFs to evade host immune responses by binding to cellular IRFs and blocking transcriptional activation of IRF targets [30].

Polymorphisms in the gene coding for a transcription factor with such far-reaching effects as *IRF1* could have profound effects on the proper immune response and clearance of vaccinia virus. Mice deficient in interferon receptors are especially susceptible to vaccinia virus infection, suggesting an important role for these molecules in controlling vaccinia infection [31]. Vaccinia dedicates several host modifying genes to counteracting interferons. For example, the viral gene B18R encodes a protein that serves as a viral IFN-α/β binding protein that binds interferons from several species [32]. This protein also can bind to the cell surface after secretion, thus preventing host interferon from binding to cellular interferon receptors [33]. Although the SNPs identified in *IRF1* and *IL4* do not change amino acids in the encoded proteins, recent evidence suggests that synonymous SNPs, such as rs839, can alter regulation of mRNA or splice junctions [34,35]. It is also plausible that one or both SNPs are in LD with the causal variant not tested in this study.

Interleukin-4

Genetic polymorphisms in this major cytokine gene involved in adaptive immunity to viruses also may be associated with AEs, however with a p-value of 0.06 in our relatively small replication study. We found three SNPs in *IL4* that may be associated with AEs in both studies. There was high intragenic LD ($r^2 > 0.9$) between the tested SNPs within each gene, *IRF1* and *IL4*, and haplotypes inferred separately for each of these genes mirrored the significant risk patterns of the SNPs observed individually. Thus, the fact that multiple SNPs in high LD were identified in regions of *IRF1* and *IL4* strongly suggest that there are additional markers in LD, several of which could functionally contribute to the risk for AEs.

The *IL4* gene encodes a pleiotropic cytokine produced by a variety of immune cells, especially activated T cells. *IL4* controls humoral immune responses, isotype switching, and suppression of cytotoxic T cell function and expansion. Thus, genetic polymorphisms related to inappropriate regulation of *IL4* expression and/or activity of IL-4 cytokine could be associated with over-stimulated inflammatory responses leading to the development of clinical AEs. Previous studies on the role of *IL4* in poxvirus pathogenesis have shown it to have a central role in altering the adaptive immune response. *IL4* over-expression during infection with recombinant poxviruses encoding *IL4* suppresses the induction of cytotoxic T cell activity by inhibiting CD8+ T cell proliferation, which increased the pathogenicity of such recombinant viruses even in previously immunized animals [36]. *IL4* also plays a role in preventing optimum innate immune responses to poxviruses. IL-4 secretion during vaccinia virus infection of individuals with atopic dermatitis alters the cytokine milieu, resulting in a block of production of the antimicrobial peptide LL-37, accounting in part for the increased risk of vaccinia virus infection in subjects with atopic dermatitis [37].

Model of pathogenesis

Since the outcome of interest here was the aggregation of specific AEs, it is logical that more than one gene may be involved. The genes with variants for which we discovered an association with AEs are all potentially involved in pathways that are in line with our previously hypothesized mechanism of AEs involving excess stimulation of inflammatory pathways and the imbalance of tissue damage repair pathways. This model was developed from studies of circulating cytokines and relevant immunological effector cells [3–5]. For subjects experiencing AEs, vaccination appears to trigger an acute inflammatory response that is excessive. Antigen presentation to T cells in the dermis leads to the release of T-cell cytokines that trigger a cascade of cytokines and chemokines whose release enhances the inflammatory response by promoting the migration of monocytes into the lesion and their maturation into

macrophages and by further attracting T cells [38,39]. Taken together, these previous findings suggest that systemic AEs following smallpox vaccination may be consistent with low-grade macrophage activation syndrome caused by virus replication and vigorous tissue injury and repair.

There are limitations to this study. The subject numbers are small for a genetic association study of low-penetrance high-frequency alleles. The association of the *IL4* variations with AEs was weaker than that of the other genes. Nevertheless, findings of the same variants in two independent clinical trials, the high biologic plausibility of these associations in light of what is known about poxvirus biology, and the potential public health significance suggest the findings are of interest.

Conclusions and Future Directions

These data present the rare opportunity to study two independent cohorts of smallpox vaccinees relating common genetic variation to the occurrence of post-vaccination AEs. Statistical analysis of the first study revealed potentially significant associations between SNPs in biologically interesting candidate genes. Of the AE-associated genes identified in the first study, two replicated in an independent study, with one additional candidate gene just beyond our statistical significance cut-off but with a high level of biologic plausibility. It is possible that our findings could be due to chance, but we avoided multiple testing issues by testing only the most promising results in the validation sample. While all SNPs were tested in the first study, only those SNPs significantly associated with AEs were tested in the second study, and our empirically derived probability of replication by chance alone was less than 0.1%. The association of SNPs in three genes across both studies and their biologically plausible connection with AEs lends credence to the reproducibility of these associations.

As with any statistical association, follow-up studies are needed to identify the particular genetic susceptibility variants and examine the functional consequences of polymorphisms in the AE-associated genes. Since we found multiple AE-associated SNPs in regions of *IRF1* and *IL4*, focused studies should be undertaken to characterize the genetic variability in these candidate regions. Indeed, haplotypes in *IRF* and *IL4* displayed altered susceptibility to a specific systemic AE (fever) after smallpox vaccination [40]. While the association of AEs with a non-synonymous polymorphism in the gene for *MTHFR* points toward functional significance of this SNP, fine mapping of this locus should determine whether this is indeed the case. For all three candidate genes, both follow-up replication and functional studies are needed to establish the plausibility of the association of common genetic polymorphisms with the hypothesized etiological pathways.

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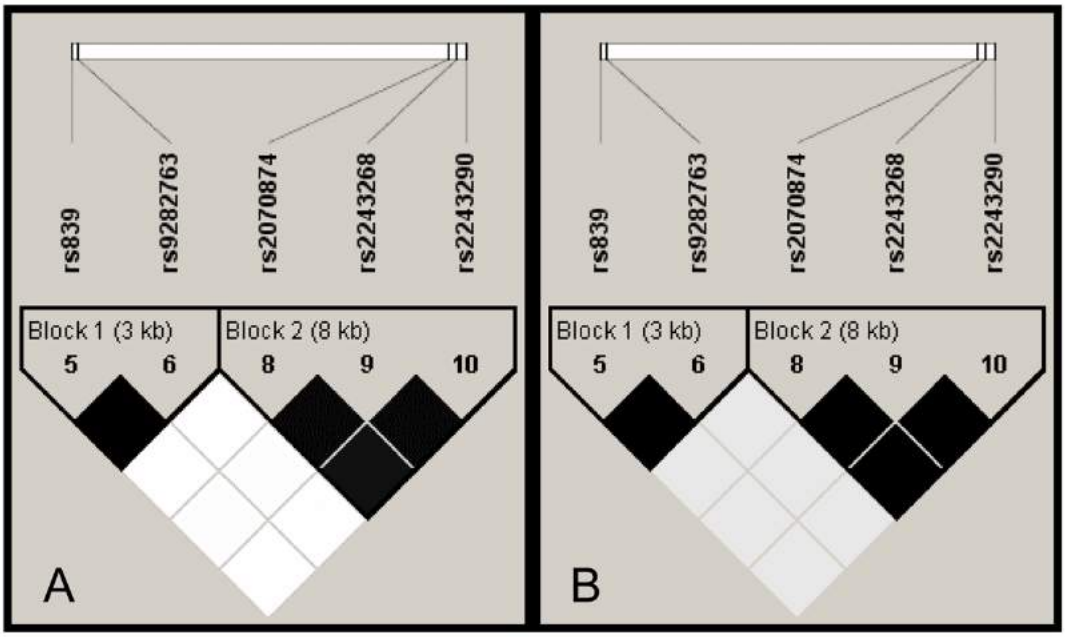

Figure 1. Haploview plot of SNPs at chromosome 5q31.1

Panel A =first study; panel B =second study. Squares are shaded to indicate strength of evidence for LD between the pairwise markers. Dark = strong evidence ($r^2 > 0.90$), light gray = weak evidence ($r^2 < 0.10$), white = no evidence ($r^2 < 0.0$). The same two LD blocks are apparent in both studies, encompassing SNPs in *IRF1* (rs839 and rs9282763) or *IL4* (rs2070874, rs2243268, and rs2243290).

Table 1

Summary of AE status, age, gender, and race for both studies.

Dataset	AE/nonAE	Age[a]	Gender (M/F)	Race (W/B/A)[b]
First study ($N = 85$)	16/69	23.2 (3.9)	40/45	84/0/1
Second study ($N = 46$)	24/22	24.2 (3.8)	27/19	44/1/1
[c] P-value of difference	< 0.01	0.15	0.20	0.25

[a] Mean (standard deviation)

[b] W = white, B = black, A = Asian

[c] Two-sided p-value for t-test (age) or two-sample test of proportions (AE/nonAE, gender, race)

Table 2

Genetic polymorphisms associated with AEs in both studies.

Gene	SNP (rs#)	SNP Location (Base pair) [a]	Chromosomal Location	First Study		Second Study	
				Odds Ratio[b]	p-value (X^2)[b]	Odds Ratio[b]	p-value (X^2)[c]
MTHFR	1801133	6393745	1p36.3	2.3 (1.1–5.2)	0.04	4.1 (1.4–11.4)	< 0.01
IRF1	9282763	34237146	5q31.1	3.2 (1.1–9.8)	0.03	3.0 (1.1–8.3)	0.03
	839	34234139	5q31.1	3.2 (1.1–9.8)	0.03	3.0 (1.1–8.3)	0.03

[a] Base pair according to dbSNP (NCBI Human Genome Build 36.1).

[b] Estimated odds ratio (95% confidence interval)

[c] Likelihood ratio chi-square (X^2) test with one degree of freedom

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Table 3

Distribution of genotypes at SNPs in *MTHFR*, *IRF1*, and *IL4*.

Gene	SNP (rs #)	SNP Location (Base Pair)	Genotype	First Study Count (Percent)	Second Study Count (Percent)
MTHFR	1801133	6393745	CC	36 (42)	18 (39)
			CT	39 (46)	21 (46)
			TT	10 (12)	7 (15)
IRF1	9282763	34237146	AA	39 (46)	17 (37)
			AG	43 (51)	24 (52)
			GG	3 (4)	5 (11)
	839	34234139	GG	39 (46)	17 (37)
			AA	43 (51)	24 (52)
			AG	3 (4)	5 (11)
IL4	2070874	34424723	CC	52 (62)	34 (74)
			CT	28 (33)	12 (26)
			TT	4 (5)	0 (0)
	2243268	34428976	AA	52 (62)	34 (74)
			AC	27 (32)	12 (26)
			CC	5 (6)	0 (0)
	2243290	34433182	CC	53 (62)	34 (74)
			AA	26 (31)	12 (26)
			AC	6 (7)	0 (0)

Table 4

Haplotypes inferred for AE-associated SNPs in *IRF1* (rs839 and rs9282763) and *IL4* (rs2070874, rs2243268, rs2243290).

Gene	SNP (rs#)	Baseline Haplotype[a]	Risk Haplotype[b]	First Study		Second Study	
				Odds Ratio[c]	p-value (X^2) [d]	Odds Ratio[c]	p-value (X^2) [d]
IRF1	9282763	A	G	3.2 (1.0–10.2)	0.03	3.0 (1.0–9.0)	0.03
	839	G	A				
IL4	2070874	C	T	2.4 (1.0–5.7)	0.05	3.8 (1.0–14.4)	0.06
	2243268	A	C				
	2243290	C	A				

[a] Most common haplotype considering 2 SNPs in *IRF1* or 3 SNPs in *IL4*

[b] Rare (variant) haplotype considering 2 SNPs in *IRF1* or 3 SNPs in *IL4*

[c] Estimated odds ratio comparing risk haplotype to baseline haplotype (95% confidence interval)

[d] Likelihood ratio chi-square (X^2) test with one degree of freedom

HYPERSENSITIVITY TO VACCINATION

The purpose of a vaccine is to induce immunity by means of the reaction of the immune system and for that reason its administration can give rise to certain undesired effects.

It should be remembered that all drugs, including vaccines, are not exempt to cause mild, moderate or serious adverse reactions during their administration. There are certain factors intrinsic to the product, genetic, immune and environmental factors that can interact with each other and, therefore, interfere in the individual response of each person with its administration.

Vaccines, unlike other medicines, are administered to healthy people with a preventive purpose and therefore it is necessary an optimum safety profile of the drug. In addition, it is important to know the precautions and contraindications of each vaccine in order to avoid risks in the vaccinated population.

Most of the adverse effects produced by vaccination are mild and transient, linked to local reactions that are limited to transient pain, swelling and/or redness in the area of administration.

The adverse reactions that can appear after the vaccination, are classified according to the WHO, in the following groups.

-Reactions induced by vaccination:

Local and systemic (fever, irritability, malaise, systemic symptoms, headache, arthralgia). These adverse reactions can be subdivided into common reactions that are usually mild, and rare that can be more serious (seizures, type I hypersensitivity reactions and II, neurological reactions, thrombocytopenia).

-Reactions due to defects in the quality of the vaccine:

Due to the intrinsic characteristics of the vaccine, the maintenance in optimal conditions of the preservatives, antibiotics and other substances that allow its stabilization.

-Reactions due to program errors (storage, transport, handling or administration)

-Reactions due to anxiety for the same act of vaccination:

Vasovagal syncope is described as a secondary reaction at the time or after the application, due to a feeling of fear to the application of an injectable.

In order to cope with this situation, there is an important educational, preventive and surveillance function. In addition, the knowledge of the intrinsic characteristics of the person, together with the genetic susceptibility of the same, can help in the resolution of these reactions, with their identification and anticipation, contributing the opportune measures in each moment.

Identifying the genetic factors associated with the adverse effects, would allow a screening and knowledge prior to the administration of vaccines, which could stratify and foresee the individual susceptible effects in order to optimize and resolve them.

GENE OR REGION STUDIED

- MTHFR
- IL1A
- IL1R1

OPEN ACCESS Freely available online

PLoS one

Adverse Events following 12 and 18 Month Vaccinations: a Population-Based, Self-Controlled Case Series Analysis

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Abstract

Background: Live vaccines have distinct safety profiles, potentially causing systemic reactions one to 2 weeks after administration. In the province of Ontario, Canada, live MMR vaccine is currently recommended at age 12 months and 18 months.

Methods: Using the self-controlled case series design we examined 271,495 12 month vaccinations and 184,312 18 month vaccinations to examine the relative incidence of the composite endpoint of emergency room visits or hospital admissions in consecutive one day intervals following vaccination. These were compared to a control period 20 to 28 days later. In a post-hoc analysis we examined the reasons for emergency room visits and the average acuity score at presentation for children during the at-risk period following the 12 month vaccine.

Results: Four to 12 days post 12 month vaccination, children had a 1.33 (1.29–1.38) increased relative incidence of the combined endpoint compared to the control period, or at least one event during the risk interval for every 168 children vaccinated. Ten to 12 days post 18 month vaccination, the relative incidence was 1.25 (95%, 1.17–1.33) which represented at least one excess event for every 730 children vaccinated. The primary reason for increased events was statistically significant elevations in emergency room visits following all vaccinations. There were non-significant increases in hospital admissions. There were an additional 20 febrile seizures for every 100,000 vaccinated at 12 months.

Conclusions: There are significantly elevated risks of primarily emergency room visits approximately one to two weeks following 12 and 18 month vaccination. Future studies should examine whether these events could be predicted or prevented.

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Introduction

The measles, mumps and rubella (MMR) have been used extensively in children and have been demonstrated to be safe and effective in preventing disease [1]. However, because it is a live vaccine the MMR vaccine has the potential to cause adverse events one to 2 weeks following vaccination [2]. Most reactions to this vaccine will be mild with fevers occurring in 5 to 15% and rashes in 5% [3]. More serious reactions are extremely rare and may not be identified during pre-licensure trials [4]. Post market surveillance has identified an incidence of febrile seizures following the MMR vaccine of 25 to 34 per 100 000 vaccinated and a two to three-fold increased relative risk [5,6]. However, at a population level, mass exposures to a vaccine with a rare side effect profile could have detectable important population level effects. No study has examined the impact on aggregate health service utilization following the MMR vaccination.

In the province of Ontario, Canada, the MMR and meningococcal C vaccines are currently recommended at 12 months of age and a second dose of MMR vaccine along with a booster dose of pentavalent (diphtheria, acellular pertussis, tetanus, polio and *Haemophilus influenzae* type b) vaccine is recommended at 18 months of age. We sought to examine the population wide effects of these

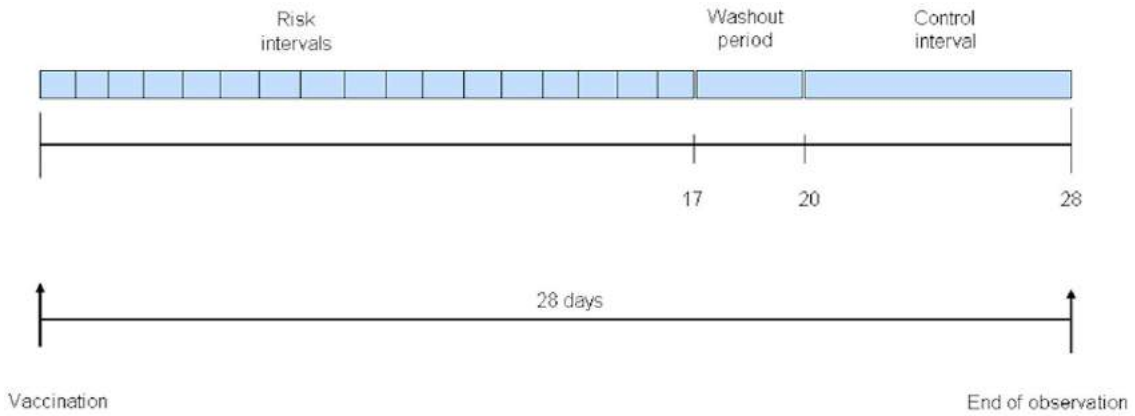

Figure 1. Illustration of the self-controlled case series design. The observation period for each patient begins with pediatric vaccination date (leftmost upward arrow) and continues for a total of 28 days. In the primary analyses, each day post vaccination is considered a *risk interval*, and consecutive days with a statistically significant t elevation in relative incidence were pooled to create a combined risk interval. Days 20–28 comprise the *control interval*. The intervening days represent the wash-out period.
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vaccinations on the combined endpoint of emergency room visits and hospital admissions in selected periods post-vaccination.

Methods

Design

The overall goal of this study was to determine the risk of serious adverse events in all children vaccinated in Ontario at 12 and 18 months of age with recommended pediatric vaccines. This was measured by comparing the risk of either presentation to emergency room (ER), or hospital admission in consecutive one day periods after the date of vaccination compared to a later control period. This analysis was conducted on all children born between April 1st 2006 and March 31st 2009. Our primary analysis of the composite risk of ER visits and hospitalizations was conducted using the *self-controlled case-series design*, described by

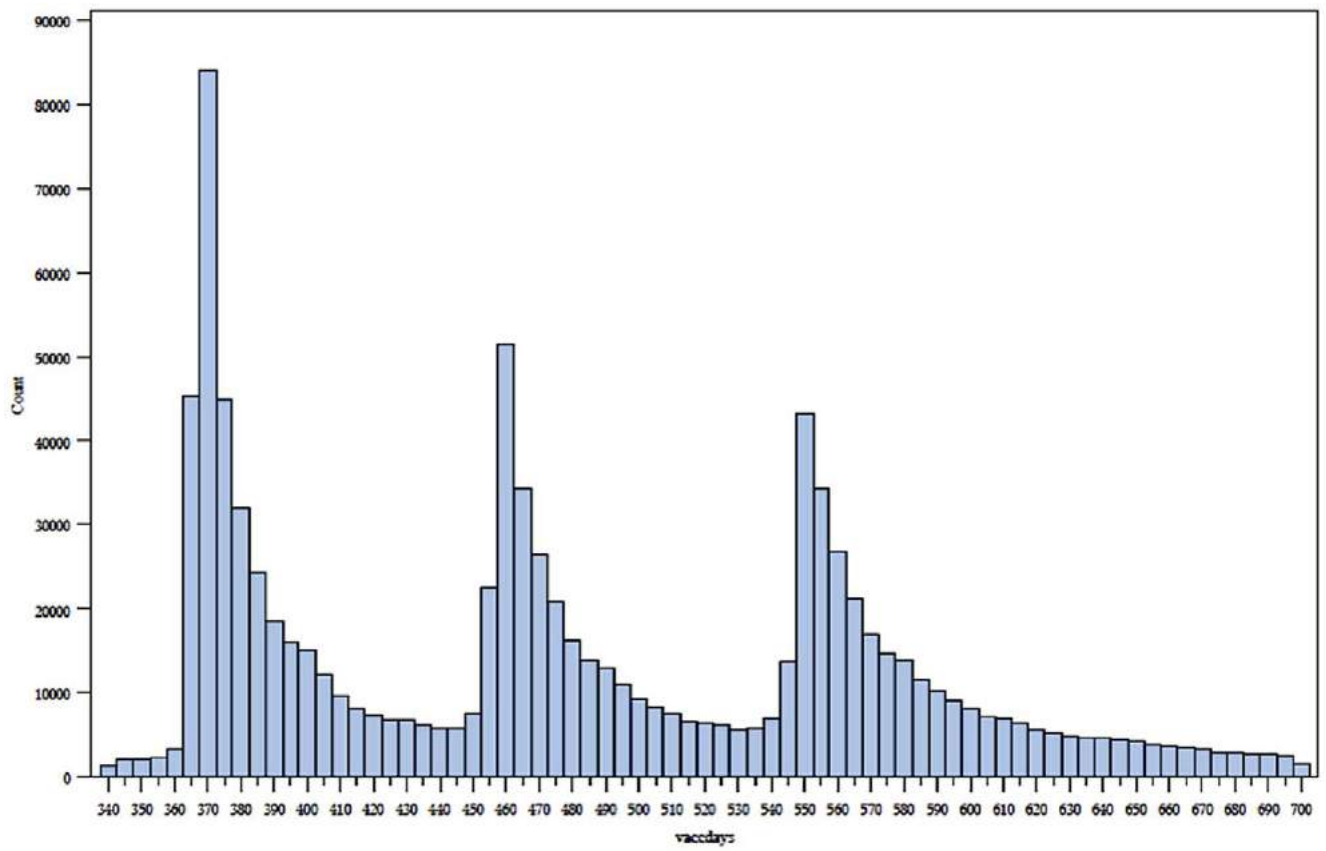

Figure 2. Vaccination events by days since birth from days 340 to 700. Count = number of individuals vaccinated on a given day. **Days** = number of days after date of birth.
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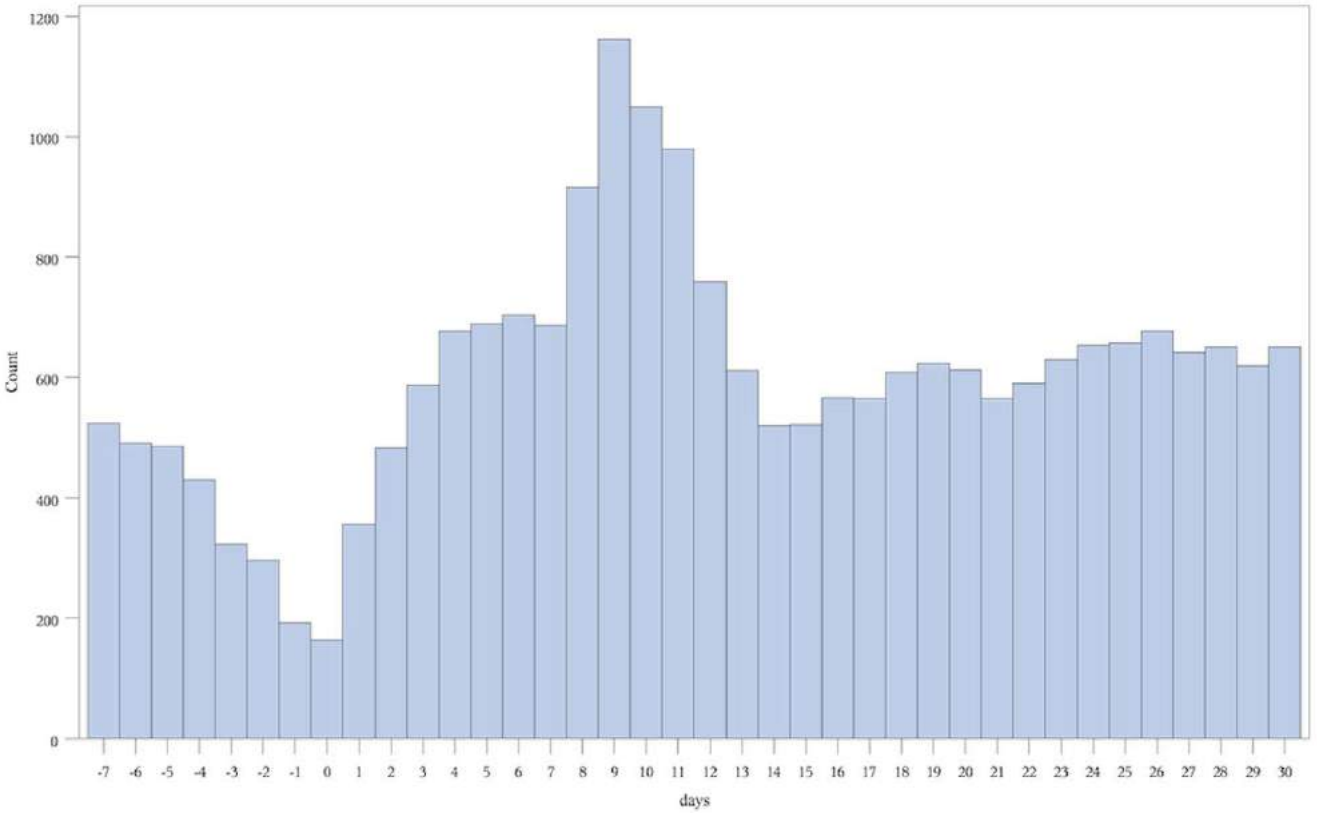

Figure 3. Number of combined endpoints versus days before/after 12 month vaccination. Count = number of combined endpoints of emergency room visit or hospitalization. **Days** = number of days before or after vaccination, day 0 being the day of vaccination.
doi:10.1371/journal.pone.0027897.g003

Farrington and associates [7,8]. We analyzed events following the 12 and 18 month vaccinations separately.

Data

Our study cohort included all children in the Newborn Screening Ontario data set between April 1st 2006 and March 31st 2009. This database captures over 99% of Ontario births. Our exposure of interest, pediatric vaccination, was identified using the Ontario Health Insurance Plan (OHIP) database. We used codes for general vaccination, as, except for influenza, vaccine-specific codes are not available. To identify the 12 and 18 month vaccinations separately we identified vaccination occurring on exactly the respective due dates as well as vaccinations occurring up to 60 days after the respective date. To allow adequate follow-up after the 12 month vaccination, only vaccinated children born on or before December 31st 2008 could be included in the analysis (N = 271,495 children). Likewise, only vaccinated children born on or before June 30th 2008 could be included in the analysis of adverse events after the 18 month vaccination (N = 184,312 children). Only subjects with both vaccinations and events in the observation period contribute to the conditional self-controlled case series analysis, therefore infants with no ER visits or hospitalizations in close proximity to the vaccination were not included. If infants had more than one vaccination in the database during the two month target period the first vaccination was used as the index vaccination. If another vaccination occurred within the observation period (0 to 28 days after the index vaccination), or the infant died, then this individual was excluded from analysis (see Appendix S1).

The Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD) captures all hospital admissions, including children in both tertiary and community hospitals, and was used to ascertain hospital admission. CIHI's National Ambulatory Care Registration System (NACRS) was used to ascertain ER visits, the Canadian Triage and Acuity Score (CTAS) rating and the diagnosis made by the most responsible physician for the visit. The Registered Persons Database was used to ascertain cases of death. These datasets are housed at the Institute for Clinical Evaluative Sciences (ICES), and linkage between datasets was achieved using encrypted health card numbers as unique identifiers. The study was performed within ICES' status as a Prescribed Entity in Ontario's privacy legislation and Research Ethics Board approval was received at OHRI and ICES (Sunnybrook).

Analysis

We graphed the number of combined endpoint events in the days before and after vaccination. In the self-controlled case series model, the date of vaccination serves as the index date for exposure for each patient. Previous studies have identified that children are at increased risk for systemic reactions at different times from 5–14 days after vaccination [5,6,9,10]. Because *a priori* we did not know with certainty the time period following vaccination for which there would be an increased risk of our combined endpoint, we modified the standard self-controlled case series approach by looking for an elevation in risk during each post-vaccination day up to day 17 (Figure 1). We then classified days 20–28 as unexposed, establishing a washout period in

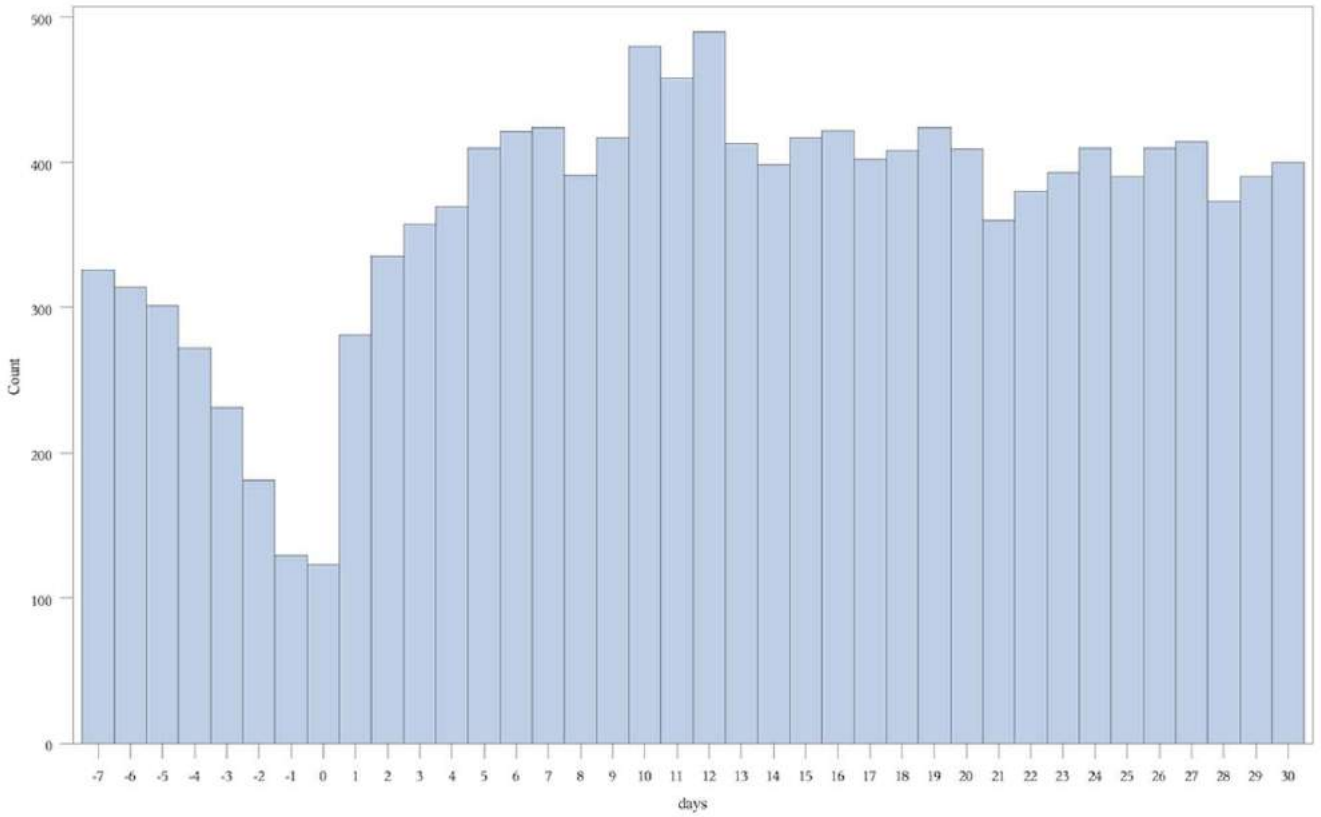

Figure 4. Number of combined endpoints versus days before/after 18 month vaccination. Count = number of combined endpoints of emergency room visit or hospitalization. **Days** = number of days before or after vaccination, day 0 being the day of vaccination.
doi:10.1371/journal.pone.0027897.g004

between the exposed and unexposed periods (Figure 1). When multiple events occurred to a given individual, the first occurrence of the composite outcome in the post-vaccination period was used (eg., someone attending the ER who was then admitted would have one event counted in that period). The relative incidence rate of the composite endpoint during the exposed period compared with the unexposed period was analyzed using a fixed effects Poisson regression model. This model included a term for exposure period and a term for patient, thereby allowing each individual to serve as his or her own control and accounting for intra-individual correlation. An offset term was also included to account for the differing durations of the exposed and unexposed periods. Deaths after the 12 and 18 month vaccinations were explored in a separate analysis due to the fact that a subject dying effectively truncates their follow-up potentially biasing the results of the SCCS analysis. As noted above, children who died during the follow-up period were excluded from the SCCS analysis of ER visits and hospitalizations.

To define the at-risk period we combined consecutive days with statistically significant elevations in relative incidence. We considered statistical significance to be a p-value less than or equal to 0.001 based on a Bonferroni correction to account for multiple testing (38 separate tests) [11]. We conducted separate analyses for the 12 and 18 month vaccinations. We also conducted secondary analyses to determine the association between vaccination and ER visits, hospital admissions, and deaths separately. All p values were 2 sided, and analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

In order to assess the types of cases captured by our endpoints we conducted a post-hoc analysis where we compiled the reasons for presentation to the ER as determined by the most responsible physician for the risk period for the 12 month vaccination. This was compared to the prevalence of the same diagnoses in the control period. We examined a tracer condition, ear/face nose injury, for which we do not expect a difference in rates. We also identified the CTAS ratings for presentations during the affected period and compared them to those during the control period using the Wilcoxon Rank-Sum test. CTAS ratings range from 1 to 5 with 1 representing a severe condition requiring resuscitation and 5 representing a less severe condition requiring non-urgent care [12]. In another post-hoc analysis we graphically examined the pattern of events following 12 and 18 month vaccination in the years 2002–2005 when the MMR vaccine was still given at 12 months, however, the booster was given at five years and not eighteen months.

Results

In total, we examined 455,807 separate vaccination events in these 413,957 children that occurred at 12 and 18 months plus 60 days (Figure 2). We present the number of endpoint events versus days pre and post vaccination graphically for each of the vaccine periods (Figures 3 and 4).

12 month analysis

271,495 children received vaccinations between 365 and 425 days of age. Consecutive statistically significant elevations in combined endpoints began on day 4 and continued to day 12. A

Table 1. Relative incidence of combined endpoint (hospital admission or emergency room visit) following 12 month vaccination.

Risk interval*	Endpoints during risk interval (n)	Relative Incidence (95% CI)	P value
Day 4	621	1.15 (1.06–1.25)	0.0008
Day 5	641	1.19 (1.10–1.29)	<0.0001
Day 6	647	1.20 (1.11–1.31)	<0.0001
Day 7	644	1.20 (1.10–1.30)	<0.0001
Day 8	870	1.62 (1.50–1.74)	<0.0001
Day 9	1096	2.04 (1.91–2.17)	<0.0001
Day 10	991	1.84 (1.72–1.97)	<0.0001
Day 11	923	1.72 (1.60–1.84))	<0.0001
Day 12	713	1.32 (1.22–1.43)	<0.0001
Days 4 to 12** (Combined risk interval)	6462	1.33(1.29–1.38)	<0.0001
Days 20–28 (Control Interval)	4845	NA	NA

*Risk and control intervals expressed as days following vaccination.
**Total number of endpoints in the combined risk interval are less than the cumulative individual day event total because some children may have experienced events in multiple days and only the first event is counted.
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total of 6462 children experienced at least one of the combined endpoints during the combined 9 day at risk period compared to 4845 during the 9 day control period. The relative incidence of the combined endpoint was 1.33 (1.29–1.38) (Table 1). The highest relative incidence during the at-risk period occurred between days 8 and 11 peaking at 2.04 (1.91–2.17) on day 9. Overall, an excess of 595 children experienced at least one of the combined endpoints during the risk interval per 100,000 vaccinated, or one additional child experiencing at least one endpoint during the risk interval for every 168 children who received their 12 month vaccinations (Table 2). Examining the historical graph of the events post 12 month vaccination in the years 2002–2005 demonstrated a similar peak in events (Figure 5).

The primary reason for the elevation in the combined endpoint was an increase in ER visits (relative incidence 1.34(1.29–1.39)). There were an excess of 598 children experiencing 1 or more ER visits during the risk interval per 100,000 vaccinations or 1 additional child for every 168 children vaccinated. There was no increase in hospital admissions (relative incidence 1.08 (0.93–1.25)). There were five or fewer deaths (Table 3). The average CTAS score for ER visits during the risk period was 3.27 compared to 3.26 for the control period. ($p = 0.74$), suggesting no differences in severity of presentation between ER visits in the risk and control periods. There was an increase in presentation for multiple conditions during the risk period compared to the control period. The largest relative risk was associated with febrile seizures (relative incidence = 2.34, fever (RI = 2.31) and viral exanthem (RI = 2.23). We calculated that there were approximately 20 additional febrile seizures during the risk interval for every 100 000 children vaccinated. There was no increase in our tracer condition (ear/face/nose injury).

18 month analysis

184,312 children received vaccinations between 545 and 605 days of age. Consecutive statistically significant elevations in combined endpoints began on day 10 and continued to day 12. A total of 1275 children experienced at least one event included in the combined endpoint during the combined three day at risk period compared to 3065 during the nine day control period. The relative incidence of the combined endpoint was 1.25 (1.17–1.33) (Table 4). The highest relative incidence during the at-risk period was 1.34 (1.21–1.47) which occurred on day 12. Overall, an additional 137 children experienced at least one combined endpoint during the three day risk period per 100,000 vaccinated, or one additional child experiencing at least one excess event for every 730 children vaccinated (Table 3). Examining the historical graph of the events post 18 month vaccination in the years 2002–2005, when the booster dose of the MMR vaccine was not given, demonstrated no similar peak in events (Figure 5).

The primary reason for the elevation in the combined endpoint was an increase in ER visits (relative incidence 1.25(1.18–1.34)). There were an excess of 139 children experiencing one or more ER visits during the risk interval or one excess visit for every 719 children vaccinated. There was not a significant increase in hospital admissions (relative incidence 1.23(0.94–1.59)) (Table 4). No deaths occurred in the risk or control periods.

Discussion

Our analysis demonstrated that the 12 and 18 month vaccinations are not associated with an increase in adverse events immediately following vaccination. Instead it showed a reduced risk in this period, which is likely a result of the previously

Table 2. Increased risk of combined endpoints from vaccination.

Vaccination	Additional children experiencing at least one event (per 100,000 vaccinations)	Number vaccinated	Number vaccinated per excess event
12 months	595	271,495	168
18 months	137	184,312	730

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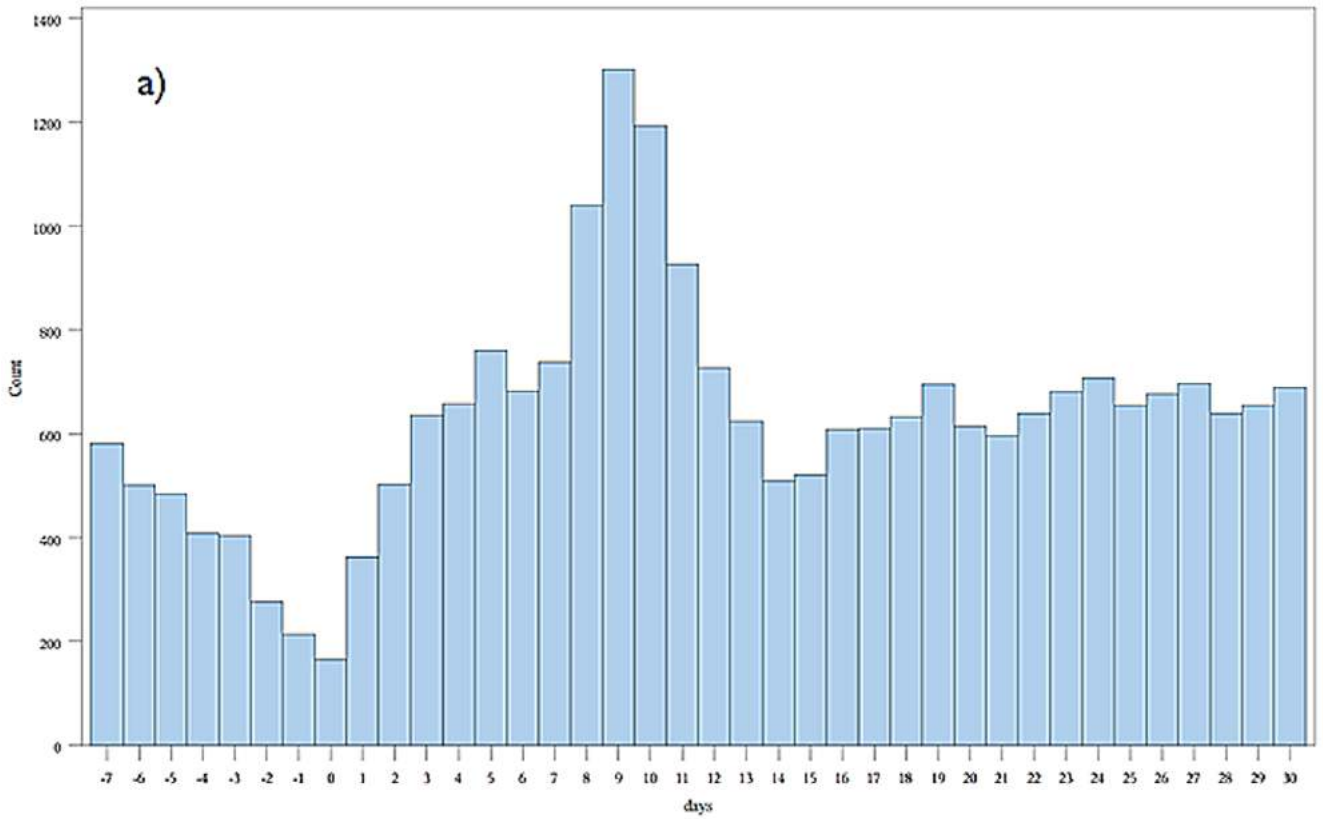
a)
Count
days

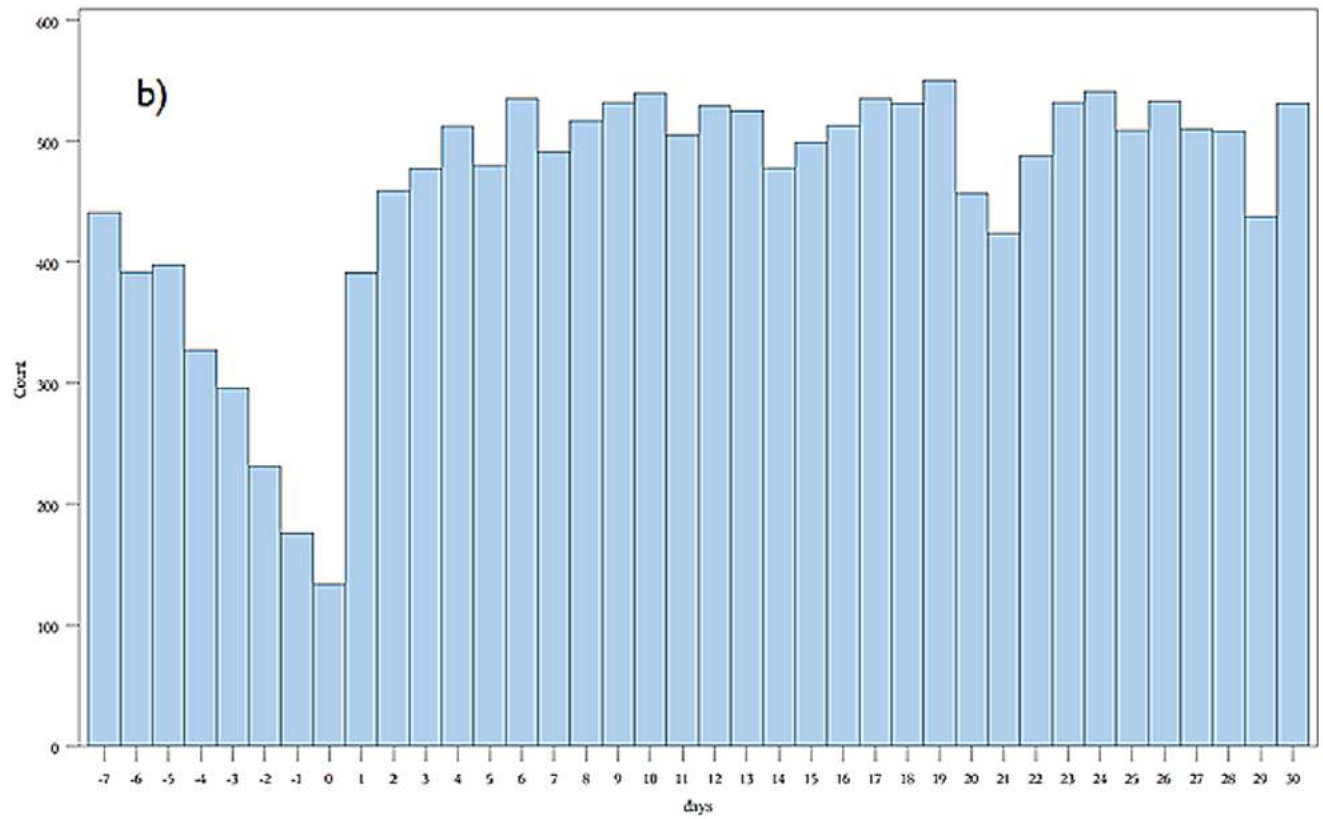
b)
Count
days

Figure 5. Historical analysis of combined endpoints versus days following 12 and 18 month vaccination: April 2002–March 2005. a) Before/after 12 month vaccination. b) Before/after 18 month vaccination. **Count** = number of combined endpoints of emergency room visit or hospitalization. **Days** = number of days before or after vaccination, day 0 being the day of vaccination.
doi:10.1371/journal.pone.0027897.g005

documented healthy vaccinee effect [9,13,14]. We identified an increase in events occurring between 4 and 12 days post-vaccination for the 12 month and, to a lesser extent and for a shorter time period for the 18 month vaccines. The majority of these events represented ER visits and at their peak, on day 9 following the 12 month vaccine, were approximately twice the baseline rate. Although there was an increase in hospital admission in each period, none of these increases were statistically significant. Overall the increase in event rate following the 12 month vaccines accounted for approximately 598 extra children experiencing one or more ER visits during the risk interval per 100,000 vaccinations. The average acuity of patients presenting to the emergency room was similar to that in the control period. The conditions for which there were the largest increase in risk for presentation to the emergency room during the risk interval compared to the control interval following the 12 month vaccine were febrile convulsions, fever and viral exanthema, consistent with the known adverse event profile of MMR and varicella vaccines. There were 20 additional febrile seizures for every 100,000 children vaccinated at 12 months.

The development of an inflammatory response approximately one week after vaccination is recognized in the literature. For example, the Centres for Disease Control and Prevention list days 7 to 12 post vaccination as the highest risk period for developing fever and possibly a rash [15]. This closely coincides with our observation of the time period during which emergency room visits peaked. A previous twin study also identified the development of systemic symptoms between days 6 and 14 and peaking on day 10 [9]. A study of febrile seizures following MMR vaccination identified the highest at risk period to be 8 to 14 days following vaccination and a relative risk of 2.83 and other studies have made similar observations [5,6,16]. These are consistent with our findings. While it is known that vaccines can produce these adverse events, our study demonstrated the population wide impact of this effect and that these events are resulting in an increase in health services utilization. The estimated 595 additional children experiencing at least one event for every 100 000 vaccinated translates into approximately one child experiencing at least one event per 168 children vaccinated. The explanation for this effect is likely the controlled replication of the virus creating a mild form of the illness the vaccine is designed to prevent. The top diagnoses for the presentations to the emergency room during the 12 month risk interval would all be consistent with a mild viral illness.

The reduced effect at 18 months is likely due to this vaccination in most instances being a second exposure to the antigen to which the vast majority of children would have developed adequate immunity. Residual events during this period may represent the small percentage of children who did not immunologically respond to the first dose of the vaccine.

Our study has several strengths. The use of the self-controlled case series design allows for individuals to serve as their own controls implicitly controlling for all fixed covariates [8,17]. Seasonal confounding is unlikely to have influenced our findings since the 12 and 18th month vaccines are provided throughout the year. The potential for confounding due to co-existent exposures at 12 and 18 months exists, however, if such an exposure were to be significant we would have expected to observe an effect at 18 months in our historical analysis. Our study included nearly all children born in Ontario during the study period which strengthens the generalizability of these findings. The combination of the self-controlled case series design and our sample size increased the power of our study to identify small effects. While our study cannot establish causality it has many features that support a causal relationship between vaccination and delayed adverse events. These include the consistency with other studies and a compelling biological model which explains the diagnoses in the affected children and the reduction in effect with the 18 month vaccinations. Furthermore, our historical analysis demonstrates that the effect seen at 18 months after MMR vaccination in 2006–2009 is not present in 2002–2005, when the MMR vaccine was given only at 12 months and not at 18 months. The effect is still clearly visible after the 12 month vaccination in the 2002–2005 data.

There are important limitations of this study. The first is that, as mentioned, the healthy vaccinee effect may have masked an association in the immediate post-vaccination period. Second, we cannot know whether a specific vaccine was associated with the adverse events as multiple vaccines are typically administered at each visit. However, we have previously demonstrated the safety of the pentavalent vaccine which is given with the 18 month MMR vaccine [18]. It is possible that the effects seen at 12 month are in part due to the potential co-administration of the meningococcal C vaccine, however, this is not a live vaccine and should create inflammation in the immediate post-vaccination period as opposed to one week later. Third, the codes we used for identifying the reasons for presentation to the emergency room have not been validated. However, we would expect that the diagnoses of febrile convulsion to have a low misclassification error and has previously been validated as a useful ER code in a separate dataset [19]. We also did not look for increases in visits to physician offices that did not result in presentation to the emergency room or admission and cannot comment on the impact of immunization on that outcome.

Table 3. Relative incidences of individual endpoints (emergency room visit, hospital admission, death) during highest risk interval compared to control period.

Outcome	12 months	Events (risk/control)	18 months	Events (risk/control)
Emergency visits	1.34 (1.29–1.39)	6395/4772	1.25 (1.18–1.34)	1264/3024
Admissions	1.08 (0.93–1.25)	356/330	1.23 (0.94–1.59)	78/191
Deaths	-	< = 5/< = 5	-	0/0

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Table 4. Relative incidence of combined endpoint (hospital admission or emergency room visit) following 18 month vaccination.

Risk interval*	Endpoints during risk interval (n)	Relative Incidence (95% CI)	P value
Days 10	447	1.31 (1.19–1.45)	<0.0001
Days 11	428	1.26 (1.14–1.39)	<0.0001
Days 12	455	1.34 (1.21–1.47)	<0.0001
Days 10 to 12 (Combined risk interval)	1275	1.25 (1.17,1.33)	<0.0001
Days 20 to 28 (Control Interval)	3065	NA	NA

*Risk and control intervals expressed as days following vaccination.
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Our findings have important implications for those providing care to children. The immediate risk of a serious adverse event following immunization is low with both the vaccination visits that contain the MMR and varicella vaccines. However, the 12 month vaccines which typically contain the first dose of the MMR vaccine is associated with an increased risk of an emergency room visit approximately 4 to 12 days after immunization, peaking between days 8 and 11. This increase in rate of a child experiencing at least one event for every 158 vaccinated individuals is associated with a similar acuity as the control period. If the presentation to the emergency room was due to parental anxiety we would have expected to see a reduction in acuity during the risk period. The findings also suggest that the reactions are not severe since acuity was not higher than the control period and furthermore, there were few hospital admissions. Additional reassurance can be derived from previous studies that identified no long-term consequences related to vaccine associated febrile seizures [5,6]. The increase in ER visits we observed could be a result of insufficient information being provided to parents who may not expect their child to develop a reaction a week after vaccination. In particular, the likelihood of this risk may be underestimated by physicians. Our study also reinforces the reduced risk of events following the second dose of MMR vaccine.

Given the effectiveness of the MMR vaccine in eliminating both measles and rubella, and the highly infectious nature of these diseases, high vaccination coverage is essential. The diseases that the vaccines are preventing are not benign and vaccination can eliminate many of the serious sequelae of these infections [20]. Complications from measles include otitis media (7–9% of cases), pneumonia (1–6% of cases), encephalitis (1 per 1,000–2,000 cases), subacute sclerosing panecephalitis (1 per 100,000 cases), and death (1 per 3000 cases) [3,21]. Further studies attempting to predict which children develop post-vaccination reactions, as well as determining the effectiveness of prophylactic treatment with antipyrectics prior to the high risk period for symptom development are warranted.

Supporting Information

Appendix S1 Figure A1: Flowchart Describing SCCS Study Cohort.
(TIF)

Author Contributions

Conceived and designed the experiments: KW SH DM JK SD NC. Performed the experiments: SH. Analyzed the data: KW SH CV DM JK. Wrote the paper: KW SH JK MP SD NC BP PC.

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Increased Risk of Noninfluenza Respiratory Virus Infections Associated With Receipt of Inactivated Influenza Vaccine

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We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had an increased risk of virologically-confirmed non-influenza infections (relative risk: 4.40; 95% confidence interval: 1.31-14.8). Being protected against influenza, TIV recipients may lack temporary non-specific immunity that protected against other respiratory viruses.

Influenza vaccination is effective in preventing influenza virus infection and associated morbidity among school-aged children [1, 2]. The potential for temporary nonspecific immunity between respiratory viruses after an infection and consequent interference at the population level between epidemics of these viruses has been hypothesized, with limited empirical evidence to date, mainly from ecological studies [3–15]. We investigated the incidence of acute upper respiratory tract infections (URTIs) associated with virologically confirmed respiratory virus infections in a randomized controlled trial of influenza vaccination.

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METHODS

Recruitment and Follow-up of Participants

In a double-blind randomized controlled trial, we randomly allocated children aged 6–15 years to receive 2008–2009 seasonal trivalent influenza inactivated vaccine (TIV; 0.5 mL Vaxigrip; Sanofi Pasteur) or placebo [16]. Serum specimens were obtained from participants before vaccination from November through December 2008, a month after vaccination, in midstudy around April 2009, and at the end of the study from August through October 2009. Participants were followed up for illnesses through symptom diaries and telephone calls, and illness reports in any household member triggered home visits during which nasal and throat swab specimens (NTSs) were collected from all household members. We defined the follow-up period for each participant from 14 days after receipt of TIV or placebo to collection of midstudy serum samples as the winter season and from collection of midstudy samples through final serum sample obtainment as the summer season.

Proxy written informed consent was obtained for all participants from their parents or legal guardians, with additional written assent from those ≥8 years of age. The study protocol was approved by the Institutional Review Board of Hong Kong University.

Laboratory Methods

NTSs were tested for 19 respiratory viruses by the ResPlex II Plus multiplex array [17–19] and for influenza A and B by reverse-transcription polymerase chain reaction (RT-PCR) [16, 20] (Supplementary Appendix). We refer to infections determined by these assays as "confirmed" infections. Information on influenza serology is provided in the Supplementary Appendix .

Statistical Analysis

We defined an acute respiratory illness (ARI) determined by self-reported signs and symptoms as ≥2 of the following signs or symptoms: body temperature ≥37.8°C, headache, sore throat, cough, presence of phlegm, coryza, and myalgia [16]. We defined febrile acute respiratory illness (FARI) as body temperature ≥37.8°C plus cough or sore throat. Because duration of follow-up varied by participant, we estimated the incidence rates of ARI and FARI episodes and confirmed viral infections overall and during the winter and summer seasons and estimated the relative risk of these episodes for participants who received TIV versus placebo with use of the incidence rate ratio using Poisson regression (Supplementary

Table 1. Characteristics of Participants and Duration of Follow-up

Characteristic	TIV (n = 69)	Placebo (n = 46)
Age group, No. (%)		
6–8 years	19 (28)	16 (35)
9–11 years	41 (59)	27 (59)
12–15 years	9 (13)	3 (7)
Female sex, No. (%)	30 (43)	23 (50)
Median duration of follow-up, days	272	272
Mean no. of individuals per household	3.7	3.6

Abbreviation: TIV, trivalent inactivated influenza vaccine.

Appendix). All statistical analyses were conducted using R, version 2.11.0 (R Development Core Team, Vienna, Austria). Data and syntax to reproduce these statistical analyses are available on the corresponding author's Web site.

RESULTS

Among the 115 participants who were followed up, the median duration of follow-up was 272 days (interquartile range, 264–285 days), with no statistically significant differences in age, sex, household size, or duration of follow-up between TIV and placebo recipients (Table 1). We identified 134 ARI episodes, of which 49 met the more stringent FARI case definition. Illnesses occurred throughout the study period (Supplementary Appendix Figure 1). There was no statistically significant difference in the risk of ARI or FARI between participants who received TIV and those who received placebo, either during winter or summer 2009 (Table 2).

We were able to collect 73 NTSs for testing from participants for 65 of 134 (49%) ARI episodes, which included 22 of 49 (45%) FARI episodes. The mean delay between ARI onset and collection of first NTS was 1.22 days, and 5% of NTSs were collected >3 days after illness onset, with no statistically significant differences between TIV and placebo recipients. We detected respiratory viruses in 32 of 65 NTSs (49%) collected during ARI episodes, which included 12 of 22 (55%) FARI episodes. We collected 85 NTSs from participants at times when one of their household contacts reported an acute URTI but the participants were not ill, and identified viruses in 3 of the specimens (4%), including influenza A (H3N2), coxsackie/echovirus, and coronavirus 229E.

There was no statistically significant difference in the risk of confirmed seasonal influenza infection between recipients of TIV or placebo, although the point estimate was consistent with protection in TIV recipients (relative risk [RR], 0.66; 95% confidence interval [CI], .13–3.27). TIV recipients had significantly lower risk of seasonal influenza infection based on serologic evidence (Supplementary Appendix). However, participants who received TIV had higher risk of ARI associated with confirmed noninfluenza respiratory virus infection (RR, 4.40; 95% CI, 1.31–14.8). Including 2 additional confirmed infections when participants did not report ARI, TIV recipients had higher risk of confirmed noninfluenza respiratory virus infection (RR, 3.46; 95% CI, 1.19–10.1). The majority of the noninfluenza respiratory virus detections were rhinoviruses and coxsackie/echoviruses, and the increased risk among TIV recipients was also statistically significant for these viruses (Table 3). Most respiratory virus detections occurred in March 2009, shortly after a period of peak seasonal influenza activity in February 2009 (Figure 1).

Table 2. Incidence Rates of Acute Upper Respiratory Tract Infection Among 115 Participants Aged 6–15 Years Who Received Trivalent Inactivated Influenza Vaccine or Placebo

	TIV (n = 69)		Placebo (n = 46)			
Variable	Rate[a]	(95% CI)	Rate[a]	(95% CI)	Relative Risk (95% CI)	*P* Value
Winter 2009						
ARI[b] episodes	2080	(1530–2830)	2260	(1550–3300)	0.92 (.57–1.50)	.74
FARI[b] episodes	609	(346–1070)	753	(392–1450)	0.81 (.34–1.92)	.63
Summer 2009						
ARI[b] episodes	1510	(1130–2020)	1160	(757–1780)	1.30 (.78–2.18)	.31
FARI[b] episodes	658	(424–1020)	442	(221–884)	1.49 (.65–3.38)	.33

Abbreviations: ARI, acute respiratory illness; CI, confidence interval; FARI , febrile acute respiratory illness; TIV, trivalent inactivated influenza vaccine.

[a] Incidence rates were estimated as the number of ARI or FARI episodes per 1000 person-years of follow-up.

[b] ARI was defined as at least 2 of the following symptoms: body temperature ≥37.8°C, cough, sore throat, headache, runny nose, phlegm, and myalgia; FARI was defined as body temperature ≥37.8°C plus cough or sore throat.

Table 3. Incidence Rates of Respiratory Virus Detection by Reverse-Transcription Polymerase Chain Reaction and Multiplex Assay

	TIV (n = 69)			Placebo (n = 46)			
Variable	No.	Rate[a]	(95% CI)	No.	Rate[a]	(95% CI)	*P* Value
Any seasonal influenza	3	58	(19–180)	3	88	(28–270)	.61
Seasonal influenza A (H1N1)	2	39	(10–160)	2	59	(15–240)	.68
Seasonal influenza A (H3N2)	1	19	(3–140)	0	0	(0–88)	.31
Seasonal influenza B	0	0	(0–58)	1	29	(4–210)	.17
Pandemic influenza A (H1N1)	3	58	(19–180)	0	0	(0–88)	.08
Any noninfluenza virus[b]	20	390	(250–600)	3	88	(28–270)	<.01
Rhinovirus	12	230	(130–410)	2	59	(15–240)	.04
Coxsackie/echovirus	8	160	(78–310)	0	0	(0–88)	<.01
Other respiratory virus[c]	5	97	(40–230)	1	29	(4–210)	.22
ARI episode with specimen collected but no virus detected	19	369	(235–578)	14	412	(244–696)	.75
ARI episode with no specimen collected	41	796	(586–1080)	28	824	(569–1190)	.89

Incidence rates are from respiratory specimens collected from 115 participants aged 6–15 years who received trivalent influenza vaccine or placebo during 134 acute respiratory illness episodes.

Abbreviations: ARI, acute respiratory illness; CI, confidence interval; TIV, trivalent inactivated influenza vaccine.

[a] Incidence rates were estimated as the no. of virus detections or illness episodes per 1000 person-years of follow-up. ARI was defined as at least 2 of the following symptoms: body temperature ≥37.8°C, cough, sore throat, headache, runny nose, phlegm, and myalgia.

[b] In TIV recipients there were 4 detections with both rhinovirus and coxsackie/echovirus, and 1 detection with both coxsackie/echovirus and coronavirus NL63.

[c] Including positive detections of coronavirus, human metapneumovirus, parainfluenza, respiratory syncytial virus (RSV). The ResPlex II multiplex array tested for 19 virus targets including influenza types A and B (including 2009-H1N1), RSV types A and B, parainfluenza types 1–4, metapneumovirus, rhinovirus, coxsackievirus/echovirus, adenovirus types B and E, bocavirus, and coronavirus types NL63, HKU1, 229E, and OC43.

DISCUSSION

In the prepandemic period of our study, we did not observe a statistically significant reduction in confirmed seasonal influenza virus infections in the TIV recipients (Table 3), although serological evidence (Supplementary Appendix) and point estimates of vaccine efficacy based on confirmed infections were consistent with protection of TIV recipients against the seasonal influenza viruses that circulated from January through March 2009 [16]. We identified a statistically significant increased risk of noninfluenza respiratory virus infection among TIV recipients (Table 3), including significant increases in the risk of rhinovirus and coxsackie/echovirus infection, which were most frequently detected in March 2009, immediately after the peak in seasonal influenza activity in February 2009 (Figure 1).

The increased risk of noninfluenza respiratory virus infection among TIV recipients could be an artefactual finding; for example, measurement bias could have resulted if participants were more likely to report their first ARI episode but less likely to report subsequent episodes, whereas there was no real difference in rhinovirus or other noninfluenza respiratory virus infections after the winter influenza season. The increased risk could also indicate a real effect. Receipt of TIV could increase influenza immunity at the expense of reduced immunity to noninfluenza respiratory viruses, by some unknown biological mechanism. Alternatively, our results could be explained by temporary nonspecific immunity after influenza virus infection, through the cell-mediated response or, more likely, the innate immune response to infection [21–23]. Participants who received TIV would have been protected against influenza in February 2009 but then would not have had heightened nonspecific immunity in the following weeks. They would then face a higher risk of certain other virus infections in March 2009, compared with placebo recipients (Figure 1). The duration of any temporary nonspecific immunity remains uncertain [13] but could be of the order of 2–4 weeks based on these observations. It is less likely that the interference observed here could be explained by reduced community exposures during convalescence (ie, behavioral rather than immunologic factors) [14].

The phenomenon of virus interference has been well known in virology for >60 years [24–27]. Ecological studies have reported phenomena potentially explained by viral interference [3–11]. Nonspecific immunity against noninfluenza respiratory viruses was reported in children for 1–2 weeks after receipt of live attenuated influenza vaccine [28]. Interference in respiratory and gastrointestinal infections has been reported after receipt of live oral poliovirus vaccine [29–32].

Our results are limited by the small sample size and the small number of confirmed infections. Despite this limitation, we were able to observe a statistically significant increased risk

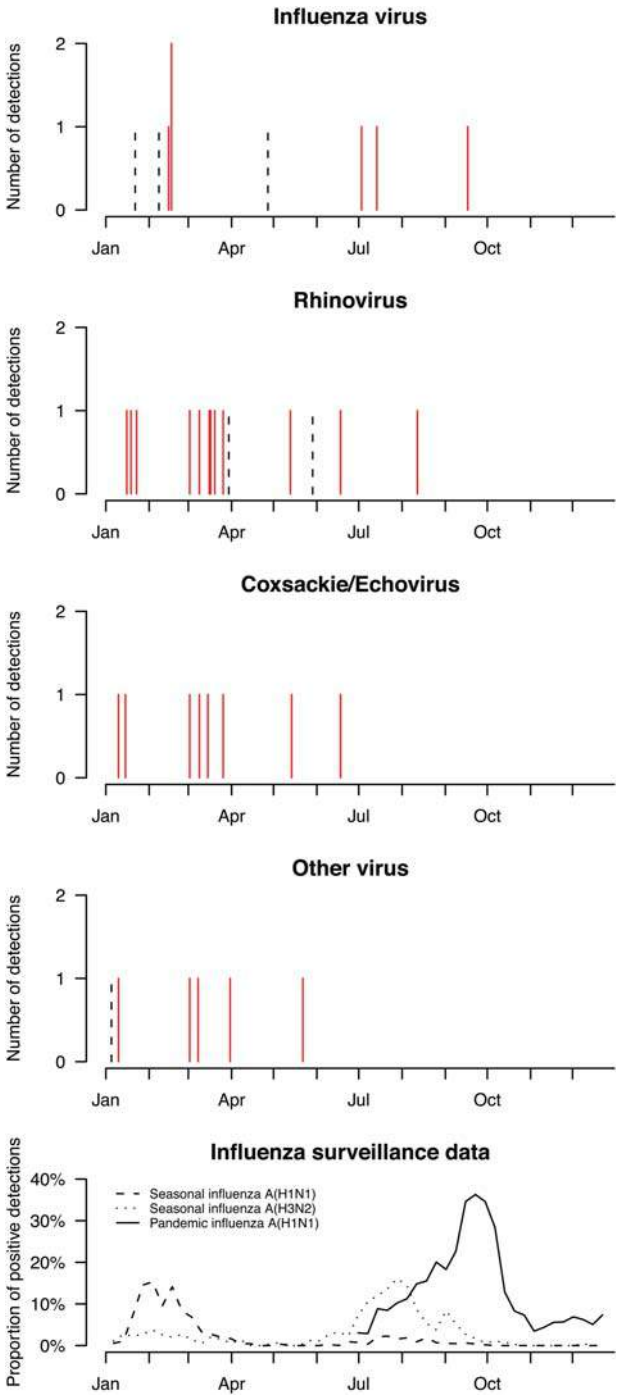

Figure 1. Timing of influenza and other respiratory virus detections in 115 participants aged 6–15 years (*A–D*), compared with local influenza surveillance data (*E*). Solid red bars indicate detections in 69 participants who received 2008–2009 trivalent inactivated influenza vaccine, and black dashed bars indicate detections in 46 participants who received placebo. The bottom panel shows local laboratory surveillance data on the proportion of influenza virus detections among specimens submitted to the Public Health Laboratory Service (PHLS). Less than 2% of PHLS specimens were positive for influenza B throughout the year. "Other viruses" included coronavirus, human metapneumovirus, parainfluenza, and respiratory syncytial virus.

of confirmed noninfluenza respiratory virus infection among TIV recipients (Table 3). A negative association between serologic evidence of influenza infection and confirmed noninfluenza virus infection in winter 2009 was not statistically significant (odds ratio, 0.27; 95% CI, .01–2.05) (Supplementary Appendix). One must be cautious in interpreting serology in children who have received TIV [2, 33]. Finally, acute URTI incidence was based on self-report with regular telephone reminders, and we may have failed to identify some illnesses despite rigorous prospective follow-up.

Temporary nonspecific immunity leading to interference between epidemics of respiratory viruses could have important implications. First, as observed in our trial, TIV appeared to have poor efficacy against acute URTIs (Table 2), apparently because the protection against influenza virus infection conferred by TIV was offset by an increased risk of other respiratory virus infection (Table 3). Second, interference between respiratory viruses could suggest new approaches to mitigating epidemics [32]. Mass administration of live polio vaccine in children has been used to control enterovirus 71 epidemics [10, 31]. Finally, viral interference could bias estimates of influenza vaccine effectiveness in test-negative case-control studies (Supplementary Appendix) [2, 34–43]. One test-negative study reported an association between receipt of TIV and the risk of influenza-like illness associated with a noninfluenza virus [38].

Additional work is required to more fully characterize temporary nonspecific immunity overall and in specific groups, such as children. Animal studies [44–50] and volunteer adult human challenge studies [51] could provide useful evidence. Additional community-based observational cohort studies and community-based experimental studies, such as our vaccine trial, may be particularly suitable for investigating temporary nonspecific immunity, because most acute URTIs do not require medical attention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Live Attenuated Influenza Vaccine Enhances Colonization of Streptococcus pneumoniae and Staphylococcus aureus in Mice

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Larry S. McDaniel, Editor

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ABSTRACT

Community interactions at mucosal surfaces between viruses, like influenza virus, and respiratory bacterial pathogens are important contributors toward pathogenesis of bacterial disease. What has not been considered is the natural extension of these interactions to live attenuated immunizations, and in particular, live attenuated influenza vaccines (LAIVs). Using a mouse-adapted LAIV against influenza A (H3N2) virus carrying the same mutations as the human FluMist vaccine, we find that LAIV vaccination reverses normal bacterial clearance from the nasopharynx and significantly increases bacterial carriage densities of the clinically important bacterial pathogens **Streptococcus pneumoniae** (serotypes 19F and 7F) and **Staphylococcus aureus** (strains Newman and Wright) within the upper respiratory tract of mice. Vaccination with LAIV also resulted in 2- to 5-fold increases in mean durations of bacterial carriage. Furthermore, we show that the increases in carriage density and duration were nearly identical in all aspects to changes in bacterial colonizing dynamics following infection with wild-type (WT) influenza virus. Importantly, LAIV, unlike WT influenza viruses, had no effect on severe bacterial disease or mortality within the lower respiratory tract. Our findings are, to the best of our knowledge, the first to demonstrate that vaccination with a live attenuated viral vaccine can directly modulate colonizing dynamics of important and unrelated human bacterial pathogens, and does so in a manner highly analogous to that seen following wild-type virus infection.

IMPORTANCE Following infection with an influenza virus, infected or recently recovered individuals become transiently susceptible to excess bacterial infections, particularly **Streptococcus pneumoniae** and **Staphylococcus aureus**. Indeed, in the absence of preexisting comorbidities, bacterial infections are a leading cause of severe disease during influenza epidemics. While this synergy has been known and is well studied, what has not been explored is the natural extension of these interactions to live attenuated influenza vaccines (LAIVs). Here we show, in mice, that vaccination with LAIV primes the upper respiratory tract for increased bacterial growth and persistence of bacterial carriage, in a manner nearly identical to that seen following wild-type influenza virus infections. Importantly, LAIV, unlike wild-type virus, did not increase severe bacterial disease of the lower respiratory tract. These findings may have consequences for individual bacterial disease processes within the upper respiratory tract, as well as bacterial transmission dynamics within LAIV-vaccinated populations

INTRODUCTION

The conventional view of pathogen dynamics posits that pathogen species act independently of one another. More recently, however, community interactions between pathogens have been recognized as necessary to modulate both health and disease

(1–7). These interactions might be expected to be most prevalent within gut, respiratory, and other mucosal surfaces that harbor complex populations of commensal and, occasionally, pathogenic microbes. In the respiratory tract, for example, viral infections are known to predispose to secondary bacterial invasive disease and pneumonia from pathogens that are most commonly benign but occasionally become virulent, particularly following a viral infection (8–10). A well-known example is the often lethal synergy between influenza virus and pneumococcal or staphylococcal bacterial secondary infections.

Infection with influenza viruses increases susceptibility to severe lower and upper respiratory tract (LRT and URT, respectively) bacterial infections resulting in complications, such as pneumonia, bacteremia, sinusitis, and acute otitis media (11). Bacterial infections may be a primary cause of mortality associated with influenza virus infection in the absence of preexisting comorbidity (12, 13). Primary influenza virus infection increases acquisition, colonization, and transmission of bacterial pathogens (14), most notably the pneumococcus **Streptococcus pneumoniae** and **Staphylococcus aureus** (11, 15).

Although the underlying mechanisms, while well studied, are not entirely defined, they likely include a combination of influenza virus-mediated cytotoxic breakdown of mucosal and epithelial barriers (16–18) and aberrant innate immune responses to bacterial invaders in the immediate postinfluenza state, characterized by uncontrolled pro- and anti-inflammatory cytokine production, excessive leukocyte recruitment, and extensive immunopathology (11, 19–22). When coupled with diminished epithelial and mucosal defenses, such an environment becomes increasingly hospitable for bacterial pathogens to flourish and invade in the days and first few weeks following influenza virus infection.

Increasingly, evidence is linking the early innate immune response triggered by infection or vaccination to sustained adaptive immunity (23). Thus, a broad goal of vaccination is to elicit an immune response analogous to that of the pathogen itself, without subsequent disease (24). The intranasally administered live attenuated influenza vaccine (LAIV) contains temperature-sensitive and attenuated virus designed to replicate efficiently in the cooler temperatures of the upper respiratory tract (URT) but which fails to do so in the warmer temperatures of the lower respiratory tract (LRT) (25, 26). Through selective replication in the URT, LAIV proteins are exposed to the host immune system in their native conformation, eliciting highly robust (IgA), serum (IgG), and cellular immune responses mimicking those of the pathogenic virus itself (27).

Although an innate immune response to vaccination is beneficial for long-term protection from influenza virus (28) and influenza virus-bacterial (29) coinfections, the direct consequences of such a response to a viral vaccine, with respect to secondary colonization and disease due to entirely unrelated bacterial pathogen species, are unknown. As increased susceptibility to and transmission of bacterial pathogens following influenza are due in large part to the innate immune response and breakdowns of the epithelial barriers of the URT, it is important to understand whether similar effects, elicited by live attenuated virus replication, may also predispose to bacterial infection. We sought here to determine the effects of a live attenuated influenza vaccine on URT and LRT bacterial infections. In particular, we ask whether LAIV vaccination alters bacterial colonization dynamics of the upper respiratory tract or disease in the lower respiratory tract of mice.

RESULTS

Using a live attenuated influenza A virus vaccine, HK/Syd 6:1:1 (LAIV), which contains many of the same mutations and demonstrates similar growth dynamics to those in the commercially available human FluMist vaccine (MedImmune, Gaithersburg, MD) (see reference 30 and **Fig. S1** in the supplemental material for vaccine details), we evaluated the effects of LAIV and its wild-type (WT) HK/Syd parent strain (referred to as WT virus) on **Streptococcus pneumoniae** (the pneumococcus) and **Staphylococcus aureus** replication and disease.

Figure S1

H3N2 HK/Syd 1:1:6 live attenuated influenza virus vaccine. LAIV vaccine was developed via site-specific mutagenesis of a parent H3N2 1:1:6 reassortant virus (HK/Syd), as described in reference **30**, containing the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) from the A/Hong Kong/1/68 (HK68) and A/Sydney/5/97 (Syd97) isolates, respectively, and the six internal protein gene segments from A/Puerto Rico/8/34 or PR8. LAIV consisted of a temperature-sensitive (ts) attenuated variant of HK/Syd (HK/Syd_{ts}) that contains site-specific mutations in the PB1 and PB2 RNA segments of the genome as described in reference **30**. These mutations are found in the attenuated A/Ann Arbor/6/60 master donor strain used to produce the commercial product FluMist (**26**). Download Figure S1, TIFF file, 0.2 MB.

LAIV virus is restricted in growth at 37°C but not at 33°C. To determine whether LAIV virus grows efficiently at temperatures seen within the nasopharynx (NP) while remaining restricted in growth at warmer temperatures of the LRT, WT influenza virus and its LAIV derivative were grown in MDCK cells at 37°C. As expected (**30**), a >3-log decrease in viral titers was measured for LAIV relative to the WT parent strain (**P** < 0.001) (**Fig. 1A**). However, when LAIV was propagated at 33°C, a temperature often associated with the nasopharyngeal environment (**31**), viral replication was no different from that of WT virus titers measured at 37°C.

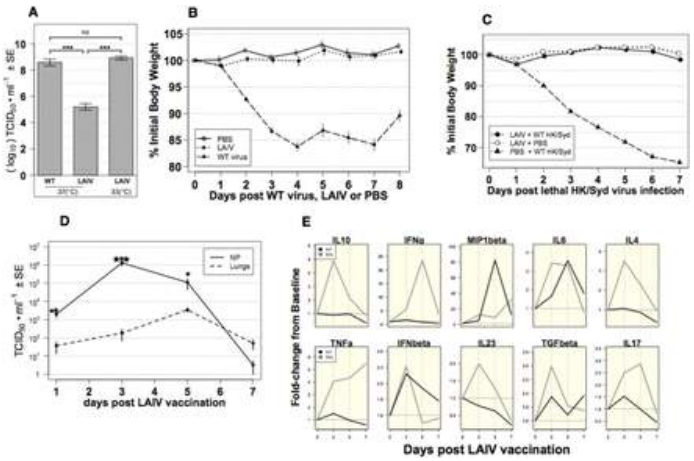

FIG 1

LAIV is safe, effective, replicates well within the URT, and elicits a robust cytokine response. (A) WT and LAIV HK/Syd viruses were grown in MDCK cells at 37°C and LAIV virus was grown at 33°C, and viral titers were measured via the median TCID50 (n = 3 per group). (B) Groups of 12 to 14 8-week-old BALB/c mice were inoculated with 2e6 TCID50 LAIV, WT HK/Syd virus, or PBS and monitored for weight loss. Three of 12 mice and 2/12 mice died at 4 and 7 days postinfection with WT HK/Syd virus, respectively, while no mice died following LAIV or PBS inoculation. (C) Groups of 8 4-week-old BALB/c mice were inoculated with 2e6 TCID50 of LAIV (2 of the 3 groups) or PBS and 4 weeks later infected with a lethal dose (5e7 TCID50) of WT HK/Syd virus or the PBS control. Infection was considered lethal if body weight fell below 70% of the initial body weight. (D) Four groups of 5 mice each were vaccinated with LAIV, and whole lung and NP viral titers were measured at 1, 3, 5, and 7 days postvaccination. (E) Four groups of 5 mice were vaccinated with LAIV, and NP and BAL specimen cytokines were measured at day 0 (unvaccinated mice) and days 3, 5, and 7 following vaccination. Error bars represent standard errors (SE) of the mean. Asterisks indicate statistically significant differences from controls by two-sided Student's t test. *, P < 0.05; **, P < 0.001; ***, P < 0.0001. NS, not significant (no difference between groups).

HK/Syd 1:1:6 LAIV vaccination is safe and effective in mice. Although LAIV is attenuated, inoculation with very high doses may cause morbidity and weight loss. Via a series of dosing experiments (data not shown), a vaccinating dose of 2e6 tissue culture infective doses ($TCID_{50}$) of LAIV in 40 μl phosphate-buffered saline (PBS) vehicle was determined to be safe, with no

weight loss or other detectable signs of morbidity in mice (Fig. 1B). This dose is in agreement with previous studies (28, 30). Inoculation with the same dose of the WT parent virus led to significant morbidity and mortality (5/12 mice succumbed by day 7 postinfection) (Fig. 1B), demonstrating the attenuated nature of the LAIV.

The vaccine efficacy and antibody response using this LAIV strain were described previously (30). To phenotypically confirm efficacy here, groups of 8 4-week-old mice were inoculated with LAIV or the PBS control and 4 weeks later with a lethal dose of the WT virus. Early vaccination with LAIV conferred complete protection from any detectable morbidity or weight loss due to infection with the WT strain, versus 100% mortality in unvaccinated control mice (Fig. 1C).

LAIV is restricted in growth in the lower but not the upper respiratory tract. To determine whether the differences in replication seen **in vitro** also occur **in vivo** in the upper (~33°C) versus lower (~37°C) respiratory tract, groups of 5 mice were vaccinated with LAIV, and viral titers were measured in whole lung and whole NP homogenates (Fig. 1D). By 3 days postvaccination, NP titers were 10,000-fold greater than in the lungs (1.3e6 versus 1.2e2 $TCID_{50}$; **P** < 0.001). In contrast, the WT virus grew to high viral titers in both the NP and lungs (>5e5 $TCID_{50}$) (data not shown), in agreement with previous reports (32), which led to significant morbidity and mortality, as demonstrated in the controls in Fig. 1B. Overall, maximal NP titers occurred earlier and were nearly 400-fold greater than maximum lung titers (1.3e6 versus 3.4e3 $TCID_{50}$; **P** < 0.001). Importantly, these NP viral dynamics are in agreement with viral shedding in NP aspirates from human subjects following vaccination with the FluMist vaccine (33).

LAIV cytokine response in the nasopharynx and lungs. While LAIV replication in the NP induces a robust systemic inflammatory response (34, 35), the cytokine response in the NP has, to our knowledge, not been observed. Nasopharyngeal homogenates and bronchoalveolar lavage (BAL) specimen cytokines were measured in groups of 5 mice each at days 0, 3, 5, and 7 postvaccination (Fig. 1E). Of particular interest, the type I interferon (IFN-β) was significantly increased in the NP and BAL specimens following LAIV vaccination, and this cytokine has been demonstrated to play a pivotal role in excess bacterial colonization of the nasopharynx following WT influenza virus infection (36). As well, macrophage inflammatory protein 1β (MIP-1β) was also significantly upregulated following LAIV, similar to what was seen following influenza virus-pneumococcal coinfections of human middle ear epithelial cells (37). In general, the responses measured here in the NP are similar to those measured from nasopharyngeal washes in humans infected naturally with seasonal influenza A viruses (38).

LAIV enhances pneumococcal bacterial dynamics in the URT in a manner highly analogous to WT influenza virus. Numerous previous investigations have demonstrated that replication of WT influenza virus within the URT predisposes to excess bacterial replication and colonization within the NP, particularly by **Streptococcus pneumoniae** (36, 39, 40). Because, as demonstrated above, LAIV replicates to near WT levels when in the cooler temperatures of the URT, we sought to study effects of LAIV on bacterial carriage density within the NP of mice and compared them to the changes in bacterial carriage following WT virus infection. LAIV vaccination or sublethal infection with the WT parent strain was delivered 7 days following inoculation with a common nasopharynx-colonizing strain of pneumococcus type 19F (Fig. 2A to C) included in the current pneumococcal conjugate vaccine (41). Following vaccination, normal bacterial clearance from the NP was halted, and bacteria reverted to exponential growth within 3 days postvaccination (Fig. 2B). Receipt of LAIV significantly increased the density of bacterial carriage and extended the mean duration of colonization from 35 to 57 days (Fig. 2C). Of particular importance, these effects were nearly identical in all aspects to the effects of the WT influenza virus on bacterial carriage density and duration (Fig. 2B and C). Although no detectable morbidity was associated with vaccination alone (Fig. 1B), vaccination in the presence of bacterial colonization resulted in very mild, though sustained weight loss (~3 to 5%; **P** < 0.05) relative to colonized, unvaccinated controls (see Fig. S2 in the supplemental material) that corresponded with time of greatest excess bacterial proliferation.

Figure S2

Weight changes in colonized mice following LAIV or PBS vehicle. Groups of 12 to 14 BALB/c mice were inoculated with a colonizing dose (1e5 CFU) 19F **Streptococcus pneumoniae** at 7 days prior to receipt of 2e6 $TCID_{50}$ LAIV vaccination or PBS vehicle control, and body weight was monitored. Asterisks indicate statistically significant differences between LAIV-vaccinated mice and PBS controls (**P** < 0.05 by two-sided Student's **t** test). Download Figure S2, TIFF file, 0.3 MB.

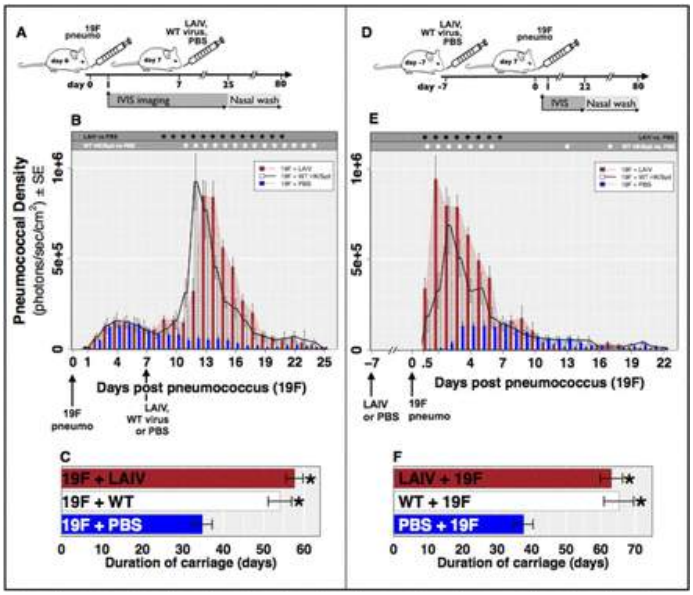

FIG 2

LAIV and WT influenza virus infection similarly enhance 19F pneumococcal carriage density and duration of colonization. Groups of 12 to 14 mice were vaccinated with LAIV and infected with WT influenza virus or PBS vehicle at 7 days following colonization with 19F pneumococcus (A to C) or 7 days prior to colonization with 19F (D to F). Bacterial strains constitutively expressed luciferase, and nasopharyngeal carriage density was measured via in vivo imaging (IVIS) at 12 h postbacterial infection and daily thereafter (B and E). Duration of colonization (C and F) was measured via bacterial plating of nasal washes taken daily after carriage density decreased below the limit of detection for IVIS imaging (~1e4 CFU/ml). Asterisks indicate significant differences between vaccinated (black asterisks in panels B and E) or WT influenza virus-infected (white asterisks in panels B and E) versus control groups (P < 0.05 by Students t test), and error bars represent standard errors around the mean.

To test whether order and timing of vaccination relative to bacterial acquisition are important, LAIV or WT virus was administered 7 days before (rather than after) 19F colonization (**Fig. 2D to F**). Early vaccination or infection with WT virus led to immediate excess bacterial outgrowth following pneumococcal inoculation relative to that in mice pretreated with PBS vehicle (**Fig. 2E**). This increase was generally more pronounced following LAIV vaccination relative to WT virus infection, but the difference only reached statistical significance at day 1 post-bacterial infection. Increases in mean durations of carriage were also demonstrated and were similar between the two groups, with duration extending from 38 days following treatment with PBS to 63 or 65 days following LAIV or WT virus infection, respectively (**Fig. 2F**).

To further define the temporal nature of these interactions and simultaneously test whether this response is strain specific, vaccination was given at either 1 or 7 days prior to infection with a slightly more invasive type 7F pneumococcus (**Fig. 3A**). The maximum bacterial density in both groups of vaccinated mice reached a near 100-fold increase versus that in PBS controls. When inoculation with bacteria followed only 1 day (versus 7 days) postvaccination, similar but delayed dynamics (**Fig. 3A**) and

cumulative bacterial titers (Fig. 3B) were measured. Interestingly, the delay was consistent with the difference in times from vaccination to bacterial inoculation between the two groups.

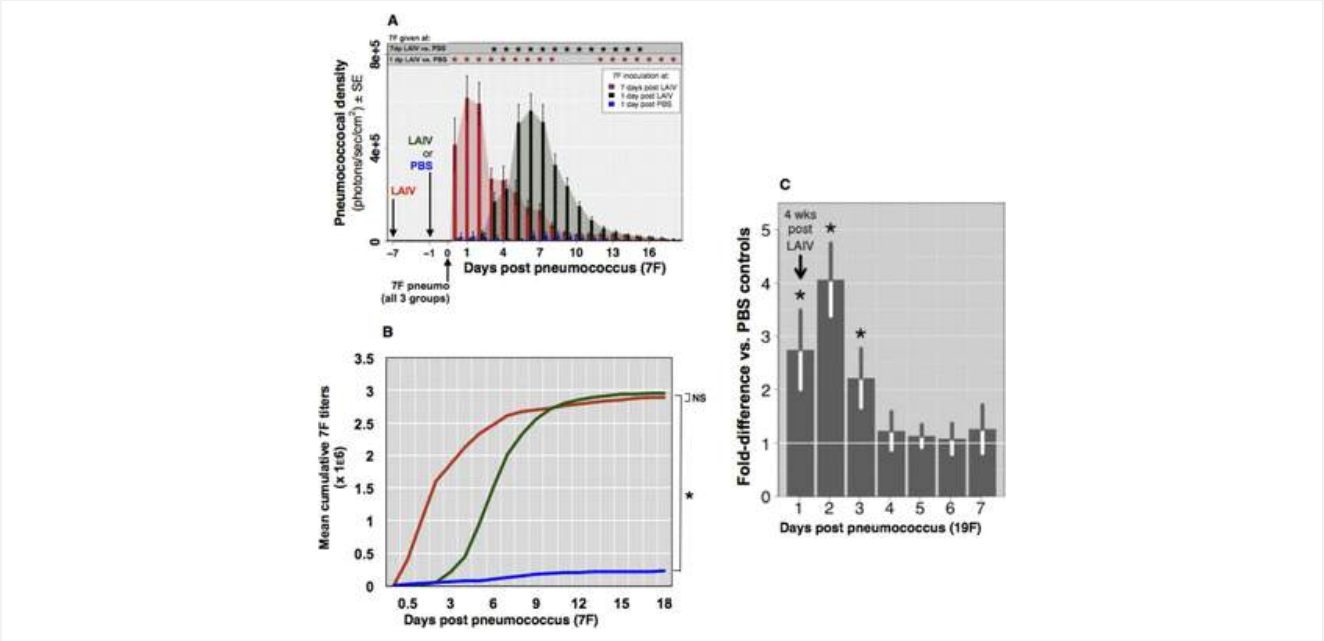

FIG 3

LAIV enhancement of pneumococcal density is time dependent and long lasting. Groups of 12 to 14 mice were vaccinated with LAIV or PBS vehicle at 1 or 7 days prior to colonization with pneumococcal (pneumo) serotype 7F. Bacterial strains constitutively expressed luciferase, and bacterial NP density was measured via IVIS **in vivo** imaging (A and B). Mean cumulative bacterial titers in panel B were calculated by first calculating the cumulative bacterial titers per individual mouse NP at each time point and then calculating the average and SE across the individual cumulative titers per time point, rather than simply averaging the areas under the mean density curves shown in panel A. Asterisks indicate significant differences in bacterial densities between the vaccinated and PBS control groups (dark green indicates LAIV given 7 days prior and red indicates LAIV given 1 day prior to 7F inoculation; **P** < 0.05 by two-tailed Student's **t** test). (C) Groups of mice were vaccinated with LAIV (**n** = 20) or PBS vehicle control (**n** = 30), respectively, at 28 days prior to colonization with 19F pneumococcus. Fold differences per day between mean bacterial densities measured in mice treated 28 days prior with LAIV versus PBS are reported. Error bars indicate standard errors of the mean and asterisks indicate significant differences (**P** < 0.05) from PBS controls (by two-tailed single-sample **t** test).

We sought to understand whether these effects of LAIV vaccination on bacterial proliferation would continue over a longer duration. Mice were infected with pneumococcus 28 days following LAIV vaccination—well after viral clearance from the NP was complete (~7 days postvaccination). Despite the 28-day lag between LAIV and pneumococcal infection, LAIV continued to yield immediate excess bacterial proliferation relative to PBS controls (Fig. 3C); however, the effect was modest and short-lived, with only 2- to 4-fold increases over PBS controls measured between days 1 and 3 postinfection, respectively. By day 4, bacterial density in the NP returned to control levels, and the duration of colonization was not increased.

LAIV enhances Staphylococcus aureus dynamics in the URT. We next sought to test the effects of LAIV on carriage of an entirely distinct but important Gram-positive bacterium, **Staphylococcus aureus**. LAIV was administered 7 days prior to infection with **S. aureus** strain Wright (Fig. 4A and B) or Newman (Fig. 4C and D). Similar to the previous experiments using two strains of pneumococcus, the density of these two strains of **S. aureus** following vaccination was increased at all measured time points for both the Wright and Newman strains (Fig. 4A and C), and duration of colonization was significantly extended 3- to 5-fold over that in the PBS controls (Fig. 4B and D).

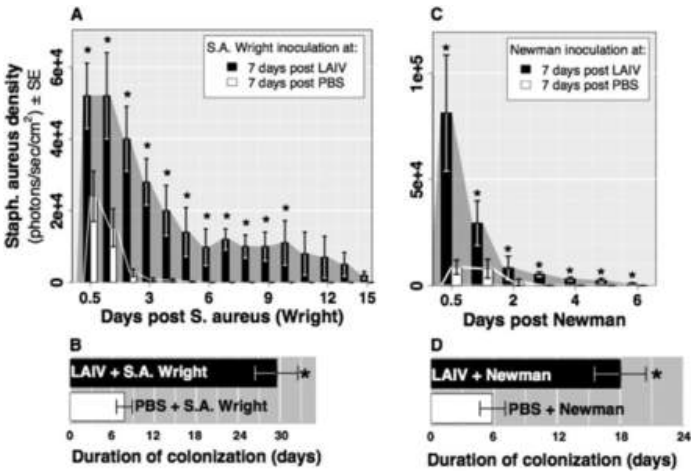

FIG 4

LAIV enhances bacterial load and duration of staphylococcal carriage. Groups of 12 to 14 mice were vaccinated with LAIV or PBS vehicle 7 days prior to colonization with **S. aureus** (S.A.) strain Wright (A and B) or Newman (C and D). **S. aureus** constitutively expressed luciferase, and bacterial density was measured via IVIS **in vivo** imaging. Duration of colonization (B and D) was measured via bacterial plating of nasal washes taken daily after the carriage density decreased below the limit of detection for IVIS imaging. Asterisks indicate significant differences between vaccinated and control groups (**P** < 0.05 by two-sided Student's **t** test), and error bars represent standard errors around the mean.

LAIV does not increase morbidity or mortality from bacterial LRT infections. Given the severe and often lethal interaction seen between circulating influenza virus strains and bacterial lower respiratory tract infections (LRIs) (11, 42), we assessed the effects of LAIV on bacterial LRIs and mortality and compared these effects to those seen following WT influenza virus-bacterial coinfection and single infections with bacteria. Mice received LAIV, WT influenza virus, or PBS control and 7 days later (a time known to maximize the lethal effects of influenza virus-bacterial coinfections [43]) were inoculated with a sublethal dose of either of the highly invasive type 2 or 3 pneumococcal serotypes D39 or A66.1, respectively (Fig. 5A to C).

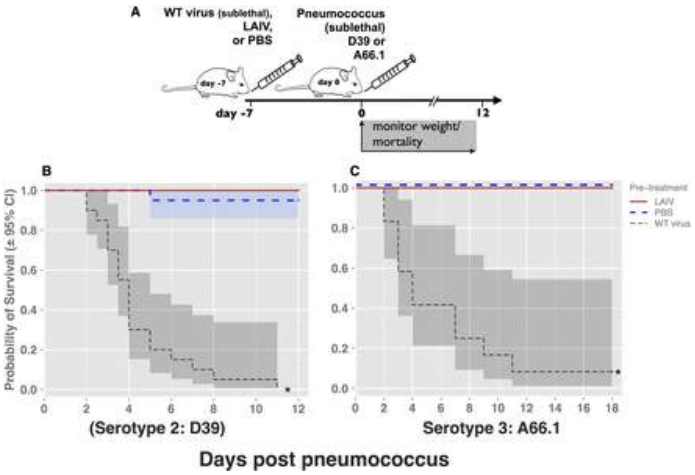

FIG 5

LAIV does not increase severe bacterial disease or mortality. Groups of mice received intranasal LAIV vaccination (solid red curves), sublethal infection with WT influenza virus (broken black curves), or PBS (broken blue curves) 7 days prior to inoculation with a sublethal dose of **Streptococcus pneumoniae** type 2 (1e5 CFU D39; **n** = 20 per group) (B) or type 3 (1e3 CFU A66.1; **n** = 12 to 15 per group) (C), and body weight and mortality were observed at least every 12 h for the first 4 days postpneumococcal inoculation and daily thereafter. Kaplan-Meier survival curves with 95% confidence intervals (CI) were constructed, and asterisks indicate statistically significant differences (**P** < 0.05 by log rank test) between LAIV- or WT virus-infected groups versus PBS controls.

In contrast to the 100% mortality observed when sublethal inoculation with D39 or A66.1 followed pretreatment with wild-type influenza virus, bacterial inoculation following pretreatment with LAIV demonstrated no increases in morbidity (i.e., weight loss; data not shown) or mortality (**Fig. 5B and C**) relative to bacterial infection alone.

DISCUSSION

The potent and often lethal effects of an antecedent influenza virus infection on secondary bacterial disease have been reported previously (**11**, **21**, **44–46**). Viral replication induced epithelial and mucosal degradation, and the ensuing innate immune response yield diminished capacity to avert secondary bacterial infections. Recent clinical and experimental data suggest that influenza virus infection may exert its influence beginning in the URT by enhancing susceptibility to bacterial colonization (**14**, **47**, **48**) and increasing NP carriage density (**36**).

Although vaccination with LAIV, in the longer term, thwarts secondary bacterial infections by inhibiting primary infections with influenza virus (**29**, **49**), the immediate effects of LAIV on bacterial replication and disease have never before been described. Indeed, although vaccines are among our greatest achievements in the constant battle against microbial pathogens, the effects of vaccination on distinct pathogen species unrelated to vaccine-targeted pathogens have, until now, remained entirely unexplored. LAIV viruses selectively replicate in the URT, partially denude the epithelium (**50**), and induce robust innate immune responses that ultimately contribute to long-term protective immunity (**28**). In so doing, LAIV viruses may, like WT influenza viruses, condition the site of replication for enhanced secondary bacterial colonization.

Here, we demonstrated that vaccination with LAIV, like a WT influenza virus, induces swift increases in bacterial density within the URT, with no discernible differences in effects on bacterial dynamics in the NP between the two virus strains. A lag between viral inoculation and excess bacterial replication of at least 3 to 5 days was consistently measured, no matter the bacterial strain. Of particular interest, the type I interferon, IFN-β, known to play a pivotal role in excess pneumococcal colonization following WT influenza virus infections (**36**), was maximally upregulated at 3 days post-LAIV vaccination, coincident with commencement of excess bacterial proliferation. After the 3- to 5-day threshold following vaccination was met, the murine NP remained conditioned for excess pneumococcal replication for at least 28 days (our furthest time point out) post-vaccination. However, as the delay between vaccination and bacterial infection was increased, the magnitude of the effects of vaccination on bacterial dynamics became considerably more modest, although statistically significant excess growth was measured even when acquisition followed 28 days post-vaccination.

While the studies described here are limited in scope to murine models, enhanced bacterial load in the URT following LAIV may agree with human data (**51**), where LAIV has been associated with increases in adverse upper respiratory tract symptoms. Although adverse URT symptoms following administration of FluMist are considered to be of viral etiology, they are most evident in children <5 years of age, where rates of bacterial carriage are greatest (**52**). Potentially corroborating this are data from a large prospective double-blind trial of FluMist (trial no. MI-CP111 [**53**]) that assessed reactogenicity and adverse URT events within the first 28 days following vaccination in ~3,000 children between the ages of 6 and 59 months. This trial demonstrated a bimodal increase in URT symptoms following FluMist vaccination, the first between days 2 and 4 post-vaccination and the second between days 5 and 10 post-vaccination (**53**). While these increased URT events (relative to controls receiving trivalent inactivated influenza vaccine) were considered normal reactions to the live vaccine, the bimodal nature of the increased symptoms suggests that two distinct mechanisms may be in place. In the context of the current findings, the first peak may correspond with viral replication, while the second, more sustained peak may, at least in part, be driven by symptoms due to excess bacterial carriage.

Perhaps the most important finding from our study, with regard to the health of the public and potential concerns regarding vaccination, is that LAIV did not enhance lower respiratory tract infections, morbidity, or mortality following bacterial infections, which are, by most accounts, the most significant issues to be concerned with in terms of respiratory tract bacterial disease.

Indeed, this finding is consistent with numerous epidemiological reports all failing to detect any serious adverse sequelae of LAIV vaccination in humans (51, 54). Furthermore, this finding is consistent with significantly diminished LAIV virus replication within the lower respiratory tract, suggesting that viral replication is a requirement for the synergistic response seen between WT influenza viruses and bacterial LRT infections.

While care should be taken to not overgeneralize the data described here to all vaccines, the broad implications suggest that live attenuated viral vaccines may have unintended consequences on important human bacterial pathogens unrelated to the vaccine target species. Furthermore, our findings suggest a role for laboratory models of multispecies interactions with vaccine strains to inform future vaccine monitoring and evaluation programs aimed at identifying thus far entirely unrealized "unconventional" effects, both beneficial and detrimental, of live attenuated viral vaccines and cross-species microbial dynamics.

MATERIALS AND METHODS

Infectious agents and vaccines. Viral infections were carried out with an H3N2 1:1:6 reassortant virus developed as described previously (30), containing the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) from A/Hong Kong/1/68 (HK68) and A/Sydney/5/97 (Syd97) isolates, respectively, and the six internal protein gene segments from A/Puerto Rico/8/34 (or PR8; referred to here as WT influenza virus). LAIV vaccinations consisted of a temperature-sensitive (**ts**) attenuated variant of HK/Syd, HK/Syd$_{att/\mathbf{ts}}$ (LAIV) that contains site-specific mutations in the PB1 and PB2 RNA segments of the genome (see Fig. S1 in the supplemental material) as described previously (30). These are the same mutations found in the attenuated A/Ann Arbor/6/60 master donor strain used to produce the influenza A virus strains found in the commercial product FluMist (30). WT and LAIV viruses were propagated in 10-day-old embryonated chicken eggs at 37 and 33°C, respectively) and characterized in Madin-Darby canine kidney cells to determine the 50% infective tissue culture dose (TCID$_{50}$) in wells. The pneumococcal carrier isolates ST425 (serotype 19F) and ST191 (serotype 7F), chosen based on their colonizing potential as previously described (14), were used for colonization experiments. The highly invasive type 2 and type 3 pneumococcal isolates D39 and A66.1, respectively, were used for pneumonia and survival studies. The 19F and 7F strains were engineered to express luciferase, as described previously (14). **Staphylococcus aureus** strains Wright (ATCC 49525) and Newman (ATCC 25905) were engineered to express luciferase by Caliper Life Sciences (Alameda, CA).

Ethics statement. All experimental procedures were approved by the Institutional Animal Care and Use Committee (protocol no. 353) at St. Jude Children's Research Hospital (SJCRH) under relevant institutional and American Veterinary Medical Association guidelines and were performed in a biosafety level 2 facility that is accredited by the American Association for Laboratory Animal Science (AALAS).

Animal and infection models. Eight-week-old BALB/c mice (Jackson Laboratories, Bar Harbor, ME) were used in all experiments, with the exception of mice treated with early vaccination to demonstrate vaccine efficacy and effectiveness. In these cases, 4-week-old BALB/c mice were vaccinated or administered PBS and monitored for 4 weeks before further inoculation. All inoculations and vaccinations were via the intranasal route under general anesthesia with inhaled 2.5% isoflurane (Baxter Healthcare, Deerfield, IL). LAIV vaccination consisted of 2e6 TCID$_{50}$ HK/Syd$_{att/\mathbf{ts}}$ LAIV in 40 µl PBS. The lethal and sublethal doses of WT HK/Syd were 5e7 and 1e5 TCID$_{50}$ in 50 µl PBS, respectively. Pneumococcal infections with 19F and 7F were performed as described previously (14), except inoculation was in 40 µl PBS. Infection with **S. aureus** strains Wright and Newman contained 1e7 CFU in 40 µl PBS. Mortality studies were performed as described previously (43) with sublethal doses of the invasive type 2 and type 3 pneumococcal serotype D39 and A66.1 isolates, consisting of 1e5 and 1e3 CFU in 100 µl PBS (to ensure bacterial entry into the lower lungs), respectively. Animals were monitored for body weight and mortality at least once per day for all survival studies. Mice were sacrificed if body weight fell below 70% initial weight.

Bacterial CFU titers for duration studies. Bacterial CFU titers were measured in nasal washes using 12 µl of PBS administered and retrieved from each nare and quantitated by serial dilution plating on blood agar plates. Washes were

performed daily only after the pneumococcal density fell below the limit of detection for IVIS imaging (~1e4 CFU/ml).

Determination of bacterial and viral titers in lungs and nasopharyngeal homogenates. Viral and bacterial titers were measured in whole lung and nasopharyngeal (NP) homogenates. Whole lungs were harvested and homogenized using a gentleMACS system (Miltenyi Biotech), as per the manufacturer's protocol. NP was isolated via careful dissection dorsally across the frontal bones, laterally via removal of the zygomatic bone, posteriorly by dislocation of the upper jaw from the mandible, and inferiorly just posterior to the soft palate. Isolated NP was homogenized via plunging in 1.5 ml PBS through a 40-μm-mesh strainer. Bacterial titers were measured via plating of serial dilutions, and viral titers were measured by determining the $TCID_{50}$ as previously described (**30**).

Determination of cytokine levels in the NP and BAL specimens by enzyme-linked immunosorbent assay. Nasopharyngeal isolates and BAL specimens were collected as described above, and cytokines were measured using commercially available kits from R&D systems (macrophage inflammatory protein 1β [MIP-1β], transforming growth factor β [TGF-β], and beta interferon [IFN-β]) or eBiosciences (interleukin-4 [IL-4], IL-6, IL-10, IL-17, IL-23, and gamma interferon [IFN-γ]).

Bioluminescent imaging. Mice were imaged using an IVIS charge-coupled device (CCD) camera (Xenogen) as described previously (**14**, **29**). Nasopharyngeal bacterial density was measured as total photons/s/cm^2 in prespecified regions covering the NP, and background (calculated for each mouse on a region of equal area over the hind limb) was subtracted. Each NP measurement represents an average of two pictures, one for each side of the mouse head. Quantitation was performed using LivingImage software (version 3.0; Caliper Life Sciences) as described previously (**14**).

Statistical analyses. All statistical analyses were performed within the R statistical computing environment (version 2.14R; R Foundation for Statistical Computing, R Development Core Team, Vienna, Austria). The specific statistical tests used are as indicated in the legend to each figure. The R package Survival was used for all survival analyses, Kaplan-Meier (KM) plots, and KM log rank tests. All other statistical tests were performed using R base functions.

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FOOTNOTES

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Live Attenuated Influenza Virus Increases Pneumococcal Translocation and Persistence Within the Middle Ear

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Abstract

Go to:

Background. Infection with influenza A virus (IAV) increases susceptibility to respiratory bacterial infections, resulting in increased bacterial carriage and complications such acute otitis media, pneumonia, bacteremia, and meningitis. Recently, vaccination with live attenuated influenza virus (LAIV) was reported to enhance subclinical bacterial colonization within the nasopharynx, similar to IAV. Although LAIV does not predispose to bacterial pneumonia, whether it may alter bacterial transmigration toward the middle ear, where it could have clinically relevant implications, has not been investigated.

Methods. BALB/c mice received LAIV or phosphate-buffered saline 1 or 7 days before or during pneumococcal colonization with either of 2 clinical isolates, 19F or 7F. Middle ear bacterial titers were monitored daily via in vivo imaging.

Results. LAIV increased bacterial transmigration to and persistence within the middle ear. When colonization followed LAIV inoculation, a minimum LAIV incubation period of 4 days was required before bacterial transmigration commenced.

Conclusions. While LAIV vaccination is safe and effective at reducing IAV and coinfection with influenza virus and bacteria, LAIV may increase bacterial transmigration to the middle ear and could thus increase the risk of clinically relevant acute otitis media. These data warrant further investigations into interactions between live attenuated viruses and naturally colonizing bacterial pathogens.

Keywords: live attenuated influenza virus, middle ear bacterial colonization, bacterial transmigration, acute otitis media, pneumococcus, coinfection

Infection with influenza A virus (IAV) increases susceptibility to severe lower and upper respiratory tract (URT) bacterial infections, resulting in complications such as pneumonia, bacteremia, sinusitis, and bacterial acute otitis media (AOM) [1]; the latter is a major contributor to the global burden of pediatric disease and remains one of the most common diagnoses leading to the prescription of antimicrobial agents in the United States [2]. While bacterial AOM often occurs in isolation, increasing evidence suggests that primary or concurrent viral respiratory infections of the URT may play uniquely important roles in enhancing bacterial acquisition, colonization, and, ultimately, progression from asymptomatic bacterial carriage to AOM [3], notably from ***Streptococcus pneumoniae*** and ***Staphylococcus aureus*** [1, 4].

Although the mechanisms underlying influenza virus–mediated susceptibility to bacterial AOM are not entirely defined, they likely include a combination of IAV-mediated cytotoxic breakdown of mucosal and epithelial barriers of the URT [5–8] and aberrant innate immune responses to bacterial invaders in the

immediate postinfluenza state, characterized by uncontrolled proinflammatory and antiinflammatory cytokine production, excessive leukocyte recruitment, and immunopathology [1, 9–13]. When coupled with diminished mucosal defenses, such an environment becomes increasingly hospitable for bacterial pathogens to flourish and cause clinical disease in the days and weeks following influenza virus infection.

Increasing evidence links the early innate immune response triggered by vaccination to long-term vaccine efficacy [14]. Thus, a goal of vaccination is to elicit an immune response as close to that elicited by the pathogen itself, without subsequent disease. The intranasally administered live attenuated influenza vaccine (LAIV) is composed of 1:1:6 reassortant viruses containing the hemagglutinin (HA) and neuraminidase (NA) surface proteins from wild-type viruses on a temperature-sensitive and attenuated backbone designed to enable efficient viral replication in the cooler temperatures of the URT but not the warmer temperatures of the lower respiratory tract (LRT) [15, 16]. Through selective replication in the URT, LAIV proteins are exposed to the host immune system in their native conformation, eliciting highly robust immunoglobulin A (IgA), serum immunoglobulin G (IgG), and cellular immune responses mimicking those of the pathogenic virus itself [17], without subsequent virus-mediated disease in the LRT [18, 19].

Recently, we demonstrated that LAIV, while safely providing long-term immunity against influenza and significantly reducing postinfluenza secondary bacterial infections [20], inadvertently enhances the duration and density of bacterial carriage in the nasopharynx of mice [21], a finding that has since been shown in humans [22]. Importantly, in contrast to wild-type IAV infections, LAIV did not alter bacterial outgrowth in the LRT and demonstrated no increases in the incidences of bacterial pneumonia or bacteremia. What is not known is whether LAIV virus replication in the URT may, like that of the wild-type IAV, inadvertently catalyze bacterial migration from the nasopharynx, where it is largely asymptomatic, into the middle ear, where it can increase the risk of symptomatic AOM [13, 23, 24]. Such an effect of the attenuated virus could result from LAIV-mediated inflammation of the epithelial cells of the pharyngotympanic tube [13] or from elevated bacterial density within the nasopharynx [25].

MATERIALS AND METHODS

Go to:

Vaccinations and Infectious Agents

LAIV viruses were developed from a parent H3N2 1:1:6 reassortant virus developed as described previously [26]. The surface glycoproteins HA and NA were from the A/Hong Kong/1/68 (HK68) and A/Sydney/5/97 (Syd97) isolates, respectively, and the 6 internal protein gene segments were from A/Puerto Rico/8/34 or PR8 (referred to hereafter as WT virus). LAIV consisted of a temperature-sensitive (***ts***) attenuated variant of the WT virus (HK/Syd_{ts}) that contains site-specific mutations in the PB1 and PB2 RNA segments of the genome as described previously [26, 27]. These mutations are found in the attenuated A/Ann Arbor/6/60 master donor strain used to produce the commercial product known as FluMist (MedImmune, Gaithersburg, Maryland) [16]. LAIV viruses were propagated in 10-day-old embryonated chicken eggs at 33°C and quantitated in Madin–Darby canine kidney cells using the median tissue culture infective dose ($TCID_{50}$). In vitro and in vivo growth dynamics have been reported elsewhere [21]. The pneumococcal carrier isolates ST425 (serotype 19F) and ST191 (serotype 7F) have been previously described [3]. These strains were engineered to express luciferase, as described elsewhere [3, 28].

Animal and Infection Models

Eight-week-old BALB/c mice (Jackson Laboratories, Bar Harbor, Maine) were used in all experiments. All inoculations were via the intranasal route. LAIV consisted of 2×10^6 $TCID_{50}$ HK/Syd_{ts} virus in 40 µL of phosphate-buffered saline (PBS). Pneumococcal infections with 19F and 7F ***Streptococcus pneumoniae*** were as described previously [3]. Briefly, bacterial cultures were grown in Todd–Hewitt broth (Difco Laboratories, Detroit, Michigan) containing 0.5% yeast (THY) until mid- to late-log phase (OD, approximately 0.3,) and aliquots were stored at −80°C in 10% glycerol and quantified via serial dilution on blood agar plates. Inoculations were prepared from frozen aliquots and consisted of 1×10^6

and 1×10^5 colony-forming units of serotype 19F and 7F pneumococci, respectively, in 25 µL of PBS. Infections were initialized via careful administration of 12.5 µL of bacteria to each naris under general anesthesia with 2.5% inhaled isoflurane (Baxter Healthcare, Deerfield, Illinois). All experiments were conducted in biosafety level 2 facilities in a manner in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animals.

Bioluminescent Imaging

Mice were imaged using an IVIS CCD camera (Xenogen) as described elsewhere [3]. Middle ear bacterial density was measured as total photons sec^{-1} cm^{-2} in prespecified regions covering the middle ear canal, and background (calculated for each mouse on a region of equal area over the hind limb) was subtracted. Positivity for bacteria within the middle ear was defined as a value of >40 000 photons sec^{-1} cm^{-2}. This threshold has been previously described for this infection model, using the same instruments and laboratory environment [29]. Quantitation was performed using Living Image software (v. 3.0; Caliper Life Sciences) as described previously [3].

Although bioluminescent imaging of ***lux***-expressing bacteria has previously been shown to be an efficient and accurate method for measuring bacterial density in the nasopharynx and lungs of mice and ferrets in vivo [3, 21, 29, 30], to ensure imaging was also appropriate for measuring bacterial presence and density within the middle ear, we compared values obtained from imaging to bacterial titers obtained by traditional methods. In short, the middle ear was dissected and completely homogenized in 1 mL of PBS, and serial dilutions were plated on 5% blood agar plates for quantification. Bacterial counts obtained from serial dilution plating were plotted against values obtained via IVIS just before dissection and showed strong linear correlation ($R^2 = 0.92$; Supplementary Figure 1).

A single episode of bacterial middle ear colonization (MEC) was defined as any continuous detection of bacteria that was not interrupted by an interval of >2 days. This 2-day interval was important to account for normal fluctuations in bacterial density, whereby densities can temporarily fall below the threshold of detection (described above) without actually being cleared and then return to high levels. Additionally, episodes were categorized as early or late onset. Early onset was defined as an initial episode of MEC in a given mouse that occurred within 5 days of bacterial inoculation. Late onset was defined as any episode that commenced at least 2.5 days after clearance of a previous episode or at least 5 days after pneumococcal infection.

Statistical Analyses

All statistical analyses were performed within the R statistical computing environment (R, version 2.14; R Foundation for Statistical Computing, R Development Core Team, Vienna, Austria). Kaplan–Meier curves were constructed for freedom from MEC for each mouse per group, and the log-rank test was used to calculate statistically significant differences between groups. The frequency of MEC was plotted using Loess smoothing (span 0.2), and differences between daily frequencies in the vaccinated groups and those in the PBS controls were calculated using the Fisher exact test for differences in proportions. Differences in mean duration of MEC were calculated using 2-tailed 2-sample Students ***t*** tests. The false detection rate was used to adjust for multiple comparisons where appropriate, and statistical significance was considered when the calculated probability had an α level of <0.05.

RESULTS

Go to:

LAIV Increases the Incidence of MEC in Mice Colonized With Pneumococci Before LAIV Receipt

Nasopharyngeal carriage of pneumococcus is believed to be a prerequisite for MEC and subsequent pneumococcal AOM, and elevated bacterial density has been associated with transition from asymptomatic carriage to middle ear infections [25]. To determine whether LAIV vaccination of pneumococci-colonized mice may enhance bacterial transmigration to the middle ear, groups of 12–14 mice were colonized with serotype 19F pneumococcus (a clinical isolate often found colonizing the

nasopharynx of children and a well-established model organism for colonization and AOM in mice [3]) 7 days before LAIV or PBS inoculation. A delay of 7 days was used because this was shown to be a sufficient interval over which bacteria reached stable colonization, as assessed via IVIS imaging of the nasopharynx and as previously reported [31]. Within 12 hours after LAIV inoculation, mice demonstrated an increased incidence of MEC (Figure 1), as determined by in vivo imaging of the middle ear (see "Materials and Methods" section). By day 4 after LAIV receipt, 85% of mice had at least 1 episode of MEC, compared with only 25% of PBS controls. In the majority of cases, initial onset of MEC in the LAIV group occurred within the first 4 days following vaccination, and freedom from MEC stabilized in both groups after day 5 (with the exception of a single new case in the PBS group, which was detected on day 9). By day 10 following LAIV or PBS inoculation, the incidence of MEC in LAIV recipients remained significantly greater than that in PBS controls (85% in LAIV recipients vs 50% in PBS controls; ***P*** = .017).

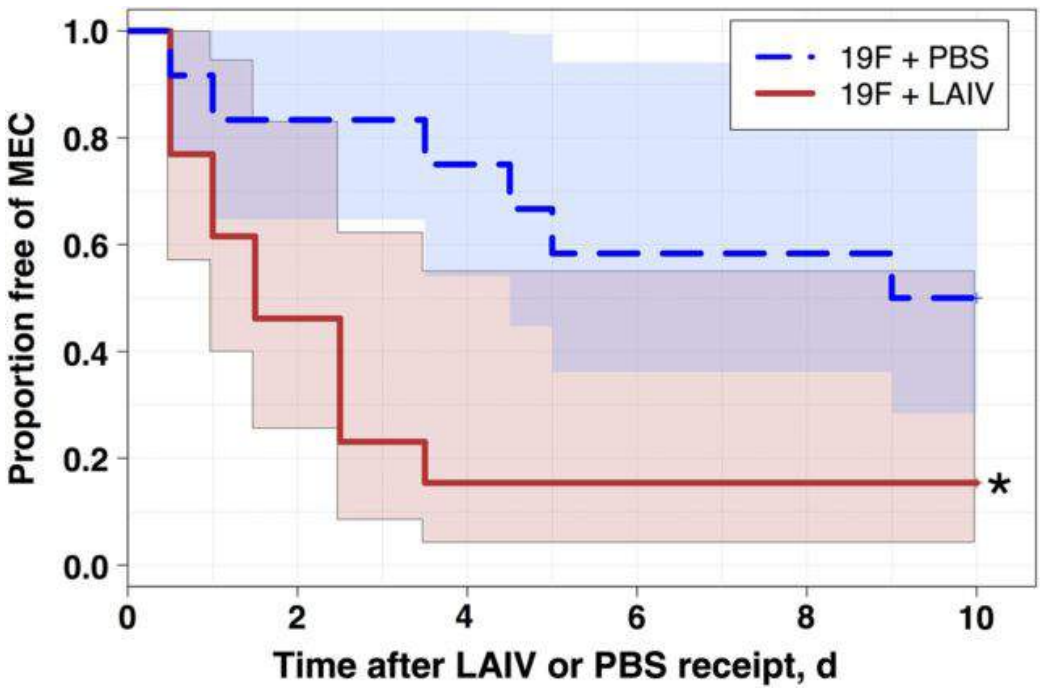

Figure 1.

Live attenuated influenza virus (LAIV) enhances the incidence of bacterial middle ear colonization (MEC) in precolonized mice. Groups of 12–14 8-week-old BALB/c mice were colonized intranasally with serotype 19F pneumococcal bacteria engineered to express luciferase. Seven days later, mice were inoculated with LAIV or phosphate-buffered saline (PBS) vehicle as a control. MEC was measured via in vivo imaging of the middle ear at 12-hour intervals for the first 2 days following LAIV or PBS receipt and daily thereafter. Initial onset of bacterial MEC was recorded for each mouse, and Kaplan–Meier survival curves were constructed. Data are reported as freedom from MEC after LAIV or PBS inoculation, and the log-rank test was used to determine statistically significant differences between groups. *$P < .05$, compared with PBS controls.

Antecedent Receipt of LAIV Predisposes to Bacterial Transmigration

To address whether antecedent inoculation with LAIV predisposes to MEC after bacterial infection, and to ensure that the effect of LAIV on bacterial transmigration is not specific to serotype 19F pneumococci, mice received a colonizing dose of pneumococcal serotype 7F (a slightly more invasive clinical strain and a well-described model organism for pneumococcal AOM in mice [3]) at either 7 days

or 1 day after LAIV receipt (n = 26 for each group) or 1 day after PBS receipt (n = 20; Figure 2). Inoculation with LAIV 7 days before pneumococcal infection led to immediate increases in the incidence of MEC, with only 30% (8 mice) remaining free from bacterial MEC 24 hours after infection; compared with 81% (21 mice) infected 1 day after LAIV receipt and 75% (15 mice) infected 1 day after PBS receipt. Following initial enhancement of MEC in mice infected 7 days after LAIV receipt, only 2 new cases (ie, cases in mice previously free from MEC) were seen over the following 2 weeks, at days 5 and 8 after bacterial infection.

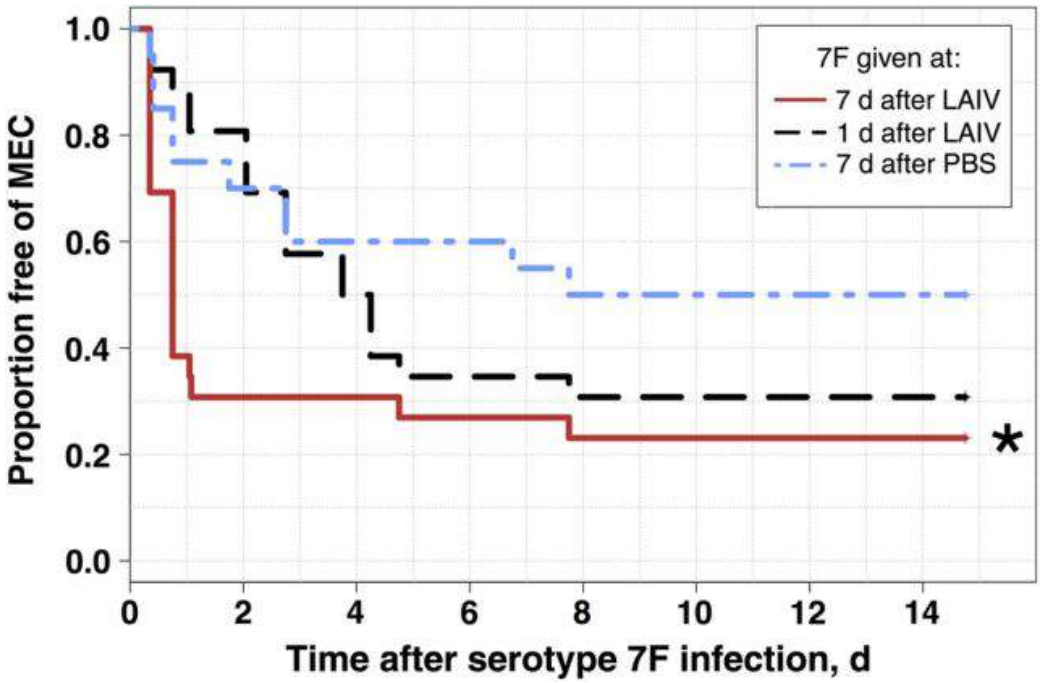

Figure 2.

Freedom from middle ear colonization (MEC) following bacterial infection in recently vaccinated mice. Groups of 8-week-old BALB/c mice received live attenuated influenza virus (LAIV) 7 days (n = 26), LAIV 1 day (n = 26), or phosphate-buffered saline (PBS) 1 day (n = 20) before inoculation with serotype 7F pneumococcal bacteria engineered to express luciferase. In vivo imaging was used to detect bacterial MEC every 12–15 hours for the first 2 days following pneumococcal infection and at least daily thereafter. Initial onset of pneumococcal MEC was recorded for each mouse, and Kaplan–Meier survival curves were constructed to describe freedom from pneumococcal MEC. ***P*** < .05, by the log-rank test, compared with PBS controls, corrected for multiple comparisons using the false-discovery rate.

An increased incidence of MEC was also detected in the group infected 1 day after LAIV receipt, but onset was distributed in this group, commencing between days 3 and 5 after infection, which corresponded to days 4–6 after LAIV receipt, a time previously demonstrated to maximize bacterial colonization of the nasopharynx [21].

LAIV-Mediated Enhancement of Bacterial Transmigration Is Delayed After Vaccination

To better understand the dynamics of bacterial transmigration and MEC, we investigated the overall frequency per day of MEC for each group (Figure 3), which differs from our Kaplan–Meier analysis above in that the Kaplan–Meier analysis considers only time of first onset in a given mouse, rather than overall proportion with MEC at any particular time in our experimental groups. Consistent with the Kaplan–Meier analysis, mice vaccinated 7 days before pneumococcal infection had significantly

increased frequencies of MEC for the first 24–48 hours after infection, compared with PBS controls. The frequency peaked in this group approximately 24 hours after infection, with slightly >60% (16 mice) with MEC. In contrast, only 20–30% of mice receiving LAIV or PBS 1 day before bacterial infection had evidence of MEC, and these episodes were very short lived, with almost no MEC in these groups by day 2. While the maximum frequency of MEC was reached 24 hours after infection in the group infected 7 days after LAIV receipt, mice infected only 1 day following LAIV receipt had a second wave of MEC episodes that began 4 days after LAIV receipt (Figure 3). This second wave of MEC, while lower in maximum frequency (approximately 40%) than in the group infected 7 days after LAIV receipt, had a broader and more sustained peak that lasted from day 4 to day 8 after bacterial infection.

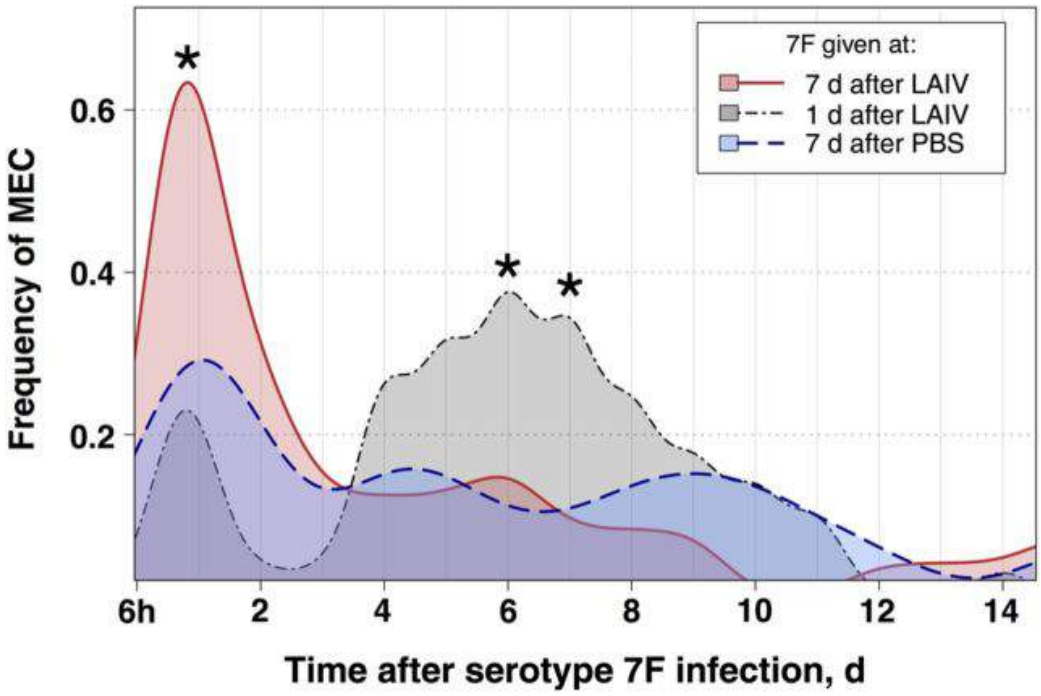

Figure 3.

Frequency of middle ear colonization (MEC) following bacterial infection in recently vaccinated mice. Mice were inoculated with live attenuated influenza virus (LAIV) 7 days (n = 26), LAIV 1 day (n = 26), or phosphate-buffered saline (PBS) 1 day (n = 20) before infection with serotype 7F pneumococcus engineered to express luciferase, and in vivo imaging of the middle ear was performed to measure the presence of pneumococcal MEC. The frequency of MEC is plotted for each group, and differences in the daily frequency between groups were tested for statistical significance using the Fisher exact test for differences in proportions. ***P*** < .05, compared with the PBS group.

LAIV Increases the Persistence of MEC

The duration of MEC was measured for each episode per mouse, as defined above, and mean durations were calculated for each group. The duration was significantly increased across all vaccinated groups, regardless of pneumococcal strain (ie, serotype 19F or 7F) or whether LAIV was given before or following pneumococcal infection. When LAIV or PBS was administered to mice with preestablished serotype 19F colonization, bacteria persisted in the middle ears nearly 2-fold longer than in PBS controls (2.3 vs 1.2 days; ***P*** < .05; Figure 4***A***). Similarly, when mice received LAIV 7 days or 1 day before bacterial infection, the mean durations of MEC episodes were 3-fold and 2-fold greater, respectively, than those for PBS controls (***P*** < .05 for each comparison; Figure 4***B***). Interestingly, when episodes were classified into early and late onset (see “Materials and Methods” section for classification criteria),

durations of early onset cases in the group infected 7 days after LAIV receipt were almost identical to durations of late-onset cases in the group infected 1 day after LAIV receipt (approximately 3.75 days in each group) and, in each case, the duration was >2-fold greater than that for their respective PBS controls (approximately 1.5 days; ***P*** < .05; Figure 4***C***). Alternatively, the duration of early onset episodes in the group infected 1 day after LAIV receipt and the duration of late-onset episodes in the group infected 7 days after LAIV receipt were no different than for PBS controls. Taken together with the findings of Kaplan–Meier analyses described above, these data demonstrate a strong influence of time since LAIV inoculation, rather than time since bacterial infection, with a minimum of 4 days after vaccination required before enhanced bacterial transmigration to and colonization of the middle ear is detected.

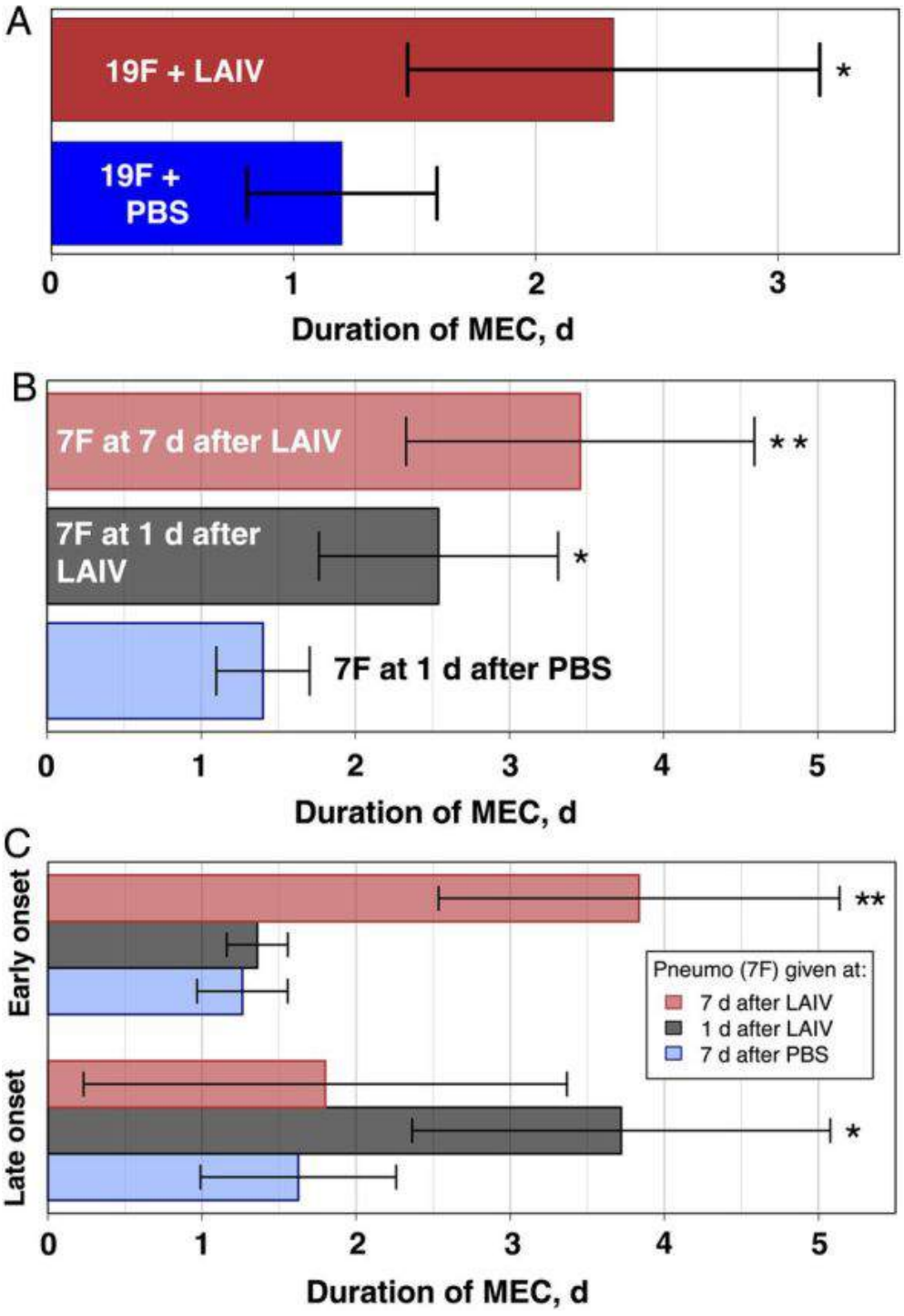

Figure 4.

Live attenuated influenza virus (LAIV) enhances persistence of middle ear colonization (MEC). ***A*** and ***B***, Groups of mice were colonized with serotype 19F pneumococcus 7 days before inoculation with LAIV (n = 14) or phosphate-buffered saline (PBS; n = 12; ***A***) or received LAIV 7 days (n = 26), LAIV 1 day (n = 26), or PBS 1 day (n = 20) before infection with serotype 7F pneumococcus (***B***). The durations of MEC episodes were measured, and mean durations reported for serotype 19F (***A***) and serotype 7F (***B***) MEC, in which a single episode was defined as any continuous detection in a given mouse that was not interrupted by >2 days. ***C***, Episodes of serotype 7F MEC were further classified as early onset (onset within the first 5 days following infection) or late onset (>2 days following termination of an early episode or >5 days after infection), and mean durations reported for each group. Statistically significant differences (vs PBS controls) were tested using 2-tailed 2-sample Student ***t*** tests with correction for multiple comparisons, using the false-discovery rate. Error bars represent 95% confidence intervals around the mean. ****P*** < .05, *****P*** < .001.

DISCUSSION

Go to:

The potent and often lethal effects of a previous influenza virus infection on secondary pneumococcal invasive disease and pneumonia have been reported [1, 11, 32–34]. Viral replication induced epithelial and mucosal degradation, and the ensuing innate immune response yield diminished capacity to avert secondary bacterial infections. Recent clinical and experimental data suggest that influenza viruses may exert their influence, beginning in the URT, by enhancing susceptibility to bacterial colonization [3, 30, 35], increasing nasopharyngeal carriage density [23], and enhancing the incidence of AOM [13].

Although LAIV, in the longer-term, thwarts influenza virus and bacterial coinfections by inhibiting the viral infection [18, 31], LAIV vaccines have recently been found to enhance the density and duration of bacterial colonization within the nasopharynx of mice, and evidence has also been put forth for humans [21, 22, 36]. Importantly, unlike WT IAV, LAIV did not result in increased bacterial proliferation or disease in the LRT, presumably because of the temperature-sensitive nature of LAIV viruses, abrogating viral growth within the warmer temperatures of the lungs. Although LAIV did not effect clinical bacterial LRT infections, the effects of LAIV on transition from colonization to bacterial disease within the URT, a region where LAIV replicates efficiently, had not been studied.

Here, we found that vaccination with a mouse-adapted LAIV significantly increased bacterial transmigration to the middle ear and the duration of MEC, irrespective of bacterial serotype or order of viral versus bacterial inoculation. Interestingly, a minimum period of approximately 4 days was required before enhancement in pneumococcal transmigration and MEC was noted, when LAIV preceded pneumococcal infection.

The dynamics of increased MEC, with regard to time since vaccination, closely match increased pneumococcal colonizing dynamics of the nasopharynx following WT IAV or LAIV virus [21, 31] and support the notion that nasopharyngeal colonizing density may be associated with progression to AOM. Interestingly, the delay in increased onset of migration and MEC in mice vaccinated only 1 day before bacterial inoculation was approximately the same as the time to peak LAIV viral titers in the URT [21]. Thus, a majority of excess MEC occurs during or soon after viral clearance from the URT. This finding supports numerous reports [1, 10–12, 23] that point toward a complex coupling of poorly coordinated antibacterial innate immune defenses and epithelial damage following influenza virus infection, underlying the excess susceptibility to bacterial disease after influenza virus infection.

On the other hand, the steady increase in onset of MEC measured immediately following LAIV vaccination in serotype 19F–precolonized mice suggests that introduction of LAIV virus in the presence of existing bacterial colonization yields enhanced MEC that is concurrent with viral replication and precedes viral-mediated enhanced nasopharyngeal colonization, which tend to increase beginning on day 4 after LAIV inoculation. This suggests that the mechanisms of virus-induced bacterial AOM may differ according to order of inoculation. Indeed, it may be that even low levels of viral replication in the URT, while not immediately affecting overall bacterial carriage density in the nasopharynx, may rapidly

disrupt a delicate balance that naturally exists to prevent asymptomatic carriage from transitioning to bacterial AOM.

It must be clearly emphasized here that any animal study, particularly mouse studies [37], must be viewed in light of the many caveats that exist when extrapolating findings from animal studies to humans. Although animal studies have been integral to our understanding of infectious diseases (and many other biological systems), the individual processes and dynamics often differ between the animal model—mice, in this case—and the human system, as has been shown [37].

While our data suggest that LAIV may enhance pneumococcal transmigration into the middle ear, it is clear that the overall effect of LAIV measured in humans has been that of significant reductions in viral influenza infections and otitis media [38]. While our data suggest a potential effect of LAIV to increase bacterial transmigration to the middle ear, a lack of detection in numerous large clinical trials in humans suggests that any effect is largely subclinical. As well, LAIV-mediated protection from primary influenza virus infections significantly reduces the opportunity for worse secondary bacterial infections [20], further reducing the incidence of LRT and URT bacterial disease, including bacterial AOM.

While we are confident that the overall effects of LAIVs are beneficial to reduce all-cause AOM across populations, as has been reported [39], our data here and previous reports [21] suggest a need for future investigations to more closely evaluate the effects of LAIV on bacterial respiratory pathogen dynamics, including unintended beneficial effects [20]. Indeed, as medicine becomes increasingly personalized [40], it may become possible to tailor classes of vaccines and avenues of vaccine delivery to the individual. In this particular example, considering the benefits of LAIV over inactivated injectable influenza vaccines [41], one could envision that the choice between a killed injectable vaccine and an intranasal LAIV might incorporate the risk of pneumococcal carriage or acquisition (based on factors such as the number of children in the household, the age of the vaccine recipient, and proximity to immunocompromised individuals) as a potential variable in the decision-making process.

Supplementary Data

Go to:

Supplementary materials are available at ***The Journal of Infectious Diseases*** online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Supplementary Data:

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Notes

Go to:

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Effect of pneumococcal conjugate vaccine on nasopharyngeal bacterial colonization during acute otitis media.

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Abstract

The heptavalent pneumococcal conjugate vaccine (PCV7) has been shown to reduce the incidence of acute otitis media (AOM) caused by Streptococcus pneumoniae by 34% and reduces the overall incidence of AOM by 6% to 8%. More recent studies have shown increases in the proportion of Haemophilus influenzae and Moraxella catarrhalis in the middle-ear fluid of PCV7-immunized children. There has been no report on the effect of PCV7 on all 3 bacterial pathogens combined, either in the middle-ear fluid or nasopharynx of individual children with AOM. We investigated the impact of PCV7 on nasopharyngeal colonization with bacterial pathogens during AOM in the pre-PCV7 and post-PCV7 vaccination eras. Four hundred seventeen children (6 months to 4 years of age) were enrolled onto AOM studies between September 1995 and December 2004. Of these, 200 were enrolled before the vaccine use (historical controls), and 217 were enrolled after the initiation of PCV7 vaccination (101 were underimmunized, and 116 were immunized). Although the nasopharyngeal colonization rate for S pneumoniae was not different between the 3 groups, a significantly higher proportion of PCV7-immunized children with AOM were colonized with M catarrhalis. Overall, the mean number of pathogenic bacteria types isolated from immunized children (1.7) was significantly higher than in controls (1.4). The increase in bacterial colonization of the nasopharynx during AOM could be associated with an increase in AOM pathogens and theoretically can predispose PCV7-immunized children with AOM to a higher rate of antibiotic treatment failure or recurrent AOM.

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[Indexed for MEDLINE]

Science News from research organizations

Children Who Get Flu Vaccine Have Three Times Risk Of Hospitalization For Flu, Study Suggests

Date: May 20, 2009

Source: American Thoracic Society

Summary: The inactivated flu vaccine does not appear to be effective in preventing influenza-related hospitalizations in children, especially the ones with asthma. In fact, children who get the flu vaccine are more at risk for hospitalization than their peers who do not get the vaccine, according to new research. While these findings do raise questions about the efficacy of the vaccine, they do not in fact implicate it as a cause of hospitalizations, according to researchers.

FULL STORY

The inactivated flu vaccine does not appear to be effective in preventing influenza-related hospitalizations in children, especially the ones with asthma. In fact, children who get the flu vaccine are more at risk for hospitalization than their peers who do not get the vaccine, according to new research that will be presented on May 19, at the 105th International Conference of the American Thoracic Society in San Diego.

Flu vaccine (trivalent inactivated flu vaccine—TIV) has unknown effects on asthmatics.

"The concerns that vaccination maybe associated with asthma exacerbations have been disproved with multiple studies in the past, but the vaccine's effectiveness has not been well-established," said Avni Joshi, M.D., of the Mayo Clinic in Rochester, MN. "This study was aimed at evaluating the effectiveness of the TIV in children overall, as well as the children with asthma, to prevent influenza-related hospitalization."

The CDC's Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend annual influenza vaccination for all children aged six months to 18 years. The National Asthma Education and Prevention Program (3rd revision) also recommends annual flu vaccination of asthmatic children older than six months.

In order to determine whether the vaccine was effective in reducing the number of hospitalizations that all children, and especially the ones with asthma, faced over eight consecutive flu seasons, the researchers conducted a cohort study of 263 children who were evaluated at the Mayo Clinic in Minnesota from six months to 18 years of age, each of whom had had laboratory-confirmed influenza between 1996 to 2006. The investigators determined who had and had not received the flu vaccine, their asthma status and who did and did not require hospitalization. Records were reviewed for each subject with influenza-related illness for flu vaccination preceding the illness and hospitalization during that illness.

They found that children who had received the flu vaccine had three times the risk of hospitalization, as compared to children who had not received the vaccine. In asthmatic children, there was a significantly higher risk of hospitalization in subjects who received the TIV, as compared to those who did not ($p = 0.006$). But no other measured factors—such as insurance plans or severity of asthma—appeared to affect risk of hospitalization.

"While these findings do raise questions about the efficacy of the vaccine, they do not in fact implicate it as a cause of hospitalizations," said Dr. Joshi. "More studies are needed to assess not only the immunogenicity, but also the efficacy of different influenza vaccines in asthmatic subjects."

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Case Report

Haemophilus influenzae Type b Meningitis in the Short Period after Vaccination: A Reminder of the Phenomenon of Apparent Vaccine Failure

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We present two cases of bacterial meningitis caused by *Haemophilus influenzae* type b (Hib) which developed a few days after conjugate Hib vaccination. This phenomenon of postimmunization provocative time period is reviewed and discussed. These cases serve as a reminder to clinicians of the risk, albeit rare, of invasive Hib disease in the short period after successful immunization.

1. Introduction

Haemophilus influenzae type b (Hib) was the leading cause of bacterial meningitis in children worldwide until the introduction of the Hib conjugate vaccine in the early 1990s [1]. Since then, the incidence of Hib disease has declined dramatically in high-income countries and virtually eliminated in parts of the United States and Europe [1].

In 1994, the Hib-conjugated vaccine was introduced into the Israeli National Immunization Program. In 1997, a four-dose vaccine schedule was adopted, given at 2, 4, 6, and 12 months of age. Prospective surveillance estimated that vaccine effectiveness was 95% (95% CI 92–96%) against any invasive disease and 97% (95% CI 93–98%) against bacterial meningitis [2].

Nevertheless, over the past 20 years, there have been some reports of invasive Hib disease within a short period after administration of the vaccine [3–5]. This report describes two children in whom Hib meningitis developed a few days after vaccination. These cases serve as a reminder for clinicians of a phenomenon of elevated risk for infection and apparent vaccine failure in the short period after Hib immunization.

2. Case Reports

2.1. Case 1. A 10-week-old girl presented to another hospital with fever, refusal to eat, grunting respirations, and hypertonicity of 48-hour duration. All symptoms began one day after she had received the first dose of the combination Infanrix-IPV+Hib vaccine (a combined vaccine against diphtheria, tetanus, pertussis, polio, and Hib infections). Her parents reported that she had been perfectly healthy the day before vaccination.

Past medical history revealed that the patient had been born at 31 weeks' gestation after premature rupture of the membranes; maternal fever was documented during delivery. She was hospitalized in the neonatal intensive care unit and treated with empiric antibiotics for 3 days pending blood culture results. The rest of her hospitalization was uneventful, and she was discharged at the age of 5 weeks in good medical condition.

At the present admission to the other hospital, bacterial meningitis was suspected on the basis of abnormal cerebrospinal fluid (CSF) cell count (2358/mm^3, with neutrophil predominance 60%), protein, and glucose (235 mg/dL, 1 mg/dL, resp.) despite negative findings on

direct microscopy of a CSF sample. Empiric treatment with ceftriaxone, vancomycin, and dexamethasone was started. Two days later, both blood and CSF cultures grew *Haemophilus influenzae*, which was identified as type b using latex agglutination-based antigen detection test. The patient's clinical status gradually improved over the next 4 days, when a secondary fever was noted in addition to new-onset seizures. Treatment with phenobarbital was initiated, and the patient was transferred to our tertiary medical center.

At admission to our department, magnetic resonance imaging (MRI) study revealed subdural fluid collections in the posterior fossa and around the hemispheres. Given the patient's clinical and neurological deterioration as well as the high levels of inflammatory markers, a tentative diagnosis of subdural empyema was made. The patient was transferred to the neurosurgery department where she underwent bilateral craniotomy. Findings included a subdural empyema with severe brain edema. The empyema was drained. The antibiotic treatment was continued and combined with anticonvulsant and supportive treatment, leading to gradual improvement.

The patient was discharged from our institute after 20 days, during which she received ceftriaxone. On her discharge, she was clinically stable and had normal findings on neurologic examination except for mild hypertonicity of the left arm and mild left torticollis. On follow-up visits, 2 months later and at age 1 year, brainstem-evoked response audiometry (BERA) was within normal range. There was a mild global developmental delay with normal findings on neurologic examination.

2.2. Case 2. A 5-month-old boy presented to our hospital with fever, apathy, vomiting, and diarrhea of 24-hour duration. All symptoms began 6 days after he received the second dose of the Infanrix-IPV+Hib vaccine. His parents reported that he had been perfectly healthy on the day before vaccination.

Past medical history was unremarkable. The patient was born after a normal term pregnancy and vaginal delivery. He received the first dose of Infanrix-IPV+Hib vaccine at age of 2 months without adverse events.

At admission, the patient was febrile and apathetic, with grunting respiration and a bulging fontanel. Lumbar puncture revealed a white blood cell count of 4,000 cells/mm^3, 95% segmented neutrophils, and glucose level of 8.4 mg/dL (protein level was not calculated because of technical problem). Gram staining of the CSF was negative. Empiric treatment with ceftriaxone, vancomycin, and dexamethasone was started. After 36 hours, blood culture grew *Haemophilus influenzae*, which was later identified as type b using latex agglutination-based antigen detection test.

Over the next days, the patient continued treatment with ceftriaxone, with gradual improvement. BERA study was normal. He was discharged home after 11 days in excellent condition, with no neurologic deficits.

3. Discussion

The Hib vaccine targets the organism's capsular polysaccharide, polyribosylribitol phosphate (PRP). To increase immunogenicity and induce immune memory, several conjugate vaccines were developed through covalent linkage of PRP to a carrier protein. Four conjugated vaccines were found safe and were introduced into routine immunization programs worldwide [1].

While the introduction of conjugate vaccine against Hib has had a substantial impact on Hib infection, over the past 20 years, sparse reports of cases of invasive disease after Hib vaccination have been published [3–5]. Booy et al. [3] investigated all cases of invasive Hib infection that occurred over a 3-year period in children in the United Kingdom after they received at least one dose of the Hib-conjugate vaccine. They identified two kinds of vaccine failures: apparent (early) and true (late). True failures were defined as Hib invasive disease occurring either >1 week after a child up to the age of 12 months received at least two doses of the vaccine, or >2 weeks after a single dose was received by a child >12 months of age. Hib invasive infections that occurred within one week after the administration of one or two doses of vaccine were considered apparent vaccine failures. Thus, in the present report, both cases represent apparent (early) vaccine failures.

The "apparent vaccine failure" was a known phenomenon of the early polysaccharide vaccine [6], but relatively rare when attributed to conjugate vaccine. In Booy's work [3], they reported of 46 apparent vaccine failures out of the 164 cases of invasive disease among the entire population of United Kingdom vaccinated children. Singleton et al. reviewed data from Alaska's Statewide Disease Surveillance conducted during 1980–2004 [4]. Study population included 103,000 children younger than 10 years of age. They reported of 3 early vaccine failures out of 44 cases of invasive disease in immunized children. Cowgill et al. reviewed hospitalization data of a main district hospital in Kenya and reported of 24 cases of invasive disease in immunized children, 12 of them early failures [5].

Already in 1901, Wright [7] coined the term "negative phase" to describe the decrease in bactericidal activity; he observed 1 to 21 days after administration of typhoid vaccine. This phenomenon of postimmunization provocative disease was also confirmed in early studies of conjugated and unconjugated Hib vaccines which reported that subjects with preexisting anticapsular antibodies showed a decrease in antibody concentrations after immunization [8, 9]. The nadir in antibody decline was reached 2-3 days after immunization, and concentrations normalized by day 7. The magnitude of the decline was negatively correlated with the preimmunization concentration [9]. This decrease is presumed to occur with all 4 available Hib conjugate vaccines [9]. Some authors attributed these findings to the formation of a complex between the vaccine antigens and the preexisting serum antibodies, which induces a transient decline in antibody concentration [10]. This could pose a risk of invasive disease if it occurs during a period of asymptomatic colonization with Hib [10].

In order to understand whether the individual having received the Hib vaccine is adequately protected against the organism, the level of anti-PRP antibodies should be assessed. The exact mechanism underlying the invasive infection in our patients could not be determined because

the concentration of Hib antibodies was not measured in either case before or after immunization. However, these cases are reported to serve as a reminder to clinicians of the risk, albeit rare, of invasive Hib disease in the short period after successful immunization. Clinicians should bear this possibility in mind when starting empiric antibiotic treatment in children who present with signs of infection within a week of receiving the vaccine. Large-scale studies that focus on this time frame are still needed.

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Vaccines linked to mental disorders by Yale study

KEVIN WANG | 1:18 AM, FEB 21, 2017
STAFF REPORTER

A recent Yale study has called into question the safety of vaccines and could lend fuel to anti-vaccine advocates like Robert F. Kennedy Jr., who has already written a piece covering the study on the news site EcoWatch.

The study, published last month in the journal Frontiers in Psychiatry, reports that patients diagnosed with neuropsychiatric disorders like obsessive-compulsive disorder and anorexia nervosa were more likely to have received vaccinations three months prior to their diagnoses. Though the collaboration between researchers at Pennsylvania State University and the Yale Child Study Center yielded results that seem to dispute the safety of vaccines, the authors asserted that the study needs replication on a larger scale and does not establish a causal relationship between vaccines and neuropsychiatric disorders.

"There's a fair amount of interest in the vaccine safety question, so let's try to be critical and do further studies that will help examine this issue in a more thorough way," said James Leckman, professor of pediatrics and one of the study's five authors.

Using information from a health insurance claims database, Leckman and his co-authors examined the correlations between specific vaccines and various neurological disorders in six- to 15-year-old children. Children with open wounds and broken bones were used as the two control groups.

While only about 10 percent of children with open wounds had received vaccinations, vaccines had been given to over 20 percent of children later diagnosed with anorexia. Higher numbers of vaccinated children were also found among those who were diagnosed with OCD, anxiety disorder and ADHD as soon as three months after their vaccinations.

Other findings in the study, however, reveal that these correlational results should be taken with a grain of salt.

The broken bone control group also included a higher percentage of vaccinated children, though not as high as that of the anorexia group. Furthermore, vaccinations were more likely to be associated with a lower incidence of major depression and bipolar disorder.

The researchers found correlations for one vaccine in particular: the influenza vaccine, which was associated with higher rates of OCD, anorexia, anxiety disorder and tic disorder.

A biological explanation for these correlations has not been found, but a potential mechanism could lie in the body's immune response to vaccines, the study suggested.

Vaccines work by prodding the immune system to produce antibodies against viruses and bacteria, thus priming the body against these pathogens before they enter it. Some antibodies, however, can react against not only the intended pathogen proteins, but also against human proteins — a phenomenon called cross-reactivity. A 2015 study published in Science Translational Medicine discovered that antibodies elicited by the Pandemrix influenza vaccine cross-reacted with a human brain protein — hypocretin receptor 2.

Autoimmunity, in which antibodies attack human proteins, is also known to play a critical role in normal brain development, Leckman noted. According to Leckman, if children were experiencing inflammation — a process that promotes autoimmunity — at the time of vaccination, the combination of inflammation and vaccination could have deleterious effects on brain development. Such data on vaccination timing was not included in the database on which the study was based.

Another biological explanation could involve genetic factors, Leckman said. Prior studies in Scandinavian countries and China found that the H1N1 influenza vaccine was associated with narcolepsy. The influence of multiple genes found in specific populations could be responsible, he added.

Yale professor of pathology John Rose suggested that the act of vaccine administration, rather than the vaccine itself, could even have an effect on neuropsychiatric development, recalling his childhood experience of being one of the first children to receive the polio vaccine.

"We had to line up in school, and we were getting needles stuck in our arms," Rose said. "That kind of trauma could be leading to these kinds of neuropsychiatric disease. The age range of the children in the study is quite sensitive."

Rose, who developed a vaccine template that was used for the development of the current Ebola vaccine, said he trusts the current process of drug development to establish safety measures for vaccines. On average, a vaccine takes 15–20 years to be fully approved, Rose said.

Leckman said the accuracy of the diagnoses reported by the administrative database could also be questioned.

John Treanor, chief of infectious diseases at the University of Rochester Medical Center, voiced concerns about the database, citing issues of immeasurable confounding variables and the extent to which the control groups actually serve as effective controls. Nevertheless, he emphasized the importance of vaccine safety and further research to understand it.

Rose expressed concern that the study would "activate anti-vaccine people in a very serious way" and agreed with the study's assertion that the results are very preliminary and do not establish a cause and effect relationship. Animal models, Leckman noted, could help establish such a cause and effect relationship by allowing researchers to manipulate and control for multiple variables.

Even the authors noted that the results of the study are too inconclusive to warrant any reconfiguration of public health strategies.

"Given the modest magnitude of these findings in contrast to the clear public health benefits of the timely administration of vaccines in preventing mortality and morbidity in childhood infectious diseases, we encourage families to maintain vaccination schedules according to [the Centers for Disease Control and Prevention] guidelines," they wrote in the study.

Format: Abstract

Full text links

Front Psychiatry. 2017 Jan 19;8:3. doi: 10.3389/fpsyt.2017.00003. eCollection 2017.

Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study.

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Author information

Abstract

BACKGROUND: Although the association of the measles, mumps, and rubella vaccine with autism spectrum disorder has been convincingly disproven, the onset of certain brain-related autoimmune and inflammatory disorders has been found to be temporally associated with the antecedent administration of various vaccines. This study examines whether antecedent vaccinations are associated with increased incidence of obsessive-compulsive disorder (OCD), anorexia nervosa (AN), anxiety disorder, chronic tic disorder, attention deficit hyperactivity disorder, major depressive disorder, and bipolar disorder in a national sample of privately insured children.

METHODS: Using claims data, we compared the prior year's occurrence of vaccinations in children and adolescents aged 6-15 years with the above neuropsychiatric disorders that were newly diagnosed between January 2002 and December 2007, as well as two control conditions, broken bones and open wounds. Subjects were matched with controls according to age, gender, geographical area, and seasonality. Conditional logistic regression models were used to determine the association of prior vaccinations with each condition.

RESULTS: Subjects with newly diagnosed AN were more likely than controls to have had any vaccination in the previous 3 months [hazard ratio (HR) 1.80, 95% confidence interval 1.21-2.68]. Influenza vaccinations during the prior 3, 6, and 12 months were also associated with incident diagnoses of AN, OCD, and an anxiety disorder. Several other associations were also significant with HRs greater than 1.40 (hepatitis A with OCD and AN; hepatitis B with AN; and meningitis with AN and chronic tic disorder).

CONCLUSION: This pilot epidemiologic analysis implies that the onset of some neuropsychiatric disorders may be temporally related to prior vaccinations in a subset of individuals. These findings warrant further investigation, but do not prove a causal role of antecedent infections or vaccinations in the pathoetiology of these conditions. Given the modest magnitude of these findings in contrast to the clear public health benefits of the timely administration of vaccines in preventing mortality and morbidity in childhood infectious diseases, we encourage families to maintain vaccination schedules according to CDC guidelines.

KEYWORDS: anorexia nervosa; anxiety disorder; influenza; meningococcus; obsessive–compulsive disorder; tic disorder; vaccination

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Nonfebrile Seizures after Mumps, Measles, Rubella, and Varicella-Zoster Virus Combination Vaccination with Detection of Measles Virus RNA in Serum, Throat, and Urine

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ABSTRACT

Go to:

We report the case of a child presenting with nonfebrile seizures 6 and 13 days after the first vaccination with a measles, mumps, rubella, and varicella (MMRV) combination vaccine. Measles virus RNA was detected in the patient's serum, throat, and urine. Genotyping revealed the Schwarz vaccine virus strain.

CASE REPORT

Go to:

An 11-month-old boy was presented to the pediatric unit after experiencing three seizures in the morning of the same day. The seizures were initiated by a sharp outcry with symmetric tonic-clonic movement of the arms and legs. During the seizures, the child was not reacting to his mother and had cyanotic lips. Seizures stopped spontaneously, without the administration of anticonvulsants, after approximately 1 to 2 min. Immediately after the seizures, body temperature, as measured by the mother as well as by the emergency physician, was not elevated (37.3°C). Upon admission, the child was sleepy but conscious and without signs of meningitis. The child had a slight rash on his trunk and pale skin color; otherwise, the clinical examination was unremarkable.

There was no history of seizures before or any other known medical conditions. Six days before the seizure, the first vaccination with the regular measles, mumps, rubella, and varicella (MMRV) vaccine (Priorix-Tetra; GlaxoSmithKline) was performed. In the meantime, there were no signs of infection or fever. All blood parameters on admission were unremarkable except slight leukopenia of 4.3×10^3/μl (normal range, 6.0×10^3 to 17.0×10^3/μl). All values determined by testing the cerebrospinal fluid (CSF) taken on admission were within the range of normal (CSF protein, 221 mg/liter [normal range, 150 to 450 mg/liter]; glucose, 64 mg/dl [normal range, 50 to 75 mg/dl]; lactate, 1.4 mmol/liter [normal range, 1.2 to 2.1 mmol/liter]; leukocyte count, 2 cells/μl [normal, <4 cells/μl]; erythrocyte count, 0 cells/μl [normal, 0/μl]). CSF tested negative by PCR or reverse transcription (RT)-PCR for herpes simplex viruses 1 and 2, varicella-zoster virus, rubella virus, mumps virus, and measles virus (MeV) (Table 1). A cranial magnetic resonance scan revealed no pathological findings. In a blood sample and a throat swab taken upon admission as well as in a urine sample collected the following day, MeV RNA was detected by real-time RT-PCR by amplifying a 114-nucleotide fragment of the MeV nucleoprotein N gene.

Table 1

Detection of measles, mumps, rubella, herpes simplex viruses 1 and 2, and varicella-zoster virus by PCR or RT-PCR in serum, throat swab, urine, and CSF

RNA or DNA[a]	Detection of RNA or DNA in clinical specimens[b]			
	Serum[c]	Throat swab[c]	Urine[d]	CSF[d]
Measles virus RNA	+; <1,000 copies/ml	+; 5.81×10^5 copies/ml	+; <1,000 copies/ml	–
Mumps virus RNA	–	–	–	–
Rubella virus RNA	–	–	–	–
Herpes simplex virus 1 and 2 DNA	–	–	–	–
Varicella-zoster virus DNA	–	–	–	–

[a]Primers and protocols are available upon request.
[b]+, detection of viral genome; −, viral genome not detected.
[c]Specimen collected 6 days postvaccination.
[d]Specimen collected 7 days postvaccination.

Viral concentration was low in serum and urine but remarkably higher in the throat swab. Genotyping by amplification of a total of 507 nucleotides of the variable genomic region of the MeV nucleoprotein N gene was performed by using one nested and two heminested PCRs and revealed an MeV genotype A virus. The amplified sequence included the 450 nucleotides encoding the C-terminal 150 amino acids of the MeV nucleoprotein N; this is the minimum amount of data required for determining the MeV genotype, as recommended by the WHO (1). The MeV nucleotide sequence was identical to that of the Schwarz MeV vaccine strain (Fig. 1).

Fig 1

Strategy for identification and genotyping of the measles virus (MeV). (A) Scheme of the MeV genome. The conserved and variable regions used for MeV virus screening and genotyping, respectively, are indicated with arrows. (B) Comparison of the nucleotide sequence for the 507-bp MeV genome fragment obtained from the case patient by the genotyping RT-PCRs (upper rows) and the sequence of the Schwarz MeV vaccine strain (lower rows) (GenBank accession no. FJ211590) using the BLAST algorithm (http://www.ncbi.nlm.nih.gov/blast). Numbers before and after each row refer to the nucleotide position of the respective nucleotide sequence. The minimum requirement for MeV genotyping as defined by WHO within the sequenced genome fragment is indicated in blue.

No IgG antibodies against measles, mumps, and rubella viruses were detectable upon admission (detection of MeV antibodies was performed by IgG and IgM enzyme-linked immunosorbent assay [ELISA; Enzygnost anti-measles virus/IgG

and Enzygnost anti-measles virus/IgM; Siemens Healthcare Diagnostics, Eschborn, Germany]).

After an unremarkable hospital course, a fourth seizure episode occurred on the 13th day after the vaccination, while the child was still in the hospital. While the seizures did not fulfill all criteria of a provoked seizure due to the absence of fever, anti-epileptic treatment with levetiracetam was started. The remaining course of hospitalization was uneventful, and the child was discharged on the 9th day of hospitalization in good health. Temperature was measured regularly during the complete course of disease and was elevated only once, up to 38.3°C, on the 3rd day of hospitalization; however, no seizure was observed in association with this episode.

Regular follow-up visits have not revealed any signs of epilepsy so far, and now, more than 1 year after the vaccination, the child remains well. The therapy with levetiracetam was continued without any side effects. In a blood sample taken 3 months after the vaccination, high antibody values against mumps, measles, and rubella viruses were found, but no antibodies against varicella-zoster virus could be detected.

MeV is one of the most contagious infectious diseases in humans and among the leading causes of death in children (2). Vaccination with live attenuated measles vaccine is the most effective measure for control and eradication (3, 4). Most vaccines used today are based on the Schwarz vaccine strain (genotype A) (5).

Fever is the most common complication of immunization and occurs most often after administration of live attenuated vaccines, toxin-containing vaccines, or whole-cell preparations (6). Adverse events after vaccination against measles, mumps, rubella, and varicella are generally mild. Besides a local reaction at the site of injection, fever, and rash, the most common neurologic adverse events are febrile seizures, commonly 7 to 10 days after vaccination (7, 8). Febrile seizures in general have a favorable outcome and are not associated with neurologic sequelae. While a higher risk for febrile seizures was observed with the MMRV combination vaccine than with the MMR vaccine (8), nonfebrile seizures in association with MMRV or MMR vaccination have not been described so far.

Therefore, a search was performed in the database of the German Federal Institute for Vaccines and Biomedicines (Paul Ehrlich Institute [PEI], Langen, Germany), which collects and evaluates the reports of adverse events, and two further cases were revealed. In the first case, a 9-year-old male experienced convulsions leading to hospitalization 14 days after he had received the second dose of MMRV (MMRVaxPro; Sanofi Pasteur MSD). His symptoms resolved (the duration of symptoms was unspecified), and the patient was discharged after 2 days of hospitalization. The second case was an 11-month-old female who presented with a tonic-clonic seizure, allergic reaction, and exanthema 1 day after having received an unspecified dose of MMRV (Priorix-Tetra; GlaxoSmithKline) on 10 February 2011. Further seizures without fever in the same child occurred on two more occasions, two and three days after having received vaccinations on 14 March 2011 against diphtheria, tetanus, pertussis, Haemophilus influenzae type b, hepatitis B, poliomyelitis (Infanrix hexa; GlaxoSmithKline), and Streptococcus pneumoniae (Synflorix; GlaxoSmithKline), without any further pathological findings noted in the hospital report. So far, it is not possible based on these cases to assess a causal relationship between nonfebrile seizures and vaccination. Further awareness is necessary to evaluate whether nonfebrile seizures temporally associated with vaccine exposure have to be considered a potential adverse effect. However, it should be stressed that all children with seizures, either febrile or nonfebrile, had a favorable outcome according to available follow-up data.

Even though live attenuated measles vaccines have been used for more than 40 years, data are scarce on the extent to which vaccine virus replicates in or is shed by vaccinees (5). Isolation of infectious vaccine virus from the blood and pharynx of vaccinated children by propagation on canine renal cell culture was successfully performed in early studies with the Edmonston strain (9), from experimentally vaccinated Cynomolgus monkeys after vaccination with the Schwarz vaccine strain (10), and in a study evaluating fever and rash appearing 3 to 9 days after measles vaccination (11). In this study, in 6 of 7 children, wild-type virus was isolated from peripheral blood leukocytes or throat swabs, suggesting vaccination during the incubation period of wild-type MeV. In only 1 of 7 patients, vaccine virus (strain Handai) was isolated from blood leukocytes, and this child had the mildest clinical course (mild fever without rash appearing on day 7 after vaccination) (11). It is not stated in the above-mentioned study if the children, in whom Edmonston vaccine virus isolation was achieved, presented with any symptoms or were asymptomatic (9). Further, Edmonston vaccine virus RNA was detected by RT-PCR 13 days after vaccination in the serum of an HIV-positive, 1-year-old boy who presented with measles-like illness 10 days after MMR vaccination (12).

For the Schwarz vaccine strain, there are two case reports about healthy children that describe demonstration of vaccine virus in the throat of a 3-year-old boy (13) and detection of vaccine virus RNA in the throat and urine of a 14-month-old child (14). The first child presented with fever, pharyngitis, and adenopathy 8 days after vaccination. MeV was isolated in cell culture from a throat swab taken 4 days after fever onset. The 14-month-old child in the second case report presented with facial erythema without fever 5 days after vaccination, followed by fever and rash 8 days after vaccination. MeV RNA was detected by RT-PCR from a throat swab taken 5 days and from a urine sample taken 6 days after the onset of fever. In both children, the virus RNA could be characterized as the Schwarz strain, and both children had a favorable follow-up. Taken together, the results from the three reports, including ours, show that Schwarz vaccine strain RNA is present in blood at least at day 6 postvaccination and is detectable in throat and urine at days 7 to 15 postvaccination. However, the clinical relevance

of detection of vaccine virus or its RNA from the different body compartments, if any, remains unclear. To the best of our knowledge, so far there are no reports of transmission of vaccine measles virus.

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Go to:

We thank the mother of the child for giving her informed consent and allowing us to report the details of this case. We also thank Ulrike Reber for excellent technical assistance.

We report no conflicts of interest.

FOOTNOTES

Go to:

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Journal of Medical Case Reports

CASE REPORT Open Access

Optic neuritis following diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccination: a case report

Preston O'Brien[1*] and Robert W. Wong[1,2*]

Abstract

Background: Diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccine is widely used in young children as part of a series of immunizations before they start attending school. Case studies of demyelinating conditions following administration of diphtheria, tetanus, pertussis, and polio vaccine have been reported, but none so far resulting in optic neuritis. This report further contributes to the database of central nervous system demyelinating conditions affiliated with receipt of vaccines.

Case presentation: A previously healthy 27-year-old Hispanic man presented to an emergency department with headache, periorbital pressure, pain with ocular movements, and intermittent blurred vision that developed 1 day after administration of the diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccine. A diagnosis of optic neuritis was made via ophthalmic examination with fundus photography and automated Humphrey visual field analysis. His vision recovered following treatment with high-dose intravenously administered methylprednisolone followed by a tapered dose of orally administered prednisolone.

Conclusions: Although the association between immunizations and the onset of central nervous system demyelinating conditions is well documented, this report, to the best of our knowledge, is the first case of optic neuritis following diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccination. Inclusion of this case report in the medical community will allow for broader understanding of possible conditions that may present shortly after receipt of vaccination.

Keywords: Diphtheria, Tetanus, Pertussis, Virus, Optic neuritis

Background

Diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccine (DTaP-IPV) is widely used in young children as part of a series of immunizations before they start attending school. Although clinical trials have shown an excellent safety profile [1], there have been reports of encephalitis, angioneurotic edema, seizures, and serious local reactions following its administration [1, 2]. Although cases of central nervous system (CNS) demyelinating conditions following DTaP-IPV vaccine have been reported [3], to the best of our knowledge, we present the first case of optic neuritis.

Case presentation

A 27-year-old Hispanic man with no significant past medical history presented to an emergency department with a 5-day history of headache, pain with ocular movements, and intermittent blurred vision starting 1 day after being immunized with DTaP-IPV. Magnetic resonance imaging and a magnetic resonance venogram of his brain were unremarkable. A lumbar puncture revealed a normal opening pressure and cerebrospinal fluid studies were positive for

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It is our aim with the submission of this case report to the *Journal of Medical Case Reports* to present a new association between receipt of the diphtheria, tetanus, pertussis, and inactivated poliovirus combined vaccine by our patient and his presenting with optic neuritis. It is important that we make efforts to ensure that the medical community is aware of potential central nervous system demyelinating conditions coinciding with receipt of vaccines so that they can follow the observations, treatment, and precautions in dealing with similar circumstances.
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myelin basic protein but negative for oligoclonal bands and neuromyelitis optica autoantibody serology.

On examination, his best corrected vision was 20/100 in his right eye and 20/70 in his left eye. Intraocular pressures, pupil examination, ocular alignment, and extraocular movements were normal. Confrontational visual fields were restricted in both eyes. Posterior segment examination showed optic nerve swelling and hyperemia in both eyes (Fig. 1) and two microaneurysms in the mid periphery of his left eye. No evidence of vitritis, retinal vasculitis, or choroiditis was seen in either eye.

Serum laboratory testing showed elevated glycated hemoglobin (A1C) at 6.9%, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Other liver tests including bilirubin, alkaline phosphatase, and hepatitis serologies were normal. Tests for infectious and inflammatory etiologies including angiotensin-converting enzyme (ACE), lysozyme, antinuclear antibody (ANA), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA), lupus panel, rapid plasma reagin (RPR), fluorescent treponemal antibody absorption (FTA-ABS), chest X-ray, and QuantiFERON Gold assay, which were normal. Over the next 5 days, his vision declined to counting fingers at 30.5 cm (1 foot) in both eyes. A relative afferent pupil defect and dyschromatopsia developed on the left. Automated Humphrey visual field (HVF) testing demonstrated global depression in both eyes (Fig. 2).

He was diagnosed as having DTaP-IPV vaccination-related optic neuritis and started on intravenously administered Solu-Medrol (methylprednisolone). One week later, his headache resolved and vision improved to 20/20 in his right eye and 20/25 in his left eye with less optic nerve hyperemia and swelling. He was discharged on a prednisone taper and an orally administered diabetic medication. One month later, his vision improved to 20/20 with resolution of the optic neuritis without residual visual field deficit in both eyes.

Discussion

In 2008, the DTaP-IPV vaccine was licensed and indicated for use in children of 4–6 years in age. From 2009 to 2012, a large-scale trial monitoring for adverse events found no significant increased risk of meningitis or encephalitis following DTaP-IPV [1]. Although the overall risk of developing a demyelinating CNS syndrome after vaccination is relatively low

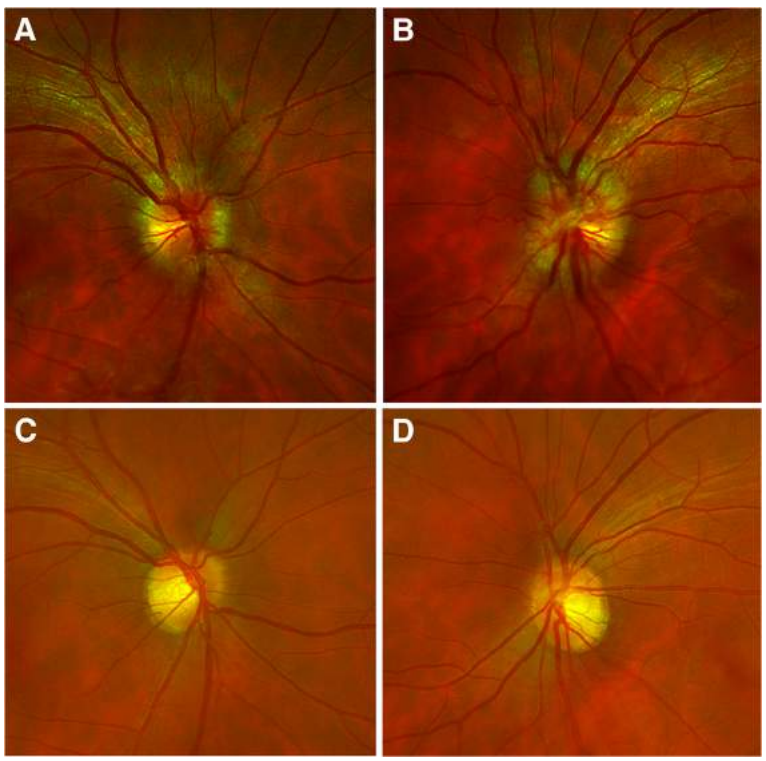

Fig. 1 Color fundus photography of the optic nerve 5 days after initial presentation when vision dropped to counting fingers at 30.5 cm (1 foot) in both eyes of (**a**) right eye and (**b**) left eye. Resolution of optic nerve hyperemia seen on the right eye (**c**) and the left eye (**d**) after treatment with corticosteroids

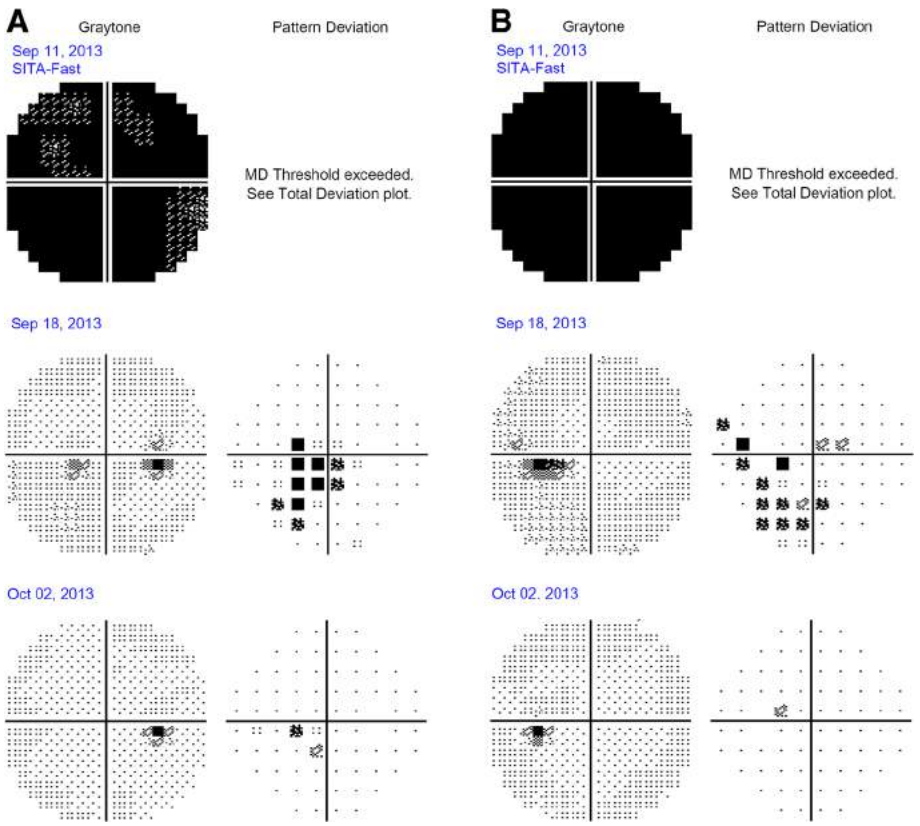

Fig. 2 Automated 30–2 Humphrey visual field testing using Swedish Interactive Testing Algorithm-Fast protocol of (**a**) the right eye and (**b**) the left eye showing gray tone and pattern deviation. The patient was started on intravenously administered Solu-Medrol (methylprednisolone) on September 11, 2013 (*top line*). Follow-up perimetry 1 week (*middle line*) and 3 weeks (*bottom line*) after the initiation of systemic corticosteroids showing improvement and resolution of the visual field deficits. *MD* mean deviation, *SITA* Swedish Interactive Testing Algorithm

(estimated to be 0.1%), it is not negligible [3]. Molecular mimicry from the viral proteins or the adjuvants used in the preparation of the vaccine have been suspected in the development of demyelinating disease following vaccination [3, 4]. Molecular mimicry occurs when similarities exist between proteins of viruses used in vaccinations and the components of CNS myelin which may disrupt self-tolerance and cause production of autoantibodies resulting in CNS inflammation including optic neuritis [3, 5]. Our case is consistent with other cases of post-vaccination optic neuritis, most of which develop 1–3 weeks after vaccination, typical of an immune-triggered mechanism [3].

In most cases, symptoms of optic neuritis were mostly resolved after treatment with steroids such as intravenously administered methylprednisolone followed by tapered oral prednisolone for several weeks [3, 5]. Early recognition of ocular signs and symptoms of optic neuritis following DTaP-IPV vaccination may lead to prompt treatment and preserved vision.

Conclusions

Although the association between immunizations and the onset of CNS demyelinating conditions is well documented, this report, to the best of our knowledge, is the first case of optic neuritis following DTaP-IPV vaccination. Inclusion of this case report in the medical community will allow for broader understanding of possible conditions that may present shortly after receipt of vaccination.

Abbreviations

A1C: Glycated hemoglobin; ACE: Angiotensin-converting enzyme; ALT: Alanine aminotransferase; ANA: Antinuclear antibody; AST: Aspartate aminotransferase; c-ANCA: Cytoplasmic antineutrophil cytoplasmic antibodies; CNS: Central nervous system; DTaP-IPV: Diphtheria, tetanus, pertussis and inactivated poliovirus combined vaccine; FTA-ABS: Fluorescent treponemal antibody absorption; p-ANCA: Perinuclear antineutrophil cytoplasmic antibodies; RPR: Rapid plasma reagin

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Availability of data and materials
The authors agree to making the images and data described in the manuscript freely available for use.

Authors' contributions
Both PO and RW contributed equally to the design, drafting, and editing of this manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was sent to the University of Texas at Austin Institutional Review Board and need for further approval was waived.

Consent for publication
Written and informed consent was obtained from the patient for publication of the case report and the accompanying images. Copies of the written consent forms are available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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Clin Neurol Neurosurg. 2017 Sep;160:116-118. doi: 10.1016/j.clineuro.2017.07.002. Epub 2017 Jul 11.

Optic neuritis in pregnancy after Tdap vaccination: Report of two cases.

Cabrera-Maqueda JM[1], Hernández-Clares R[2], Baidez-Guerrero AE[1], Pío-Rendón JIB[3], Fernández JJM[1].

Author information

Abstract

Two pregnant women developed one-eye blurring vision within three weeks after Tdap vaccination. Neurophtalmologic and MR examination confirmed an unilateral optic neuritis without evidence of underlying disease. Both patients had a full recovery, one after intravenous metilprednisolone. This is the first report of optic neuritis related with Tdap vaccination in pregnancy.

KEYWORDS: Pertussis vaccination; Postvaccination optic neuritis; Tdap vaccination

PMID: 28719871 DOI: 10.1016/j.clineuro.2017.07.002

[Indexed for MEDLINE]

Vaccine Reports

Volume 6, December 2016, Pages 86-88

Short communication

Rapid onset optic neuritis following measles vaccine in India: Case report

Jyoti Joshi [a], Anju Seth [b], Satinder Aneja [b], Awnish Kumar Singh [a], Mahesh Kumar Aggarwal [c], Nidhi Gupta [a]

Show more

https://doi.org/10.1016/j.vacrep.2017.01.001

Abstract

Though rare, neurological serious adverse events following measles immunization are well documented in scientific literature. However, we could retrieve only 7 published reports of optic neuritis following measles/measles containing vaccines. We report a case of bilateral optic neuritis that developed within 24 h of administration of monovalent measles vaccine in an eight-year-old male child during special measles immunization campaign in India.

Previous Next

Keywords

Optic neuritis; Measles vaccine; Adverse events; Vaccine safety

Recommended articles Citing articles (1)

Pediatr Infect Dis J. 2011 Jan;30(1):84-6. doi: 10.1097/INF.0b013e3181f11126.

Adverse neurologic reactions after both doses of pandemic H1N1 influenza vaccine with optic neuritis and demyelination.

Lapphra K[1], Huh L, Scheifele DW.

Author information

Abstract

When a neurologic condition develops after vaccination of a patient, the causal relationship is difficult to determine. We report an unusual case in which neurologic signs occurred in a previously healthy child after both doses of H1N1 2009 influenza vaccine, culminating in bilateral optic neuritis and disseminated encephalomyelitis. A causal association is more likely with repeated injury following influenza vaccination.

PMID: 20686434 DOI: 10.1097/INF.0b013e3181f11126

[Indexed for MEDLINE]

Format: Abstract

Full text links

Acta Neurol Scand. 1989 Nov;80(5):425-31.

The role of infection and vaccination in the genesis of optic neuritis and multiple sclerosis in children.

Riikonen R[1].

Author information

Abstract

This article describes the association between previous infection and/or vaccination and the development of optic neuritis (ON) in 18 children. Ten of these children subsequently developed clinically definite multiple sclerosis (MS), while in 8 patients a clinically definite etiology could not be confirmed. Vaccination preceded the first ON attack in 6 patients, all but one of whom subsequently developed MS. It also preceded subsequent demyelinating events in 6 patients. Ten of the patients had a bacterial or viral infection within the 2 weeks prior to the first symptoms of ON. Intrathecal antibody synthesis against 2 or more viruses could be shown in 5 out of 8 patients studied; 5 out of 6 patients had oligoclonal antibodies in CSF and 12 out of 16 patients a high IgG index. Neither intrathecal antibody synthesis against 2 or more viruses nor elevated IgG indexes could be found in the control patients. Measles and mumps occurred at a significantly later age in the children who subsequently developed MS than in the control children, and these patients had significantly more events that might have impaired the blood-brain barrier than the controls. These results indicate that immunological events leading to MS may be triggered during childhood. Vaccination and infection often precede ON in childhood. Intrathecal viral antibody production can occur already in childhood at the time of the first symptoms of MS.

PMID: 2589009

[Indexed for MEDLINE]

MeSH terms, Substance

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Original Article

Human and Experimental Toxicology
30(9) 1420–1428

DOI: 10.1177/0960327111407644
het.sagepub.com

Infant mortality rates regressed against number of vaccine doses routinely given: Is there a biochemical or synergistic toxicity?

Neil Z Miller and Gary S Goldman

Abstract

The infant mortality rate (IMR) is one of the most important indicators of the socio-economic well-being and public health conditions of a country. The US childhood immunization schedule specifies 26 vaccine doses for infants aged less than 1 year—the most in the world—yet 33 nations have lower IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of $r = 0.70$ ($p < 0.0001$) was found between IMRs and the number of vaccine doses routinely given to infants. Nations were also grouped into five different vaccine dose ranges: 12–14, 15–17, 18–20, 21–23, and 24–26. The mean IMRs of all nations within each group were then calculated. Linear regression analysis of unweighted mean IMRs showed a high statistically significant correlation between increasing number of vaccine doses and increasing infant mortality rates, with $r = 0.992$ ($p = 0.0009$). Using the Tukey-Kramer test, statistically significant differences in mean IMRs were found between nations giving 12–14 vaccine doses and those giving 21–23, and 24–26 doses. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs is essential.

Keywords

infant mortality rates, sudden infant death, SIDS, immunization schedules, childhood vaccines, drug toxicology, synergistic effects, linear regression model

Introduction

The infant mortality rate (IMR) is one of the most important measures of child health and overall development in countries. Clean water, increased nutritional measures, better sanitation, and easy access to health care contribute the most to improving infant mortality rates in unclean, undernourished, and impoverished regions of the world.[1–3] In developing nations, IMRs are high because these basic necessities for infant survival are lacking or unevenly distributed. Infectious and communicable diseases are more common in developing countries as well, though sound sanitary practices and proper nutrition would do much to prevent them.[1]

The World Health Organization (WHO) attributes 7 out of 10 childhood deaths in developing countries to five main causes: pneumonia, diarrhea, measles, malaria, and malnutrition—the latter greatly affecting all the others.[1] Malnutrition has been associated with a decrease in immune function. An impaired immune function often leads to an increased susceptibility to infection.[2] It is well established that infections, no matter how mild, have adverse effects on nutritional status. Conversely, almost any nutritional deficiency will diminish resistance to disease.[3]

Despite the United States spending more per capita on health care than any other country,[4] 33 nations have better IMRs. Some countries have IMRs that are less than half the US rate: Singapore, Sweden, and Japan are below 2.80. According to the Centers for Disease Control and Prevention (CDC), "The relative position of the United States in comparison to countries with the lowest infant mortality rates appears to be worsening."[5]

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Table 1. 2009 Infant mortality rates, top 34 nations[8]

Rank	Country	IMR
1	Singapore	2.31
2	Sweden	2.75
3	Japan	2.79
4	Iceland	3.23
5	France	3.33
6	Finland	3.47
7	Norway	3.58
8	Malta	3.75
9	Andorra	3.76
10	Czech Republic	3.79
11	Germany	3.99
12	Switzerland	4.18
13	Spain	4.21
14	Israel	4.22
15	Liechtenstein	4.25
16	Slovenia	4.25
17	South Korea	4.26
18	Denmark	4.34
19	Austria	4.42
20	Belgium	4.44
21	Luxembourg	4.56
22	Netherlands	4.73
23	Australia	4.75
24	Portugal	4.78
25	United Kingdom	4.85
26	New Zealand	4.92
27	Monaco	5.00
28	Canada	5.04
29	Ireland	5.05
30	Greece	5.16
31	Italy	5.51
32	San Marino	5.53
33	Cuba	5.82
34	United States	6.22

CIA. Country comparison: infant mortality rate (2009). *The World Factbook*. www.cia.gov (Data last updated 13 April 2010).[8]

There are many factors that affect the IMR of any given country. For example, premature births in the United States have increased by more than 20% between 1990 and 2006. Preterm babies have a higher risk of complications that could lead to death within the first year of life.[6] However, this does not fully explain why the United States has seen little improvement in its IMR since 2000.[7]

Nations differ in their immunization requirements for infants aged less than 1 year. In 2009, five of the 34 nations with the best IMRs required 12 vaccine doses, the least amount, while the United States required 26 vaccine doses, the most of any nation. To explore the correlation between vaccine doses that nations routinely give to their infants and their infant mortality rates, a linear regression analysis was performed.

Methods and design

Infant mortality

The infant mortality rate is expressed as the number of infant deaths per 1000 live births. According to the US Central Intelligence Agency (CIA), which keeps accurate, up-to-date infant mortality statistics throughout the world, in 2009 there were 33 nations with better infant mortality rates than the United States (Table 1).[8] The US infant mortality rate of 6.22 infant deaths per 1000 live births ranked 34th.

Immunization schedules and vaccine doses

A literature review was conducted to determine the immunization schedules for the United States and all 33 nations with better IMRs than the United States.[9,10] The total number of vaccine doses specified for infants aged less than 1 year was then determined for each country (Table 2). A vaccine dose is an exact amount of medicine or drug to be administered. The number of doses a child receives should not be confused with the number of 'vaccines' or 'injections' given. For example, DTaP is given as a single injection but contains three separate vaccines (for diphtheria, tetanus, and pertussis) totaling three vaccine doses.

Nations organized into data pairs

The 34 nations were organized into data pairs consisting of total number of vaccine doses specified for their infants and IMRs. Consistent with biostatistical conventions, four nations—Andorra, Liechenstein, Monaco, and San Marino—were excluded from the dataset because they each had fewer than five infant deaths, producing extremely wide confidence intervals and IMR instability. The remaining 30 (88%) of the data pairs were then available for analysis.

Nations organized into groups

Nations were placed into the following five groups based on the number of vaccine doses they routinely give their infants: 12–14, 15–17, 18–20, 21–23, and 24–26 vaccine doses. The unweighted IMR means of all nations as a function of the number of vaccine

Table 2. Summary of International Immunization Schedules: vaccines recommended/required prior to one year of age in 34 nations

Nation	Vaccines prior to one year of age	Total[b] doses	Group (range of doses)
Sweden	DTaP (2), Polio (2), Hib (2), Pneumo (2)	12	1 (12–14)
Japan	DTaP (3), Polio (2), BCG	12	
Iceland	DTaP (2), Polio (2), Hib (2), MenC (2)	12	
Norway	DTaP (2), Polio (2), Hib (2), Pneumo (2)	12	
Denmark	DTaP (2), Polio (2), Hib (2), Pneumo (2)	12	
Finland	DTaP (2), Polio (2), Hib (2), Rota (3)	13	
Malta	DTaP (3), Polio (3), Hib (3)	15	2 (15–17)
Slovenia	DTaP (3), Polio (3), Hib (3)	15	
South Korea	DTaP (3), Polio (3), HepB (3)	15	
Singapore	DTaP (3), Polio (3), HepB (3), BCG, Flu	17	
New Zealand	DTaP (3), Polio (3), Hib (2), HepB (3)	17	
Germany	DTaP (3), Polio (3), Hib (3), Pneumo (3)	18	3 (18–20)
Switzerland	DTaP (3), Polio (3), Hib (3), Pneumo (3)	18	
Israel	DTaP (3), Polio (3), Hib (3), HepB (3)	18	
Liechtenstein[a]	DTaP (3), Polio (3), Hib (3), Pneumo (3)	18	
Italy	DTaP (3), Polio (3), Hib (3), HepB (3)	18	
San Marino[a]	DTaP (3), Polio (3), Hib (3), HepB (3)	18	
France	DTaP (3), Polio (3), Hib (3), Pneumo (2), HepB (2)	19	
Czech Republic	DTaP (3), Polio (3), Hib (3), HepB (3), BCG	19	
Belgium	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (2)	19	
United Kingdom	DTaP (3), Polio (3), Hib (3), Pneumo (2), MenC (2)	19	
Spain	DTaP (3), Polio (3), Hib (3), HepB (3), MenC (2)	20	
Portugal	DTaP (3), Polio (3), Hib (3), HepB (3), MenC (2), BCG	21	4 (21–23)
Luxembourg	DTaP (3), Polio (3), Hib (3), HepB (2), Pneumo (3), Rota (3)	22	
Cuba	DTaP (3), Polio (3), Hib (3), HepB (4), MenBC (2), BCG	22	
Andorra[a]	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), MenC (2)	23	
Austria	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), Rota (2)	23	
Ireland	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (2), MenC (2), BCG	23	
Greece	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), MenC (2)	23	
Monaco[a]	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), HepA, BCG	23	
Netherlands	DTaP (4), Polio (4), Hib (4), Pneumo (4)	24	5 (24–26)
Canada	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), MenC (2), Flu	24	
Australia	DTaP (3), Polio (3), Hib (3), HepB (4), Pneumo (3), Rota (2)	24	
United States	DTaP (3), Polio (3), Hib (3), HepB (3), Pneumo (3), Rota (3), Flu (2)	26	

[a] These four nations were excluded from the analysis because they had fewer than five infant deaths.
[b] DTaP is administered as a single shot but contains three separate vaccines (for diphtheria, tetanus, and pertussis). Thus, DTaP given three times in infancy is equivalent to nine vaccine doses.
Immunization schedules are for 2008–2009.[9,10]

doses were analyzed using linear regression. The Pearson correlation coefficient (r) and coefficient of determination (r^2) were calculated using GraphPad Prism, version 5.03 (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Additionally, the F statistic and corresponding p values were computed to test if the best fit slope was statistically significantly non-zero. The Tukey-Kramer test was used to determine whether or not the mean IMR differences between the groups were statistically significant. Following the one-way ANOVA (analysis of variance) results from the Tukey-Kramer test, a post test for the overall linear trend was performed.

Results

Nations organized into data pairs

A scatter plot of each of the 30 nation's IMR versus vaccine doses yielded a linear relationship with a correlation coefficient of 0.70 (95% CI, 0.46–0.85) and $p < 0.0001$ providing evidence of a positive correlation: IMR and vaccine doses tend to increase together.

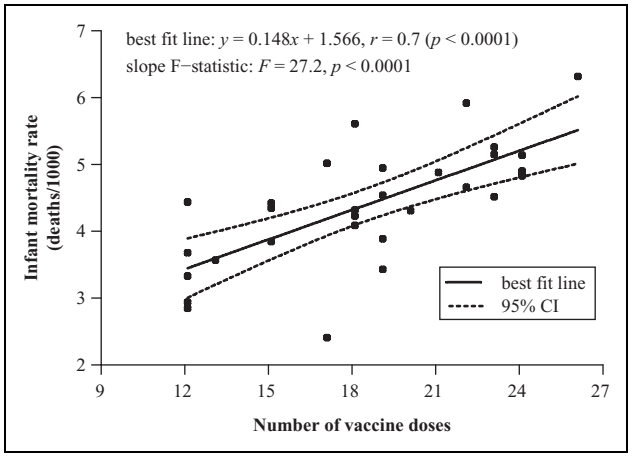

Figure 1. 2009 Infant mortality rates and number of vaccine doses for 30 nations.

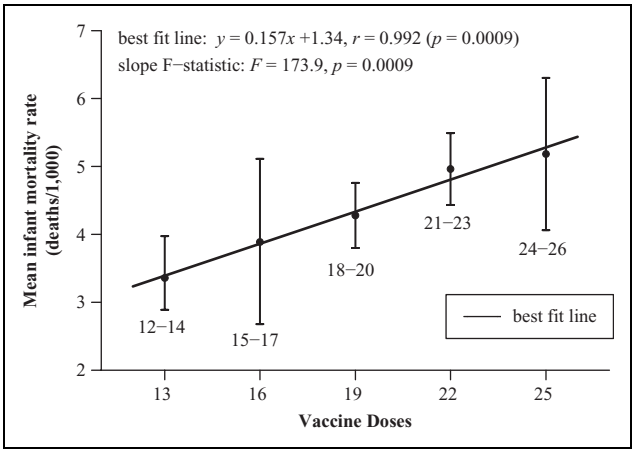

Figure 2. 2009 Mean infant mortality rates and mean number of vaccine doses (five categories).

The F statistic applied to the slope [0.148 (95% CI, 0.090–0.206)] is significantly non-zero, with $F = 27.2$ ($p < 0.0001$; Figure 1).

Nations organized into groups

The unweighted mean IMR of each category was computed by simply summing the IMRs of each nation comprising a group and dividing by the number of nations in that group. The IMRs were as follows: 3.36 (95% CI, 2.74–3.98) for nations specifying 12–14 doses (mean 13 doses); 3.89 (95% CI, 2.68–5.12) for 15–17 doses (mean 16 doses); 4.28 (95% CI, 3.80–4.76) for 18–20 doses (mean 19 doses); 4.97 (95% CI, 4.44–5.49) for 21–23 doses (mean 22 doses); 5.19 (95% CI, 4.06–6.31) for 24-26 doses (mean 25 doses; Figure 2). Linear regression analysis yielded an equation of the best fit line, $y = 0.157x + 1.34$ with $r = 0.992$ ($p = 0.0009$) and $r^2 = 0.983$. Thus, 98.3% of the variation in mean IMRs is explained by the linear model. Again, the F statistic yielded a significantly non-zero slope, with $F = 173.9$ ($p = 0.0009$).

The one-way ANOVA using the Tukey-Kramer test yielded $F = 650$ with $p = 0.001$, indicating the five mean IMRs corresponding to the five defined dose categories are significantly different ($r^2 = 0.510$). Tukey's multiple comparison test found statistical significance in the differences between the mean IMRs of those nations giving 12–14 vaccine doses and (a) those giving 21–23 doses (1.61, 95% CI, 0.457–2.75) and (b) those giving 24–26 doses (1.83, 95% CI, 0.542–3.11).

Discussion

Basic necessities for infant survival

It is instructive to note that many developing nations require their infants to receive multiple vaccine doses and have national vaccine coverage rates (a percentage of the target population that has been vaccinated) of 90% or better, yet their IMRs are poor. For example, Gambia requires its infants to receive 22 vaccine doses during infancy and has a 91%–97% national vaccine coverage rate, yet its IMR is 68.8. Mongolia requires 22 vaccine doses during infancy, has a 95%–98% coverage rate, and an IMR of 39.9.[8,9] These examples appear to confirm that IMRs will remain high in nations that cannot provide clean water, proper nutrition, improved sanitation, and better access to health care. *As developing nations improve in all of these areas a critical threshold will eventually be reached where further reductions of the infant mortality rate will be difficult to achieve because most of the susceptible infants that could have been saved from these causes would have been saved.* Further reductions of the IMR must then be achieved in areas outside of these domains. As developing nations ascend to higher socio-economic living standards, a closer inspection of all factors contributing to infant deaths must be made.

Crossing the socio-economic threshold

It appears that at a certain stage in nations' movement up the socio-economic scale—after the basic necessities for infant survival (proper nutrition, sanitation, clean water, and access to health care) have been met—a counter-intuitive relationship occurs between

the number of vaccines given to infants and infant mortality rates: nations with higher (worse) infant mortality rates give their infants, on average, more vaccine doses. This positive correlation, derived from the data and demonstrated in Figures 1 and 2, elicits an important inquiry: are some infant deaths associated with over-vaccination?

A closer inspection of infant deaths

Many nations adhere to an agreed upon International Classification of Diseases (ICD) for grouping infant deaths into 130 categories.[11–13] Among the 34 nations analyzed, those that require the most vaccines tend to have the worst IMRs. Thus, we must ask important questions: is it possible that some nations are requiring too many vaccines for their infants and the additional vaccines are a toxic burden on their health? Are some deaths that are listed within the 130 infant mortality death categories really deaths that are associated with over-vaccination? Are some vaccine-related deaths hidden within the death tables?

Sudden infant death syndrome (SIDS)

Prior to contemporary vaccination programs, 'Crib death' was so infrequent that it was not mentioned in infant mortality statistics. In the United States, national immunization campaigns were initiated in the 1960s when several new vaccines were introduced and actively recommended. For the first time in history, most US infants were required to receive several doses of DPT, polio, measles, mumps, and rubella vaccines.[14] Shortly thereafter, in 1969, medical certifiers presented a new medical term—sudden infant death syndrome.[15,16] In 1973, the National Center for Health Statistics added a new cause-of-death category—for SIDS—to the ICD. SIDS is defined as the sudden and unexpected death of an infant which remains unexplained after a thorough investigation. Although there are no specific symptoms associated with SIDS, an autopsy often reveals congestion and edema of the lungs and inflammatory changes in the respiratory system.[17] By 1980, SIDS had become the leading cause of postneonatal mortality (deaths of infants from 28 days to one year old) in the United States.[18]

In 1992, to address the unacceptable SIDS rate, the American Academy of Pediatrics initiated a 'Back to Sleep' campaign, convincing parents to place their infants supine, rather than prone, during sleep. From 1992 to 2001, the postneonatal SIDS rate dropped by an average annual rate of 8.6%. However, other causes of sudden unexpected infant death (SUID) increased. For example, the postneonatal mortality rate from 'suffocation in bed' (ICD-9 code E913.0) increased during this same period at an average annual rate of 11.2%. The postneonatal mortality rate from 'suffocation-other' (ICD-9 code E913.1-E913.9), 'unknown and unspecified causes' (ICD-9 code 799.9), and due to 'intent unknown' in the External Causes of Injury section (ICD-9 code E980-E989), all increased during this period as well.[18] (In Australia, Mitchell et al. observed that when the SIDS rate decreased, deaths attributed to asphyxia increased.[19] Overpeck et al. and others, reported similar observations.)[20,21]

A closer inspection of the more recent period from 1999 to 2001 reveals that the US postneonatal SIDS rate continued to decline, but *there was no significant change in the total postneonatal mortality rate.* During this period, the number of deaths attributed to 'suffocation in bed' and 'unknown causes,' increased significantly. According to Malloy and MacDorman, "If death-certifier preference has shifted such that previously classified SIDS deaths are now classified as 'suffocation,' the inclusion of these suffocation deaths and unknown or unspecified deaths with SIDS deaths then accounts for about 90 percent of the decline in the SIDS rate observed between 1999 and 2001 and results in a non-significant decline in SIDS"[18] (Figure 3).

Is there evidence linking SIDS to vaccines?

Although some studies were unable to find correlations between SIDS and vaccines,[22–24] there is some evidence that a subset of infants may be more susceptible to SIDS shortly after being vaccinated. For example, Torch found that two-thirds of babies who had died from SIDS had been vaccinated against DPT (diphtheria–pertussis–tetanus toxoid) prior to death. Of these, 6.5% died within 12 hours of vaccination; 13% within 24 hours; 26% within 3 days; and 37%, 61%, and 70% within 1, 2, and 3 weeks, respectively. Torch also found that unvaccinated babies who died of SIDS did so most often in the fall or winter while vaccinated babies died most often at 2 and 4 months—the same ages when initial doses of DPT were given to infants. He concluded that DPT "may be a generally unrecognized major cause of sudden infant and early childhood death, and that the risks of immunization may outweigh its potential benefits. A need for re-evaluation and possible modification of

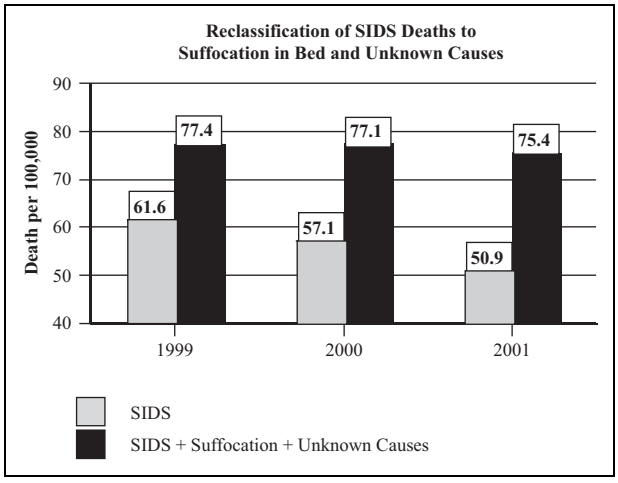

Figure 3. Reclassification of sudden infant death syndrome (SIDS) deaths to suffocation in bed and unknown causes. The postneonatal SIDS rate appears to have declined from 61.6 deaths (per 100,000 live births) in 1999 to 50.9 in 2001. However, during this period there was a significant increase in postneonatal deaths attributed to suffocation in bed and due to unknown causes. When these sudden unexpected infant deaths (SUIDs) are combined with SIDS deaths, the total SIDS rate remains relatively stable, resulting in a non-significant decline.

current vaccination procedures is indicated by this study."[25] Walker et al. found "the SIDS mortality rate in the period zero to three days following DPT to be 7.3 times that in the period beginning 30 days after immunization."[26] Fine and Chen reported that babies died at a rate nearly eight times greater than normal within 3 days after getting a DPT vaccination.[27]

Ottaviani et al. documented the case of a 3-month-old infant who died suddenly and unexpectedly shortly after being given six vaccines in a single shot: "Examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus. The cardiac conduction system presented persistent fetal dispersion and resorptive degeneration. This case offers a unique insight into the possible role of hexavalent vaccine in triggering a lethal outcome in a vulnerable baby." Without a full necropsy study in the case of sudden, unexpected infant death, at least some cases linked to vaccination are likely to go undetected.[28]

Reclassified infant deaths

It appears as though some infant deaths attributed to SIDS may be vaccine related, perhaps associated with biochemical or synergistic toxicity due to over-vaccination. Some infants' deaths categorized as 'suffocation' or due to 'unknown and unspecified causes' may also be cases of SIDS reclassified within the ICD. Some of these infant deaths may be vaccine related as well. This trend toward reclassifying ICD data is a great concern of the CDC "because inaccurate or inconsistent cause-of-death determination and reporting hamper the ability to monitor national trends, ascertain risk factors, and design and evaluate programs to prevent these deaths."[29] If some infant deaths are vaccine related and concealed within the various ICD categories for SUIDs, is it possible that other vaccine-related infant deaths have also been reclassified?

Of the 34 nations that have crossed the socio-economic threshold and are able to provide the basic necessities for infant survival—clean water, nutrition, sanitation, and health care—several require their infants to receive a relatively high number of vaccine doses and have relatively high infant mortality rates. These nations should take a closer look at their infant death tables to determine if some fatalities are possibly related to vaccines though reclassified as other causes. Of course, all SUID categories should be re-inspected. Other ICD categories may be related to vaccines as well. For example, a new live-virus orally administered vaccine against rotavirus-induced diarrhea—Rotarix®—was licensed by the European Medicine Agency in 2006 and approved by the US Food and Drug Administration (FDA) in 2008. However, in a clinical study that evaluated the safety of the Rotarix vaccine, *vaccinated babies died at a higher rate than non-vaccinated babies*—mainly due to a statistically significant increase in pneumonia-related fatalities.[30] (One biologically plausible explanation is that natural rotavirus infection might have a protective effect against respiratory infection.)[31] Although these fatalities appear to be vaccine related and raise a nation's infant mortality rate, medical certifiers are likely to misclassify these deaths as pneumonia.

Several additional ICD categories are possible candidates for incorrect infant death classifications: unspecified viral diseases, diseases of the blood, septicemia, diseases of the nervous system, anoxic brain damage, other diseases of the nervous system, diseases of the respiratory system, influenza, and unspecified diseases of the respiratory system. All of these selected causes may be repositories of vaccine-related infant deaths reclassified as common fatalities. All nations—rich and poor, industrialized and developing—have an obligation to determine whether their immunization schedules are achieving

their desired goals. Progress on reducing infant mortality rates should include monitoring vaccine schedules and medical certification practices to ascertain whether vaccine-related infant deaths are being reclassified as ordinary mortality in the ICD.

How many infants can be saved with an improved IMR?

Slight improvements in IMRs can make a substantial difference. In 2009, there were approximately 4.5 million live births and 28,000 infant deaths in the United States, resulting in an infant mortality rate of 6.22/1000. If health authorities can find a way to reduce the rate by 1/1000 (16%), the United States would rise in international rank from 34th to 31st and about 4500 infants would be saved.

Limitations of study and potential confounding factors

This analysis did not adjust for vaccine composition, national vaccine coverage rates, variations in the infant mortality rates among minority races, preterm births, differences in how some nations report live births, or the potential for ecological bias. A few comments about each of these factors are included below.

Vaccine composition

This analysis calculated the total number of vaccine doses received by children but did not differentiate between the substances, or quantities of those substances, in each dose. Common vaccine substances include antigens (attenuated viruses, bacteria, toxoids), preservatives (thimerosal, benzethonium chloride, 2-phenoxyethanol, phenol), adjuvants (aluminum salts), additives (ammonium sulfate, glycerin, sodium borate, polysorbate 80, hydrochloric acid, sodium hydroxide, potassium chloride), stabilizers (fetal bovine serum, monosodium glutamate, human serum albumin, porcine gelatin), antibiotics (neomycin, streptomycin, polymyxin B), and inactivating chemicals (formalin, glutaraldehyde, polyoxyethylene). For the purposes of this study, all vaccine doses were equally weighted.

Vaccine coverage rates

No adjustment was made for national vaccine coverage rates—a percentage of the target population that received the recommended vaccines. However, most of the nations in this study had coverage rates in the 90%–99% range for the most commonly recommended vaccines—DTaP, polio, hepatitis B, and Hib (when these vaccines were included in the schedule). Therefore, this factor is unlikely to have impacted the analyses.[9]

Minority races

It has been argued that the US IMR is poor in comparison to many other nations because African–American infants are at greater risk of dying relative to White infants, perhaps due to genetic factors or disparities in living standards. However, in 2006 the US IMR for infants of all races was 6.69 and the IMR for White infants was 5.56.[13] In 2009, this improved rate would have moved the United States up by just one rank internationally, from 34th place to 33rd place.[8] In addition, the IMRs for Hispanics of Mexican descent and Asian–Americans in the United States are significantly lower than the IMR for Whites.[6] Thus, diverse IMRs among different races in the Unites States exert only a modest influence over the United States' international infant mortality rank.

Preterm births

Preterm birth rates in the United States have steadily increased since the early 1980s. (This rise has been tied to a greater reliance on caesarian deliveries, induced labor, and more births to older mothers.) Preterm babies are more likely than full-term babies to die within the first year of life. About 12.4% of US births are preterm. In Europe, the prevalence rate of premature birth ranges from 5.5% in Ireland to 11.4% in Austria. Preventing preterm births is essential to lower infant mortality rates. However, it is important to note that some nations such as Ireland and Greece, which have very low preterm birth rates (5.5% and 6%, respectively) compared to the United States, require their infants to receive a relatively high number of vaccine doses (23) and have correspondingly high IMRs. Therefore, reducing preterm birth rates is only part of the solution to reduce IMRs.[6,32]

Differences in reporting live births

Infant mortality rates in most countries are reported using WHO standards, which do not include any reference to the duration of pregnancy or weight of the infant, but do define a 'live birth' as a baby born with any signs of life for any length of time.[12] However,

four nations in the dataset—France, the Czech Republic, the Netherlands, and Ireland—do not report live births entirely consistent with WHO standards. These countries add an additional requirement that live babies must also be at least 22 weeks of gestation or weigh at least 500 grams. If babies do not meet this requirement and die shortly after birth, they are reported as stillbirths. This inconsistency in reporting live births artificially lowers the IMRs of these nations.[32,33] According to the CDC, "There are some differences among countries in the reporting of very small infants who may die soon after birth. However, it appears unlikely that differences in reporting are the primary explanation for the United States' relatively low international ranking."[32] Nevertheless, when the IMRs of France, the Czech Republic, the Netherlands, and Ireland were adjusted for known underreporting of live births and the 30 data pairs retested for significance, the correlation coefficient improved from 0.70 to 0.74 (95% CI, 0.52–0.87).

Ecological bias

Ecological bias occurs when relationships among individuals are inferred from similar relationships observed among groups (or nations). Although most of the nations in this study had 90%–99% of their infants fully vaccinated, without additional data we do not know whether it is the vaccinated or unvaccinated infants who are dying in infancy at higher rates. However, respiratory disturbances have been documented in close proximity to infant vaccinations, and lethal changes in the brainstem of a recently vaccinated baby have been observed. Since some infants may be more susceptible to SIDS shortly after being vaccinated, and babies vaccinated against diarrhea died from pneumonia at a statistically higher rate than non-vaccinated babies, there is plausible biologic and causal evidence that the observed correlation between IMRs and the number of vaccine doses routinely given to infants should not be dismissed as ecological bias.

Conclusion

The US childhood immunization schedule requires 26 vaccine doses for infants aged less than 1 year, the most in the world, yet 33 nations have better IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of 0.70 ($p < 0.0001$) was found between IMRs and the number of vaccine doses routinely given to infants. When nations were grouped into five different vaccine dose ranges (12–14, 15–17, 18–20, 21–23, and 24–26), 98.3% of the total variance in IMR was explained by the unweighted linear regression model. These findings demonstrate a counter-intuitive relationship: *nations that require more vaccine doses tend to have higher infant mortality rates*.

Efforts to reduce the relatively high US IMR have been elusive. Finding ways to lower preterm birth rates should be a high priority. However, preventing premature births is just a partial solution to reduce infant deaths. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs, is essential. All nations—rich and poor, advanced and developing—have an obligation to determine whether their immunization schedules are achieving their desired goals.

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Simultaneous sudden infant death syndrome.

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Author information

Abstract

The simultaneous sudden deaths of twins rarely occur and therefore it has received limited attention in the medical literature. When the deaths of the twins meet the defined criteria for sudden infant death syndrome (SIDS) independently and take place within the same 24 h range it can be called as simultaneous SIDS (SSIDS). The case(s): Twin girls (3.5-month-old) were found dead by their mother in their crib, both in supine position. The infants were identical twins and delivered at a hospital by cesarean section. Both infants were healthy and did not have any serious medical history. Two days prior to the incident, the twins had received the second dose of oral polio, DPT and the first dose of hepatitis B vaccines and they had fever on the first day of the vaccination and been given teaspoonful of acetaminophen. Death scene investigation, judicial investigation, parental assessment, macroscopic and microscopic autopsy findings and the toxicological analysis did not yield any specific cause of death. The case(s) were referred to a supreme board composed of multidisciplinary medical professionals at the Institute of Forensic Medicine, Ministry of Justice, in Istanbul. The Board decided that the available data was consistent with SIDS. These SIDS case(s) are presented because twin SIDS are rare and this is the first time that a simultaneous twin SIDS have been reported in Turkey. Simultaneous SIDS cases have many implications regarding definition, diagnosis and medico-legal approach.

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In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 10, 2017

CHASE BOATMON & MAURINA CUPID, *parents of* J.B., *deceased,*	*	PUBLISHED DECISION
	*	No. 13-611V
Petitioners,	*	Special Master Gowen
v.	*	Entitlement Decision; Diphtheria-Tetanus-acellular Pertussis (DTaP) Vaccine; Inactivated Polio Vaccine (IPV); Haemophilus Influenzae (HiB) Vaccine; Pneumococcal Conjugate (PCV) Vaccine; Rotavirus Vaccine; Sudden Infant Death Syndrome (SIDS).
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Ronald C. Homer & Joseph M. Pepper, Conway, Homer P.C., Boston, MA, for petitioners. Lara A. Englund & Ryan M. Pyles, United States Department of Justice, Washington, DC, for respondent.[1]

RULING ON ENTITLEMENT[2]

On August 27, 2013, Chase Boatmon and Maurina Cupid ("petitioners"), as the representatives of the estate of their deceased minor child, J.B., filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program"),[3] 42 U.S.C. § 300aa-10 *et. seq.* (2012). Petitioners allege that as a result of receiving vaccinations for

[1] Mr. Homer is petitioners' attorney of record, while his colleague Mr. Pepper appeared at the entitlement hearing. Similarly, for respondent, Ms. Englund has always been the attorney of record, but Mr. Pyles appeared at the entitlement hearing.

[2] Because this decision contains a reasoned explanation for the action in this case, the undersigned intends to post it on the website of the United States Court of Federal Claims, pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012). The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website. *Id.*

[3] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3705, codified as amended, 42 U.S.C. §§ 300aa-1 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

Diphtheria-Tetanus-acellular Pertussis ("DTaP"), inactivated polio ("IPV"), haemophilus influenzae ("HiB"), Pneumococcal Conjugate ("PCV"), and Rotavirus vaccinations on September 2, 2011, J.B. passed away from Sudden Infant Death Syndrome ("SIDS") on September 3, 2011. *See* Petition (ECF No. 1); Amended Petition (ECF No. 15).

After carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that petitioners have met their legal burden. Petitioners have put forth preponderant evidence that the vaccines J.B. received on September 2, 2011 actually caused or substantially contributed to his death from Sudden Infant Death Syndrome. Furthermore, respondent has failed to put forth preponderant evidence that J.B.'s death was in fact caused by factors unrelated to the vaccines. Accordingly, petitioners are entitled to compensation.

I. BACKGROUND

A. Procedural History

Petitioners filed a petition for compensation pursuant to the Vaccine Act on behalf of their deceased minor son, J.B., on August 27, 2013. Petition (ECF No. 1). They filed an amended petition on February 6, 2014. Amended Petition (ECF No. 15). Petitioners filed the expert report of Dr. Douglas C. Miller, a neuropathologist, along with the medical literature referenced in his report, on May 20, 2014. Exhibit 13, 14 (ECF No. 21).[4]

On September 9, 2014, respondent filed a Rule 4(c) report advising against compensation. Rule 4(c) Report (ECF No. 28). That same day, he filed an expert report and medical literature referenced therein from Dr. Brent Harris, a pathologist. Exhibit A (ECF No. 29). Respondent also filed an expert report and medical literature from Dr. Christine T. McCusker. Exhibit C (ECF Nos. 30-32). Petitioners filed a supplemental report from Dr. Miller on November 10, 2014. Exhibit 16 (ECF No. 35). Extensive and detailed medical literature was submitted in support of all of the expert reports.[5]

At numerous stages of this case, the undersigned encouraged the parties to pursue the possibility of an informal resolution and/or to consider mediation. *See, e.g.*, Order filed December 9, 2014 (ECF No. 37). The parties ultimately did not settle the case. An entitlement hearing was held on Thursday, August 6, and Friday, August 7, 2015, in Washington, D.C. Dr. Miller testified on behalf of petitioners, and Dr. Harris and Dr. McCusker testified for respondent. The case was well tried and involved detailed expert testimony from both sides. *See*

[4] On October 14, 2014, petitioners refiled the medical literature cited in Dr. Miller's report, highlighting the specific portions being relied upon to support causation. Petitioners' Notice of Refiling Documents (ECF No. 34).

[5] I have read and digested all of the literature submitted in this case and will reference numerous but not all articles in the course of this opinion. However, all articles have been considered in coming to a conclusion in this case. More recent articles, particularly those by the same authors or groups, are referenced more frequently because they incorporate, build upon, and update the earlier literature. Petitioners and Dr. Miller filed Exhibits 13-A through 13-V and Exhibits 14 through 21. Respondent and Dr. Harris filed Exhibits A-1 through A-6. Respondent and Dr. McCusker submitted Exhibits C-1 through C-20 and Exhibits D through G.

Transcript filed on September 9, 2015 (ECF Nos. 50, 52). Petitioners filed their post-hearing brief on December 7, 2015. (ECF No. 61). Respondent filed his post-hearing brief on March 7, 2016. (ECF No. 63). Petitioners filed their reply to respondent's post-hearing brief on March 28, 2016. (ECF No. 64). This matter is now ripe for adjudication.

B. Standards for Adjudication

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

There are two avenues to compensation under the Program. The first is to demonstrate a "Table injury," that is, a specified injury within a specified period of time following administration of a vaccine listed on the Vaccine Injury Table. § 300aa-14(a). A Table injury creates a presumption of causation, which is only defeated if respondent shows that the injury was caused by a factor or factors unrelated to the vaccine. In the present case, petitioners allege that J.B. died suddenly of a cause that remained unexplained after a site investigation and autopsy, often referred to as SIDS, shortly after receiving various vaccines listed on the Table. The Table does not list SIDS occurring in any period of time after any vaccine.

Therefore, petitioners must take the second avenue towards compensation: they must establish an "off-Table injury," meaning that the vaccine(s) were the cause in fact of the vaccinee's injuries. In *Althen*, the Federal Circuit established a three-prong test: petitioners must establish (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The legal standard is by a preponderance of the evidence." §300aa-13(a)(1)(a). This does not require "conclusive scientific evidence" or "certainty." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010). Instead, the standard has been interpreted to mean that a fact is more likely than not. *Id.* at 1322 n.2. The Federal Circuit has observed that this preponderance standard enables "the finding of causation in a field bereft of complete and direct proof of how the vaccines affect the human body." *Althen*, 418 F.3d at 1280. Petitioners must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012).

Each *Althen* prong may be satisfied by medical records or a medical opinion. *Althen*, 418 F.3d at 1279; *see also Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (noting that the same piece of evidence can support several *Althen* prongs). Petitioners are not required to provide "objective confirmation" by way of "medical

documentation." *Id.* at 1278. Such a requirement would "contravene the plain language of the statute." *Id.* at 1281.

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus, a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof.

Epidemiological studies, or the lack thereof, are not dispositive of the causation in fact determination. *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992). Indeed, petitioners are not required to present medical literature or epidemiological evidence to establish any *Althen* prong. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, the special master can consider [epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury…. Medical literature and epidemiological evidence must be viewed… not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu*, 569 F.3d at 1380.

Under the second *Althen* prong, petitioners need to show that the vaccine(s) was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999). They do not need to show that the vaccine(s) was the "sole" or even the "predominant" cause. *Id.* at 1352. For example, in *Shyface*, the Federal Circuit affirmed that petitioners were entitled to compensation, based on their expert's testimony that the vaccine together with a bacterial infection caused the child's high fever and death (although the expert could not testify that the vaccine was the "sole" or "predominant" cause. 165 F.3d at 1353.

Showing a logical sequence of cause and effect between the vaccine(s) and the injury will tend to show that the injury was not caused by an alternative cause. However, a petitioner is not required to eliminate all possible alternative causes of the injury. *See Walter v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1150 (Fed. Cir. 2007) ("the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case"). This standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." *Althen*, 165 F.3d at 1280.

Once a petitioner fulfills the *Althen* test, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d 543 at 548; § 13(a)(1)(B). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.,* 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated "[do]not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or

condition." Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.

C. Summary of Relevant Facts

J.B. was born on April 7, 2011, when his mother became pre-eclamptic and underwent a Caesarean section. Exhibit 1 at 10. J.B. was born 4 weeks prematurely at 36 weeks gestation. Exhibit 2 at 3. The mother's medical records report no history of tobacco, alcohol, or illicit drugs. Exhibit 1 at 3. At birth, J.B. was noted to be "well appearing, non-dysmorphic[,] alert and in no acute distress." Exhibit 2 at 9. His Apgar scores[6] were 8 at 1 minute and 9 at 5 minutes. Exhibit 2 at 9. J.B. and his mother are both noted to be African-American. Exhibit 2 at 3, 25.

On April 14, 2011, one week after birth, J.B. received his first Hep B vaccination. Exhibit 2 at 82.[7] At his two-week well baby visit on April 21, 2011, J.B. was "well appearing, alert . . . a healthy appearing 2 [week] old with normal growth and development." *Id.* at 79-81. On June 7, 2011, J.B. – exhibiting a cough and a runny nose – was brought to the emergency room. *Id.* at 73. He underwent a chest x-ray that revealed "no radiographic evidence of acute cardiopulmonary disease." *Id.*

J.B.'s subsequent well-baby visits were scheduled to account for the fact of his being born 4 weeks prematurely. On July 22, 2011, more than three months after J.B.'s birth, he had a two-month well baby visit with his pediatrician, Laura Wright, M.D. Exhibit 3 at 8-10. Dr. Wright's evaluation was thorough and well documented. *Id.* J.B. had no feeding difficulties, slept best at night, slept in his own room, and slept on his back. *Id.* at 8. He was noted to be a "well child, almost 4 months but behind on [vaccinations]" with "normal growth and development." *Id.* at 10. J.B. received DTaP, IPV, PCV, rotavirus, and Hep B vaccinations at this visit. *Id.* at 2, 8.

On September 2, 2011, almost five months after J.B.'s birth, he had his four-month well baby visit with Dr. Wright. Exhibit 3 at 5-7. He was nearly five months post-delivery, although his gestational age was about four months given his early delivery. J.B. was sleeping up to seven hours at a time, on his back, in a crib in his own room. *Id.* at 5. He was described as "healthy appearing and cooperative . . . well-nourished and well developed." *Id.* His chest and lungs were normal with no adventitious[8] sounds. *Id.* at 6.

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[6] Apgar score is defined as "a numerical expression of the condition of a newborn infant, usually determined at 60 seconds after birth, being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." *Dorland's Illustrated Medical Dictionary* (32d ed. 2012) ("*Dorland's*") at 1682.

[7] Petitioners' expert, Dr. Miller, stated that normally an infant receives the first Hep B vaccination a day after delivery or just before going home. Exhibit 13 at 3. Dr. Miller characterized J.B. receiving the first Hep B vaccination one week after delivery as "a little unusual [but…] likely inconsequential." *Id.*

[8] Adventitious is defined as "accidental or acquired; not natural or hereditary." *Dorland's* at 34.

J.B.'s heart rate was regular with normal heart sounds and no pericardial friction rubs. *Id.* His reflexes were all 2/2 and his red reflex was normal. *Id.* His weight was 16 pounds, 8 ounces. *Id.* at 5. For infants of his age, his weight was stable at the 50th percentile, his height was up at the 50th percentile, and his head circumference was at the 75th percentile. *Id.* Nasal mucosa was normal, turbinates[9] were normal, and nares[10] were patent. Oropharynx was normal. *Id.* at 6. He was recorded as not having a fever, nasal congestion, or cough and history of wheezing. *Id.* at 5. He met numerous 4-month developmental milestones, including "head up 45 degrees, head up 90 degrees, sits – head steady." *Id.* During this visit, J.B. received DTaP, IPV, PCV, rotavirus, and Hep B vaccinations. *Id.* at 6; Exhibit 4 at 1. Dr. Wright completed her records from this visit on September 2, 2011, at 10:45 a.m., suggesting that the appointment had concluded by that time. Exhibit 3 at 7.

J.B.'s father attested that during the well-baby visit, J.B. was "smiling and cooing like normal." Exhibit 11 at 1. However, later that day after J.B. received the vaccinations, he "was not laughing or cooing like he normally did[,] he was not moving as much[, and] he seemed quiet and withdrawn." *Id.* That night, J.B. had a fever and he did not sleep well. *Id.* [11]

J.B.'s mother and father stated that on September 3, 2011, at 4:00 a.m., they gave J.B. Advil,[12] after which he went to bed in a supine position (on his back). Exhibit 8 at 2. When J.B. woke up a few hours later, he was distant, very quiet, and would not eat. Exhibit 11 at 2. He began running a fever again and was given another dose of Advil at approximately 8:00 a.m. *Id.*;

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[9] Turbinate is defined as "any of the nasal conchae.*" *Dorland's* at 1991.

[10] Nares is defined as "the external orifices of the nose; [also known as] nostrils." *Dorland's* at 1232.

[11] The following factual summary draws from:

- Exhibit 5 – Suffolk, Virginia Department of Fire & Rescue records of responding to the home on September 2, 2011.
- Exhibit 7 – Suffolk, Virginia Police Department records. This includes notes from the police's response to the home on September 3, 2011, and the police department's formal report on their response and a handwritten statement from J.B.'s mother, both completed on September 8, 2011.
- Exhibit 8 – Office of the Chief Medical Examiner, Tidewater District, Norfolk, Virginia, Records. This exhibit contains a summary of a child death reenactment with a doll, performed with J.B.'s parents in their home on September 8, 2011. Exhibit 8 at 3. The autopsy report was completed on November 2, 2011. Exhibit 8 at 1-2; 4-9.
- Exhibit 9 – Suffolk, Virginia Police Department records – photos of a bottle of Advil, taken on September 8, 2011; J.B. following the autopsy, undated; and the crib, bedroom, and exterior of the home, taken on September 3, 2011.

J.B.'s mother and father were not present to testify at the entitlement hearing.

[12] A bottle of children's Advil was taken into evidence. Exhibit 7 at 47. *But see* Exhibit 6 at 2, 5 ("aspirin"); Exhibit 8 at 2 ("infant Tylenol"); Exhibit 8 at 4-6 ("over-the-counter acetaminophen"). To the extent that it makes any difference it would seem most likely that it was the Advil that was given and the other notations were made subsequently without that same attention to this detail that the site investigation utilized.

Exhibit 7 at 11. J.B.'s mother said that J.B. sat up and played with her nephews during the morning. Exhibit 7 at 16.

In the early afternoon, J.B. became fussy and his father put him down for a nap in his bedroom, on the second floor of the house. Exhibit 7 at 3, 16; Exhibit 8 at 2. His father attested that he placed J.B. supine with his head to the right. Exhibit 7 at 5; Exhibit 8 at 3. J.B. seems to have had a pacifier in his mouth. Exhibit 7 at 16. He was placed in the middle of his crib, with a blanket across his midsection. Exhibit 8 at 3. The crib also contained a "little crib pillow – very flat," but no clutter or toys. Exhibit 7 at 5; Exhibit 8 at 3. J.B.'s mother attested that the air conditioning was always set at 76 degrees Fahrenheit. Exhibit 7 at 4. She indicated that J.B. slept on his back and that he could roll over on his own, lift his head, and pull or push himself up. Exhibit 7 at 5.

After putting J.B. down for his nap, his father left the home to get lunch. Exhibit 11 at 2. His mother remained in the home, but "heard [J.B.] fussing in crib" while she was cleaning and on the phone. Exhibit 7 at 16. After some period of time, J.B.'s mother went upstairs and put the pacifier in J.B.'s mouth. *Id.* (noting that J.B. "tend[ed] to cry when he spit the pacifier out"). When she returned, she found J.B. on his right side, with his head turned slightly, and unresponsive. Exhibit 7 at 17; Exhibit 8 at 2-3. She called J.B.'s father and said that J.B. was not breathing. Exhibit 7 at 17; Exhibit 11 at 2. The father told her to call 911 and he headed home. Exhibit 11 at 2.

J.B.'s mother said that "approximately 50 minutes passed" between his father placing J.B. down for a nap and when she found J.B. unresponsive. Exhibit 8 at 2. There was a "10-minute window" between when his mother checked on J.B. and replaced his pacifier, and when she returned to find him unresponsive. Exhibit 5 at 2. She informed the police that his nose and mouth were not covered. Pet. Ex 7 p 5.

J.B.'s mother called 911 at 2:39 p.m. Exhibit 7 at 35. She then attempted CPR. Exhibit 5 at 2; Exhibit 7 at 17. It appears that she removed him from the crib and placed him on his back on the floor. Exhibit 7 at 9-10. Officer Anderson was the first to arrive, at 2:42 p.m. – just 3 minutes and 21 seconds after the call. Exhibit 7 at 7, 9, 11, 35. Upon entering the home and going upstairs, the officer found J.B. lying on the bedroom floor, perpendicular to his crib. *Id.* at 9. J.B. was face up, with his eyes closed, and unresponsive. *Id.* He was still warm, but had no pulse or breath. *Id.* J.B.'s mother was kneeling over him. *Id.* The officer performed chest compressions until EMS arrived. *Id.*

The first responders left with J.B. at 3:02 p.m. and arrived at the emergency department of Harborview Medical Center at 3:08 p.m. Exhibit 7 at 36. J.B. was given oxygen under pressure during transport, but PEA (pulseless electrical activity) was noted on the monitor. Exhibit 5 at 1-2. Efforts at resuscitation were unsuccessful and J.B. was pronounced dead at the hospital, on September 3, 2011, at 4:01 p.m. Exhibit 7 at 10.

On September 5, 2011, a medical examiner, Dr. Jeffrey Gofton, completed an autopsy report for J.B. Exhibit 8 at 4-6. The medical examiner noted that the scene reenactment indicated that J.B. was placed to sleep on his back and was later found on his right side. *Id.* at 6. Scene photographs indicated a crib with soft blankets and a flat soft pillow, but no clutter or toys in the bed. *Id.* It was further noted that J.B. had no known medical problems, with regular infant care and immunizations. *Id.* He had a well-baby check-up on the day prior to his death, during which he received multiple vaccinations. *Id.* He had reportedly been fussy and had an intermittent temperature that seemed to be controlled with Tylenol. *Id.* J.B. was reportedly placed to sleep on his back and later found on his right side. *Id.* The medical examiner stated that J.B.'s lungs exhibited congestion and pulmonary edema.[13] *Id.* However, J.B. had no traumatic injury, congenital abnormalities, or viruses such as influenza. *Id.* Both a cerebral spinal fluid culture and a nasopharyngeal swab for viruses were negative. *Id.* J.B.'s brain weighed 876 grams (normal is 620 plus or minus 71 grams). *Id.* There was no evidence of epidural, subdural, or subarachnoid hemorrhage. *Id.* Serial sectioning showed normal configuration and infantile myelination of the cerebrum. *Id.* The brainstem was normally formed with no focal lesions. *Id.* at 5. Extensive drug testing was performed and was negative. *Id* at 6. The medical examiner, based on the "absence of findings and the reported sleeping position in a child with no anatomic or microscopic significant findings," stated that "the cause of death was SIDS and the manner was "natural." *Id.* The parties agree that the characterization of J.B.'s cause of death as SIDS is appropriate. Joint Prehearing Submission at 2.

The parties' experts in neuropathology – Dr. Miller for petitioners and Dr. Harris for respondent – reviewed 21 slides from J.B.'s autopsy, including two of J.B.'s brain. Exhibit 13 at 4-5; Exhibit A at 5. The first brain slide is a cross-section of pons at the level of the locus coeruleus (the upper pons), and the second slide is of two cingulate gyri with a portion of the adjacent corpus callosum. Exhibit 13 at 5. These brain sections demonstrated no abnormalities. *Id.* However, the medical examiner did not make slides from other parts of the brain, such as the medulla or hippocampus. *Id.* Furthermore, he did not take any photographs of the internal examination. *Id.* The parties' experts agreed that the medical examiner did not collect all of the data necessary to definitively analyze whether J.B. fit the Triple Risk Model of SIDS, introduced in the following section. Tr. 42-43 (testimony of Dr. Miller); Tr. 334 (testimony of Dr. Harris). The experts agreed that they would section considerably more of the brain in a possible SIDS autopsy than the two frontal lobes and one area of the pons that were sectioned in this case. Dr. Harris indicated that usually a SIDS autopsy should include samples of at least ten areas, including the medulla and hippocampus, which can help to show hypoxic ischemic changes as well as epilepsy related changes. Tr. 334. Both experts agreed, however, that in many SIDS cases, brains are not examined with the precision that they would recommend or that Dr. Kinney's group at Harvard did in their studies (introduced in the following section). Tr. 346.

[13] Dr. Miller and Dr. Harris agreed that congestion in the brain and lungs and other organs is a very common and non-specific finding at autopsy from which they would not draw any conclusion. Tr. 103 (Miller); Tr. 332-33 (Harris).

II. SUMMARY OF THE EVIDENCE

A. Medical Literature

The parties submitted voluminous literature to explain what is understood about sudden infant death syndrome ("SIDS"), the potential role of inflammatory cytokines generated by vaccines in acting as a necessary trigger, and the epidemiology of SIDS. Both parties submitted various studies from Hannah C. Kinney, M.D., a neuropathologist at Harvard, and others on her team which leads the research and current understanding of SIDS. The later articles tend to build upon and incorporate the earlier articles. Studies by other authors on SIDS and related subjects served to supplement and generally confirm that by Kinney et al.

A review of the literature is critical to the determination of whether petitioners have satisfied the *Althen* prongs (a reliable theory of how vaccines *can* cause death from SIDS, that the vaccines did in J.B.'s particular case, and that there was a medically acceptable temporal relationship between the vaccinations and J.B.'s death). This review is also necessary to determine whether respondent has sufficiently rebutted petitioners' theory by demonstrating that J.B.'s death was caused by factors unrelated to the vaccine.

SIDS is defined as "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, death scene investigation, and review of the clinical history."[14] "Epidemiological studies link SIDS with sleep periods, leading to the premise that SIDS occurs during sleep or transitions between sleep and waking." *Id.*

SIDS is the leading cause of infant mortality in the United States, with an incidence of 0.53 per 1,000 infants.[15] Research has revealed that infants put to sleep in the prone position, i.e., with their heads facing downward, are twice as likely to experience SIDS. *Id.* Other risk factors for SIDS related to the "sleeping environment" have been recognized, including "[being] found face-down, head covered, sleeping on an adult mattress, couch or playpen, soft bedding, [and] bed-sharing." *Id.*

In 1994, Dr. Hannah C. Kinney, Dr. James Filiano, and their colleagues synthesized many neuropathological studies into their proposed Triple Risk Model.[16] This model posits that SIDS occurs when: (1) an infant in a critical development period; (2) possessing an underlying vulnerability; (3) encounters an exogenous stressor. *Id.* The following Venn diagram has been used to illustrate the Triple Risk Model:

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[14] Filiano, J.J. & H.C. Kinney, *Arcuate Nucleus Hypoplasia in the Sudden Infant Death Syndrome*, 51 J. Neuropathol. Exp. Neurol. 394 (1992), Exhibit 13-A at 394.

[15] Trachtenberg F.L., E.A. Haas, H.C. Kinney, C. Stanley & H.F. Krous, *Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign*, 129 Pediatrics 630 (2012), Exhibit C-11 at 631.

[16] Filiano, J.J. & H.C. Kinney, *A Perspective on Neuropathologic Findings in Victims of the Sudden Infant Death Syndrome*, 65 Biol. Neonate 194 (1994), Exhibit 13-B at 195 [also filed as Exhibit A-2].

Id. at 3, Figure 1. This model emphasizes the intersection of multiple factors in the pathogenesis of SIDS. According to this model, SIDS occurs only when components of all three factors are present simultaneously, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS.[17]

1. First Risk Factor: Critical Development Period

The first factor in the Triple Risk Model of SIDS is the critical development period, which Kinney et al. initially defined as the first year of life.[18] However, their more recent literature tends to define it as the first six months of life.[19] The peak incidence of SIDS deaths has historically occurred between two and four months of age. A study by Trachtenberg, Kinney, and others published in 2012 found slightly more younger and older infants succumbing to SIDS than had been seen in earlier studies. In the groups studied, the percentage of SIDS babies who were five months or more rose from 11.8% in the pre-Back-to-Sleep[20] era, to 17.6% in the 1996-2008 post-Back-to-Sleep era.[21] Kinney and Thach wrote, "Given the wide array of homeostatic functions modulated by the medullary 5-hydroxytrptamine system, sudden death may result from a convergence of defects in protective response to homeostatic stressors during sleep that are modulated by 5-hydroxytrptamine, probably in conjunction with related neurotransmitters."[22]

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[17] Kinney, H.C. et al., *The Brainstem and Serotonin in the Sudden Infant Death Syndrome*, 4 Annu. Rev. Pathol. Mech. Dis. 517 (2009), Exhibit 13-H at 521.

[18] Filiano & Kinney (1992), Exhibit 13-A at 394.

[19] *See, e.g.*, Kinney et al. (2009), Exhibit 13-H at 521.

[20] The "Back to Sleep" campaign refers to a major public health effort to encourage parents to place their infants on their backs to sleep, particularly during the first year of life as a means of reducing the incidence of SIDS.

[21] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 634.

[22] Kinney, H.C. & B. Thach, *The Sudden Infant Death Syndrome*, 361 New England J. of Med. 795 (2009), Exhibit A-4 at 6.

2. Second Risk Factor: Vulnerable Infant

After Kinney et al. formulated the Triple Risk Model, the initial research was focused on determining why particular infants were "vulnerable", possibly because of environmental or genetic factors. Exhibit 13-H at 5. Intrinsic risk factors include "male gender, African-American race, poverty, adverse prenatal factors such as maternal smoking or alcohol use during pregnancy, and genetic polymorphisms." *Id.* It was also hypothesized as early as 1987 that most likely SIDS was related to a brainstem abnormality in the neuroregulation of cardiorespiratory control.[23] These intrinsic factors when combined with the vulnerable developmental period of the infant and a critical exogenous factor resulted in sudden infant death. As research progressed over the following decades, the above intrinsic risk factors remained but a significant emphasis was placed on the brainstem hypothesis, based upon the research of Dr. Kinney and others. In 2009, Dr. Kinney explained: "To date the most robust evidence for a neurochemical abnormality comes from research on the medullary 5-HT system,[24] in that approximately 50-70% of infants with SIDS appear to have abnormalities in this system. The medullary 5-HT system, which is considered critical for the modulation and integration of diverse homeostatic functions, is involved in ventilation and gasping, thermoregulation, autonomic control, response to carbon dioxide and oxygen, arousal from sleep, and hypoxia-induced plasticity.[25]

The 5-HT system refers to the serotonin system. "The caudal serotonergic (5-HT) system is a critical component of a medullary "homeostatic network" that regulates protective response to metabolic stressors such as hypoxia, hypercapnia and hyperthermia."[26] "Homeostasis refers to the ability of an organism to maintain a constant internal environment, thereby allowing survival over a wide range of external environmental conditions. It becomes self-sufficient at the moment of birth as the fetus takes the first breath in the extra-uterine world and begins to adjust instantaneously and independently to the myriad of changing metabolic demands. ... Receptor systems that sense deviations in any internal milieu (e.g., oxygen and carbon dioxide, glucose, and temperature levels) have been defined as well as the effector systems that are the final common pathway in mediating adjustments. Major focus has been placed upon the brain as the 'control center' which sets the range at which a particular parameter namely CO2 is maintained, and determines the protective response to deviations from this range namely hypercarbia."[27,28]

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[23] Kinney et al. (2009), Exhibit 13-H at 519.

[24] 5-HT (5-hydroxytryptamine), also called serotonin, is defined as "a monoamine vasoconstrictor, synthesized in the intestinal chromaffin cells or in central or peripheral neurons and found in high concentrations in many body tissues, including the intestinal mucosa, pineal body, and central nervous system." *Dorland's* at 1699.

[25] Kinney & Thach (2009), Exhibit A-4 at 6.

[26] Kinney, H.C. et al., *The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis*, 41 J. Chem. Neuroanat. 12 (2011), Exhibit 13-F at 182.

[27] Hypercarbia, also called hypercapnia, is defined as "excess of carbon dioxide in the blood." *Dorland's* at 887.

[28] Kinney et al. (2009), Exhibit 13-F at 183.

The serotonergic system, primarily concentrated in the medulla oblongata, which is called the caudal 5-HT system or the medullary 5-HT system, is now recognized as a key component of the brain's control system of homeostasis. *Id.* Dr. Kinney proposed that deficits in the caudal 5-HT system will lead to imbalances in respiratory, cardiovascular, and/or metabolic regulation – including in response to stress – in the pediatric age range, particularly in the first days and months following birth. *Id.* As noted by the Kinney group in a 2011 article on the serotonergic anatomy, "extensive experimental data implicate the caudal 5-HT system in homeostasis and respiratory and autonomic regulation, including upper airway control, respiration (including via modulation of the pre-Botzinger complex, the putative central rhythm generator of respiration), autoresuscitation, central chemoreceptor responses to hypercapnia and hypoxia, cardiovascular control, pain, motor function, and thermoregulation." *Id.* The article also notes that the medullary 5-HT system "interfaces with the cytokine system which is critical to homeostasis in its mediation of 'protective sickness' behaviors and cellular defenses against tissue damage." *Id.*

Dr. Kinney's team's research on the brainstem focused on a collection of neurons in the ventral medullary surface known as the arcuate nucleus "based upon cytological and positional homologies between the respiratory chemosensitive fields on the ventral medullary surface in cats. Structural underdevelopment of the arcuate nucleus was subsequently observed in SIDS cases."[29] As the research advanced, it was recognized that the "arcuate anomaly was similar to that reported in infants with clinical insensitivity to CO2 and sleep related sudden death." *Id.* By 2009, Dr. Kinney reported, "*Serotonergic neurons at the medullary ventral surface and in the midline (raphe) are now known to be preferentially chemosensitive to CO2* and although they are not the only central chemosensitive neurons they appear to play a critical potentially modulatory role…A small but important population of 5-HT neurons is embedded within the human arcuate nucleus suggesting that the putative dysfunction in chemosensitivity related to the arcuate anomaly specifically involved these embedded 5-HT neurons." *Id.* (emphasis added).

"Serotonergic neurons are well-suited to a role as central respiratory chemo-receptors, as they are closely associated with the basilar artery and its largest branches near the ventral surface of the medulla namely they are in a position to directly monitor arterial PCO_2.... 5-HT neurons respond intrinsically to increased PCO_2[30] with large increases in firing rate; this response is due to a decrease in intracellular pH induced by hypercapnia. On average these neurons increase their firing rate threefold in response to a decrease in pH of 7.4 to 7.2. Chemosensitivity increases during postnatal development, with a blunted response to pH before postnatal date 12 in rats. Physiological delay in chemosensitivity is potentially relevant to SIDS because it indicates that 5-HT neurons may be immature during the critical developmental period, throughout which all infants are susceptible to hypercapnia."[31] Harper and Kinney state the data now suggest that SIDS is associated with a brainstem (medullary) 5-HT deficiency rather than 5-

[29] Kinney et al. (2009), Exhibit 13-H at 522. Kinney defines chemosensitivity as "the ventilator response to a change in carbon dioxide/pH as sensed by tissue chemoreceptors, which are composed of neurons and/or astrocytes." *Id.*

[30] PCO_2 is defined as "the partial pressure of carbon dioxide." *Dorland's* at 2120.

[31] Kinney et al. (2009), Exhibit 13-H at 530.

HT overproduction.[32] Of note, the medullary 5-HT profile differed between infants dying of SIDS and those dying with known chronic oxygenation disorders, suggesting that chronic hypoxia does not necessarily play a major role in the pathogenesis of the impairments in the 5-HT tissue markers. *Id.*

Harper & Kinney explained that the insufficient function of the 5-HT system, which is necessary for breathing, leaves an infant vulnerable to a variety of crisis situations. These include external airway obstruction, upper airway obstruction resulting from loss of tone in the upper airway musculature in association with diaphragmatic movements, or importantly of central apnea, which has occupied a central focus of attention. These are also proposed mechanisms underlying the fatal event in SIDS. This failure can result from several components of the breathing process, including impaired sensory transduction or integration of either carbon dioxide or oxygen, or non-recruitment of gasping mechanisms, the final restorative mechanism to low oxygen. In SIDS, a principal concern is the "loss of the wakefulness drive to breathe." *Id.* at 5. The waking state activates processes which maintain breathing, while during sleep those influences are suppressed or not recruited. Thus, impaired central chemosensitivity to excess carbon dioxide or inadequate oxygen contributed to by defects in the medullary serotonin system, in addition to the normal reduction of the function of the 5-HT system during sleep, may play a central role in SIDS, which occurs primarily during sleep. *Id.* at 4-5.

Despite the emphasis on brainstem abnormality or underdevelopment, the other intrinsic risk factors are thought to continue to play an important role in the multi-factorial analysis of SIDS causation. Some of these factors may be related to the medullary 5-HT deficits described above. Several intrinsic risk factors are apparent in J.B.'s case. First, prematurity is defined as less than 37 weeks at birth[33] and J.B. was born at 36 weeks. Male gender, as boys exceed girls in SIDS deaths by a two-to-one ratio, and African-American race have also been called intrinsic risk factors because they are over-represented among SIDS victims.[34] Importantly, maternal smoking and alcohol consumption during pregnancy are considered important risk factors but are not relevant in this case, as J.B.'s mother did not smoke or drink during or after her pregnancy.

Dr. Kinney has hypothesized that males may predominate among SIDS deaths because males tend to be less responsive to the accumulation of carbon dioxide, and in the situation with a defective medullary 5-HT system may be particularly impaired from responding to excess carbon dioxide during sleep. *Id. T*he predominance of males in the occurrence of SIDS appears to be potentially related to the reduction of 5-HT binding in the medullary raphe compared to females dying of SIDS, as well as the report that plasma levels of testosterone, but not estradiol, are significantly higher in both male and female SIDS infants compared to age-matched controls. Several studies in knockout mice and piglets also "underscore gender differences in brainstem-mediated 5-HT function, with females' brains apparently relying less on 5-HT neurons in chemoreception and adapting more readily to the loss of 5-HT function. *Id.*

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[32] Harper, R.M. & H.C. Kinney, *Potential Mechanisms of Failure in the Sudden Infant Death Syndrome*, 6 Curr. Pediatr. Rev. 39 (2010), Exhibit C-12 at 7.

[33] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[34] Kinney et al. (2009), Exhibit 13-H at 532.

The role of African-American race in SIDS is less defined, other than statistically. Most authors speculate that the statistical predominance of African-American children may represent lower socioeconomic status resulting in inadequate medical care. If that be the case however, J.B.'s race should not be an increased risk factor as he was receiving regular medical care with comprehensive and well-documented well baby visits occurring in July and September. His first set of vaccinations was somewhat late, but the second dose, those received on September 2, 2011, brought him up to date. His growth and functional milestones appeared to be normal. It is also reported that 75% of white infants are placed to sleep in the supine position, while only 53% of black infants are, and that there is greater incidence of bed sharing among black infants than in other groups.[35] J.B. was placed on his back and was in his own crib.

3. Third Risk Factor: Exogenous Stressor(s)

The third and last factor is referred to as exogenous stressor[s] present at the time of death.[36] These stressors identified in the literature include "prone sleep position, face-down position, covered face in the supine position, soft bedding, bed sharing, over-bundling, elevated room temperature, and minor infection at the time of death."[37] Virtually every SIDS case includes one or more exogenous stressors, implying that they act as "triggers" for SIDS.[38] Studies also show that often multiple risk factors are present in a given SIDS case. Trachtenberg et al. found that "at least 2 extrinsic risk factors" were present in a majority of 568 cases reviewed. *Id.* at 632.

Dr. Kinney has hypothesized that exogenous stressors "lead to asphyxia, hypoxia, hypercapnia, or thermal imbalance requiring intact brainstem defense systems to protect against lethal consequences."[39] Non-vulnerable infants are generally able to recover from these conditions, but vulnerable infants are less able to recover and succumb to SIDS. *Id.* at 521.

As a result of their research, Dr. Kinney and her team proposed the Triple Risk Model to explain the occurrence of SIDS. Dr. Kinney's group then proposed the "Back to Sleep Campaign" in the early 1990s in which they recommended that babies always be put to sleep on their backs (supine) on a firm mattress, without pillows, blankets, toys, bumpers or other items that could potentially obstruct breathing. The prone or face-down sleeping position was considered to make an infant particularly vulnerable because an infant in the first six months of life with one or more intrinsic defects may re-breathe excess carbon dioxide and lack the corrective arousal mechanisms during sleep that would prevent a fatal outcome. Generally, the accumulation of excess carbon dioxide in the body causes signaling to breathe, thereby exhaling

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[35] Moon R.Y. et al., American Academy of Pediatrics – Task Force on Sudden Infant Death Syndrome, *SIDS and Other Sleep Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment,* 128 Pediatrics 1030 (2011), available at http://pediatrics.aappublications.org/content/128/5/1030.long.

[36] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[37] Kinney et al. (2009), Exhibit 13-H at 521.

[38] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 633.

[39] Kinney et al. (2009), Exhibit 13-H at 520.

carbon dioxide and inhaling room air containing oxygen. During sleep it is thought that excess carbon dioxide normally causes a person to turn the head toward fresh air and become aroused from sleep. When those mechanisms fail, the gasp reflex is triggered, which brings in oxygen and resets the rhythm of breathing. In SIDS, the dominant theory is that all of these mechanisms fail, leading to death.

The Back to Sleep Campaign has succeeded remarkably in reducing the number of SIDS deaths in the United States by approximately 50%.[40] In the U.S., the rate was reduced from more than 1 per 1,000 infants to 0.53 per 1,000, the current rate where it has plateaued. *Id.* However, SIDS remains the leading cause of post neo-natal infant death in the United States, raising some of the questions at issue in this case. *Id.* The emphasis has continued to be on the cardiorespiratory failure explanation of SIDS. Research has indicated that prone sleeping position increases the risk twofold or more. *Id.* They concluded that those not found prone sleeping were subject to alternative SIDS risk factors. *Id.* at 635.

The Trachtenberg article concluded that virtually all SIDS infants have at least one risk factor, and the majority have at least one intrinsic risk factor and two extrinsic factors. *Id.* The article also notes that the American Academy of Pediatrics risk reduction guidelines also include recommendations against side-sleeping and bed-sharing, and suggest a separate but proximate sleeping environment and pacifier use. *Id.* at 636. The data from the Trachtenberg study found a decline in prone position sleeping from 84% in the pre-Back-to-Sleep era to 48.5% in the post-era, but it also found that in the post-era 17.3% of SIDS infants were found on their sides while 22.6% were initially placed on their sides. *Id.* at 634, Table 2. Interestingly, 29% of the SIDS babies in that study were found supine while 41.7% were placed on their backs, suggesting that SIDS is not exclusively caused by prone sleeping. *Id.* at 632.

The Trachtenberg and Kinney articles emphasize the belief in the medical community that SIDS is multifactorial. As Trachtenberg noted, they were only able to evaluate which SIDS risk factors are most common, not which factors raise the odds of SIDS most significantly. *Id.* at 635. The authors suggest that the number of risks is probably underestimated and that "the majority of SIDS infants were subject to at least two extrinsic risk factors, suggesting that SIDS occurs from the simultaneous occurrence of multiple factors, rarely just one." *Id.* Additionally, Dr. Kinney has noted that under the Triple Risk Model, only infants with an underlying brainstem disease process die of SIDS, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS.[41] She states that SIDS essentially represents the occurrence of "the biologic version of the perfect storm in which the chance combination of multiple events is far more powerful than each individual event alone." *Id.* at 539. She suggests a possible scenario in which a child with the underlying brainstem deficit, during the critical developmental period, is exposed to excess carbon dioxide while he is sleeping. This may be based upon his sleeping position or he may have an issue with the laryngeal chemoreflex stimulated by reflux of gastric contents *or may have a mild infection with fever* causing the laryngeal chemoreflex induced apnea to be inordinately prolonged by mild hyperthermia" *Id.*

[40] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[41] Kinney et al. (2009), Exhibit 13-H at 521.

(emphasis added). In this scenario, "if the infant's ventilator response to the progressive hypoxia and hypercapnia during the apnea is depressed, and if the hypoxic gasping and/or arousal mechanism is abnormal, oxygen lack from uninterrupted apnea results. Ultimately, death occurs *within minutes to hours*." *Id.* (emphasis added).

Respondent filed the article by Trachtenberg et al., which emphasized that they could find no positive correlations between risk factors or risk clusters but it appeared that any combination of risks together increased the odds of SIDS. The fact that most infants have at least two extrinsic risk factors suggests that SIDS occurs as a result of the occurrence of multiple factors and rarely just one.[42] The Kashiwagi article[43] filed by petitioners suggests that vaccines provoke an inflammatory cytokine response similar to that provoked by a mild infection. Petitioners theorize that these cytokines travel to the brainstem and further suppress the function of the already impaired medullary 5-HT system in a subset of SIDS infants.

a. Cytokines, Mild Infection and Vaccines

Relevant to this case, in a 2009 article in the New England Journal of Medicine, Kinney and Thach stated, "A causal role for mild infection in sudden infant death is suggested by reports that in approximately half of SIDS cases, the infants have a seemingly trivial infection around the time of death, as well as mild tracheobronchial inflammation, altered serum immunoglobulin or cytokine levels and the presence of microbial isolates at autopsy. In infants who die unexpectedly of infection, the given organism may precipitate a lethal cytokine cascade or toxic response."[44] The question arises as to whether the cytokine response stimulated by vaccination can have the same effect as a mild or trivial infection in a baby who presumably has a defect in the medullary 5-HT system.

The role of cytokines stimulated by either mild infection or by vaccination is central to petitioners' theory in this case. Approximately 50% of SIDS babies have been found in multiple studies to have had mild or even "trivial" infections, primarily of the upper respiratory tract at the time of death. In this case, J.B. was documented the prior day as being healthy with patent nares, normal turbinates, and clear chest, but during the 28 hours after the vaccine he was reported to have a fever, which is generated by cytokine signaling. He also was distant, quiet, and would not eat, according to his parents. The case raises the issue of whether inflammatory cytokines stimulated by the innate response to the vaccines triggered the fever and his fussiness, and ultimately suppressed his 5HT system sufficiently so that he could not process the carbon dioxide in his system. The question of whether inflammatory cytokines stimulated by the innate response to the vaccine could have been the trigger that led to his death was central to the testimony and much of the literature submitted by the parties particularly in light of the clear medical evaluation on the day of the vaccination and a fever within hours afterward.

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[42] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 7.

[43] Kashiwagi Y et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib) and 7-Valent Pneumococcal (PC7) Vaccines*, 10 Hum. Vacc. Immunother. 677 (2014), Exhibit 17.

[44] Kinney & Thach (2009), Exhibit A-4 at 2.

As Dr. Kinney and her colleagues explained in 2011: "Cytokines orchestrate immune responses to microbial invasion and other insults and coordinate these responses with those of other physiological systems, including the autonomic nervous system, in the protection of the organism against tissue injury. They also mediate sickness behavior, including fever, anorexia, excessive sleepiness, blunted arousal, deep rest respiration, and lowered heart rate, which is thought to protect the organism during systemic illness by dampening excessive metabolic demands and thereby speeding repair and recovery - a form of homeostasis."[45] "Cytokines determine this sickness behavior by binding to endogenous cytokine receptors on neuronal populations in the hypothalamus and/or brainstem that mediate respiration, autonomic function, satiety, sleep, and arousal." *Id.* at 190. The cytokines which act within the brain in response to tissue injury are produced by astrocytes, and endothelial cells, microglia, *and/or peripheral immune cells* which enter the brain in response to binaural signals of tissue damage." *Id.* (emphasis added). During infection, peripherally produced IL-6 may cross the blood brain barrier and bind to IL-6 receptors on 5 HT neurons that mediate homeostasis in response to the infectious stressor and potentially mediate sickness behavior. *Id*. at 191. The role of pro-inflammatory cytokines in the pathology of SIDS is thought by multiple authors to be a potentially critical factor in tipping the molecular balance in the underdeveloped brainstem leading to death in infants in the vulnerable time period. IL-1β, IL-2, and IL-6 are pro-inflammatory cytokines that have been studied in connection with SIDS leading to theories about their potentially neuro-modulatory role in SIDS babies.

Kadhim et al. described a distinct cytokine profile in a SIDS brain in a study comparing SIDS brains with non-SIDS brains. The non-SIDS brains were from infants who died of known causes, including AIDS, cirrhosis of the liver, mononucleosis, purulent meningitis, and congenital heart disease with post-operative acidosis-shock. He found an over-expression of interleukin 1β in arcuate and dorsal vagal nuclei in all SIDS victims. In arcuate nuclei, high levels of interleukin 1β were detected in 17/17 SIDS brains vs. only 1 of 6 non-SIDS brains.[46] In dorsal vagal nuclei, interleukin 1β was also detected in high levels in 17 of 17 SIDS brains vs. only 2 of 7 non-SIDS brains. *Id.* Kadhim found a "region-specific pattern of cytokine expression in [the arcuate and dorsal vagal nuclei] of SIDS brains compared to non-SIDS brains." *Id.* at 1259. Kadhim theorized: "cytokines could exert neuromodulatory effects. Infectious inflammatory conditions and injury to the brain could up regulate pro inflammatory cytokines and produce functional alteration ... Cytokine/neurotransmitter interactions could therefore modify vital CNS functions." *Id.* Kadhim et al. further concluded that IL-1 causes prolonged apnea and depresses respiration, and that the brain appears to be less effective than the peripheral nervous system in inducing IL-1 antagonists to control IL-1 action.

[45] Kinney et al. (2011), Exhibit 13-F at 189.

[46] Kadhim, H. et al., *Distinct Cytokine Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?*, 61 Neurol. 1256 (2003), Exhibit 13-L at 1256.

In a second study from 2010, Kadhim focused on the expression of IL-2 in 28 autopsied infants who died at less than one year of age.[47] He described IL-2 as major immune-related cytokine that was originally thought to be a T-lymphocyte growth factor but is now recognized to have a wider spectrum of functions, targets and sources. *Id.* The study compared 18 SIDS brains to those of infants who died of diverse severe pathological conditions including infectious, hemodynamic, metabolic or other serious genetic conditions. In the severely ill children (non-SIDS), they found that IL-2 was preferentially expressed in specific neuronal centers within the brainstem (SNT-solitary nucleus tractus and TSNT-spinal trigeminal nucleus/tractus) in 10 of 10 cases of the fatally sick (non-SIDS) children and in the arcuate and dorsal vagal nuclei in 8 of 10. "Examination of the brainstem in the SIDS group showed a topographically similar profile with an equally intense immune reactivity within the very same neuronal circuits; precisely the strongly expressed cytokine labeling of IL-2 in SNTT and/or TSNT was observed in 17 out of 18 cases that constituted the 2nd study group (SIDS). IL-2 was also notable in the arcuate nucleus and dorsal vagus nucleus in 17 cases. These brainstem neuronal centers are known to be intricately implicated in autonomic control of vital homeostatic functions namely cardiorespiratory control mechanisms."[48] The authors concluded that it was not surprising to see the intense IL-2 expression in the infants who were severely ill before they died, but the SIDS victims are generally free from apparent potentially fatal conditions. "The SIDS victims often have preceding mild infectious/inflammatory conditions (like coryza[49]/mild upper respiratory infections, soft stools mild gastroenteritis, *postvaccinal fever*, etc.). Such trivial infections were found to induce a hypertuned immune/inflammatory response including high levels of immune inflammatory cytokines." *Id.* at 122. (emphasis added). Kadhim reviewed the Triple Risk Model, placing his study findings with regard to inflammatory cytokines in that framework; "Such mild infectious inflammatory conditions (extrinsic environmental stressors), if contracted in a vulnerable infant (intrinsic factors including prematurity and gene polymorphisms) during a critical developmental period whereby brainstem command centers undergo rapid maturation could provoke exaggerated immune responses with over expression of cytokines. We believe that this hypertuned immune response is behind the high IL-2 immune-reactivity we detected in situ in the brainstem of these victims." *Id.* at 125. Kadhim also noted that while pro-inflammatory cytokines have immune function, it is noteworthy here that cytokines have *neuro-modulatory effects* whereby they can modify neurotransmission. *Id.*

The role of mild infection was further discussed in an article by Rognum et al.[50] The Rognum group compared three groups of deceased infants. The group of 25 SIDS cases was selected from those subjects in whom no explanation for death was found. A second group died from known infectious causes and the third control group died primarily from violent causes

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[47] Kadhim, H. et al., *Interleukin-2 as a Neuromodulator Possibly Implicated in the Physiopathology of Sudden Infant Death Syndrome*, 480 Neurosci. Lett. 122 (2010), Exhibit 13-O at 123.

[48] Kadhim et al. (2010), Exhibit 13-O at 124.

[49] Coryza, also known as acute rhinitis, is defined as an "inflammation of the mucous membranes of the nose." *Dorland's* at 423, 1639.

[50] Rognum, I.J., R.L. Haynes, A. Vege, M. Yang, T.O. Rognum & H.C. Kinney, *Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome*, 118 Acta Neuropathol. 519 (2009), Exhibit 13-N at 519-30.

such as drowning, suffocation or strangulation. *Id.* at 522. The IL-6 levels were significantly higher in SIDS subjects than in controls. The IL-6 levels in SIDS infants with minor infection were comparable to those infants who succumbed to severe infection. *Id.* at 520.

Rognum et al. wrote: "We previously showed that IL-6 is elevated in the cerebrospinal fluid of SIDS infants and that this elevation may be induced by a peripheral immune reaction. Approximately one half of the SIDS cases we have studied show signs of a mild infection, but IL-6 levels are comparable to those of infants succumbing to severe infection, suggesting an overreaction to the slight infection." *Id.*

According to Rognum: "In addition to its pro-inflammatory properties, IL-6 exerts effects outside the immune system. Non-immune cells including neurons can produce and secrete IL-6 and express its receptor. Of critical relevance to the premise that cytokines interact with central neurons to affect their function, IL-6 is shown to be important in neuronal development in the modulation of neuronal signaling." *Id.* "A major site of 5-HT cell bodies in the human infant brainstem is in the arcuate nucleus, the putative site for central carbon dioxide (CO2) sensitivity in humans and animal models. In this regard the synergistic effect of prone sleeping and infection on SIDS risks may be a set up for CO2 accumulation, as both rebreathing in the face down prone position and increased metabolism due to infection may increase CO2 levels. Death may be triggered if CO2 sensing regions in the brainstem, such as the arcuate nucleus, are compromised and cannot mount an arousal response to protect the infant from the dangerous situation. The arcuate nucleus is of particular interest in the study due to the previous finding by others of high neuronal IL-1β immunoreactivity at this site in SIDS cases compared to controls." *Id.*

Rognum et al. did identify one particular confounder to this theory in that they found that the mean IL-6R (receptor) intensity grade in the arcuate nucleus was significantly higher in the SIDS group than in the control group but the gp130 transducer was significantly higher in the infection group but less so in SIDS relative to the controls. While Rognum et al. acknowledged difficulty in grading the immunosensitivity of IL-6R and gp130 in this study due to its small size as a major limitation in the study, the result led the authors to hypothesize that the increased expression of IL-6R in the arcuate nucleus may be a compensatory mechanism as defective arcuate neurons may require excessive IL-6 stimulation in order to respond to altered carbon dioxide levels and there may be an inability in the SIDS babies to upregulate gp130 to mount an effective response.[51] *Id.* at 528. Nevertheless, the study concluded that abnormal IL-6R expression was found in the arcuate nucleus of SIDS babies 44% of whom had mild infections prior to death and thereby "provides evidence for aberrant interactions in SIDS infants between Il-6 and the arcuate nucleus, a key medullary 5-HT related region involved in protective responses to hypercapnia, potentially induced by the combined effect of prone position and mild infection." *Id.* at 529.

[51] Dr. Miller explained that gp130 is a second messenger in the cell that takes the message that the receptor has bound something and does something with it to take (tell) the cell to do something else. This is a very common mechanism in membrane signaling, that there's a second messenger system that then tells the cell to do something. Tr. p 32.

Rognum et al. concluded: "The key finding in this study is abnormal IL-6R expression in the arcuate nucleus in the SIDS cases, 44% of whom had signs of mild infection immediately prior to death. *Id.* at 528. Rognum further noted that the arcuate nucleus contains 5-HT and glutamatergic neurons that have been shown in animals to be critical to chemosensitivity. It is also the site for several neurotransmitter abnormalities in SIDS, including in 5-HT, muscarinic and kainite receptor binding. It is well documented that CO2 levels are elevated during severe neonatal infection and, interestingly, even mild upper respiratory infection may increase CO2 levels in infants over 3 months of age. Animal studies indicate that the *CO2 elevation can be attributed to a hyper metabolic state induced by proinflammatory cytokines*." *Id.* at 527-28 (emphasis added).

Kashiwagi studied the production of cytokines after vaccination in 61 vaccine recipients with fever and 18 without fever within 24 hours of vaccination. Blood samples were taken within 48 hours of vaccination in both groups. He reviewed the role of the innate immune system in responding to vaccination noting that the activation of the innate immune system including the enhanced production of inflammatory cytokines is indispensable for immunogenicity and these cytokines may be related to the occurrence of adverse events.[52] This group found that cytokine production began about 6 hours after the stimulation by a single or combination of vaccines and *increased for 24 hours, showing the same level afterward. Id.* at 679. They found that higher levels of IL-1β, IL-6, G-CSF[53] and TNF-α were produced with the concurrent stimulation by multiple vaccines than with the single vaccine in PBMC cultures (peripheral blood mononuclear cells - obtained from young infants in this study). *Id.* at 679. Higher levels of IL-6, IL-10, IL 12, G-CSF, IFNγ and TNFα in both the febrile and non-febrile groups were found after vaccination and G-CSF was significantly higher in the febrile group. *Id.* at 680. He noted that innate immune systems are not fully functional at the time of birth. Kashiwagi's group found that TLR (Toll-Like Receptors) stimulated the production of pro-inflammatory cytokines (specifically IL-β, IL-6, and IL-8) which was markedly higher in neonates than in adults. He also found that higher levels of IL-1β were produced in PBMC cultures stimulated with PCV7 than with DPT or Hib. Hib induced higher levels of IL-6 and TNF-α. IL-1β increased in PBMCs stimulated concurrently with Hib/PCV7 and DPT/Hib/PCV7 with similar patterns of TNF-α and G-CSF. However, when blood was drawn 48 hours post-vaccination, IL-1β was not found. *Id.* Dr. Miller theorized that IL-1β rises rapidly and then disappears by 48 hours whereas the other inflammatory cytokines have a longer half-life. Tr. 47

Kashiwagi noted: "All effective vaccines induce the production of cytokines or chemokines, which modulate immunogenicity and are also involved in inducing adverse events, such as systemic febrile illness and immunotoxicity. In this standpoint, IL-6, IL-10, IL-12, G-CSF, IFN-γ, and TNF-α were detected in both febrile and non-febrile groups after vaccination in comparison with those in normal subjects." *Id.* at 683. Inflammatory cytokine profiles after vaccination were similar to the outpatient group infected with the influenza virus. *Id.*

[52] Kashiwagi, et al. (2014), Exhibit 17 at 678.

[53] G-CSF is granulocyte colony stimulating factor *Dorlands* at 767- It is now classified as another cytokine. Tr. 47.

Vege and Rognum reviewed the literature and their own work and noted that "in 1995 they found that half of the SIDS victims had elevated levels of interleukin-6 (IL-6) in their cerebrospinal fluid (csf). The concentrations of IL-6 in SIDS infants were comparable to those we found in infants dying from infectious diseases like meningitis and septicaemia." They concluded that there were two groups of SIDS infants—one with IL-6 levels similar to infants dying of severe infections and another having low levels similar to those dying violent deaths. They hypothesized that one group of SIDS deaths may be attributable to sleep position and another to an uncontrolled inflammatory response to infection, predominantly occurring at night when cortisol levels, another mechanism for controlling inflammatory responses, are low.[54]

Others have studied cytokine expression in animals. Brambilla demonstrated in animal studies that Interleukin 1 (IL-1) inhibited firing of excitatory or wakefulness producing neurons in the dorsal raphe nucleus and enhanced activity of GABAergic or inhibitory neurons and, as such, induces enhancement of NREM sleep.[55]

Respondent submitted an article by Siljehav, Hofstetter et al. which sheds additional light on the possible mechanism involved with apnea in infants occurring in response to infection. These authors wrote: "Our data suggest that PGE2[56] induced by IL-1β as well as hypoxia selectively modulates respiration-related neurons in the rostral ventrolateral medulla, including the preBotzinger Complex via EP3R. Other neuromodulators, including PGE1, have been shown to inhibit preBotC neurons and slow respiration-related rhythm and preBotC lesions may disrupt anoxic gasping and evoke central apneas and ataxic breathing. Moreover, these respiration-related neurons were recently shown to be critical for adequate response to hypoxia, maintaining brainstem homeostasis with gasping and autoresuscitation and thus restoring oxygen levels. PGE2-induced depression of this vital brainstem neuronal network, e.g., during an infectious response, could result in gasping and autoresuscitation failure and ultimately death."[57] The model of the IL-1β induced respiratory depression and autoresuscitation failure via a PGE2 –mediated pathway was described. "During a systemic immune response, the proinflammatory cytokine IL-1ß is released into the peripheral blood stream. It binds to its receptor (IL-1R) located on endothelial cells of the blood brain barrier. Activation of IL-1R induces the synthesis of PGH2 from arachidonic acid via COX-2 and the synthesis of PGE2 from PGH2 via the rate limiting enzyme mPGES-1. PGE2 is released into the brain parenchyma and binds to the EP3R located in respiratory control regions of the brainstem, e.g., nucleus tractus solitarius and rostral ventrolateral medulla. This results in depression of central respiration-related neurons and

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[54] Vege, A & T. Rognum, *Sudden Infant Death Syndrome, Infection, and Inflammatory Responses*, 42 FEMS Immunol. Med. Microbiol. 3 (2004), Exhibit 13-Q at 5 and 8.

[55] Brambilla, D. et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 Eur. J. Neurosci. 1862 (2007), Exhibit 13-M at 1862.

[56] PGE2 is a symbol for a prostaglandin. *Dorland's* at 1529. Prostaglandins are "any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway; they are potent mediators of numerous different physiologic processes." *Dorland's* at 1528.

[57] Siljehav, V. et al., *mPGES-1 and Prostaglandin E2: Vital Role in Inflammation, Hypoxic Response, and Survival*, 72 Pediat. Res. 460 (2012), Exhibit C-9 at 9897.

breathing, which may fatally decrease the ability to gasp and autoresuscitation during hypoxic events." *Id.* at 9898.

Stoltenberg[58] experimented on piglets and concluded IL-1 stimulates the release of beta endorphin and indicated that his group had shown that the level of beta-endorphin in cerebral spinal fluid correlates strongly with the duration of apnea. Furthermore IL-1β stimulates GABA transmission and hence increases the inhibitory postsynaptic function by opening of chloride delective channels, and this will reduce the activity in the central respiratory neurons and may produce hypoxia. He concluded that intravenous and intrathecal injections of interleukin 1β in piglets' prolonged apnea and modified autoresuscitation. Such a mechanism may play a role in depressing respiration in some infants dying of sudden infant death syndrome. *Id.* at 427.

In a study looking at the role of vaccination in producing apnea, bradycardia and oxygen desaturations in pre-term infants who received first DPT (whether whole cell or acellular pertussis, inactivated polio and Haemophilus influenza B), Lee found elevations in apnea, bradycardia and desaturations defined as cessation of respiration for 20 seconds, with a heart rate less than 100 and oxygen saturation less than 85%. Almost half had adverse cardiorespiratory events in the 72 hours post-vaccination which was statistically significantly higher than the control group which did not receive a vaccination in the prior 72 hours.[59]

Schulzke also studied apnea and bradycardia in pre-term infants, not on oxygen or respiratory support but in the NICU when they received pentavalent or hexavalent vaccines. Rate of increased apnea and bradycardia (defined the same as by Lee) was 13% in otherwise stable infants. Infants received ventilatory support and recovered. Events occurred between 8 and 24 hours after vaccination with onset of fever between 6 and 24 hours post immunization. [60]

B. SIDS Epidemiology

Although epidemiology is not required to demonstrate entitlement to compensation in the Vaccine Program, the parties submitted multiple articles, primarily from European studies, which looked at the question of the possible relationship between vaccination and the incidence of SIDS, as well as several articles that reported on cases. Articles by Venneman[61], Jonville Bera, Traversa, VonKries, Goldman, and Kuhnert studied the question of vaccine causation in SIDS by various methodologies all of which described their own limitations. Others by Ottaviani and

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[58] Stoltenberg, L. et al., *Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1β Injection*, 22 J. Perinat. Med. 421 (1994), Exhibit 13-J.

[59] Lee et al., *Frequency of apnea, bradycardia, and desaturations following first diphtheria-pertussis invactivated polio-Haemophilus influenzae type B immunization in hospitalized preterm infants,* BMC Pediatrics (2006), Exhibit 20 at 3-4.

[60] Schulzke, *Apnea and bradycardia in preterm infants following immunization with pentavalent or hexavalent vaccines,* European Journal of Pediatrics (2005), Exhibit 21 at 432-35.

[61] Vennemann M.M. et al., *Sudden Infant Death Syndrome: No Increased Risk After Immunization*, 25 Vaccine 336 (2007), Exhibit C-17.

Zinka discussed individual cases of unexplained deaths occurring in close temporal proximity to receipt of vaccinations.

Goldman looked at VAERS data from 1990 to 2010 for hospitalizations and deaths after vaccinations and found a statistically significant positive correlation between mortality and receipt of five to eight vaccines compared to one to four.[62] (J.B. received 7 counting DTaP as three as the study did). Traversa conducted a large study using data from the Italian health system where vaccines are offered for free and the belief is that 95% of children are vaccinated. The study found a statistically significant relative risk for death in the first seven days after vaccination for the first hexavalent vaccine (six vaccines) but not after subsequent doses.[63]

Kuhnert did a review of studies from Germany, England, and New Zealand and critiqued the case control methodology through the use of the self-controlled case series method (SCCS). It concluded that the re-analysis using the latter method showed that the risk of SIDS was neither increased or decreased in SIDS cases or controls during the early post-vaccination periods but did "provide more detailed insights into the methodological pitfalls of such analyses using conventional case control methods."[64] Dr. McCusker testified that the Kuhnert study looked at three different studies and applied 39 statistical tests to them. She read the study as concluding that despite the application of multiple statistical post hoc tests, they still did not see anything. Tr. 236.

Other papers submitted in evidence included Zinka[65] reporting on six deaths in Germany within 48 hours of receipt of hexavalent vaccines. Kries[66] reported on a slight elevation in day one in the first year of life after one particular hexavalent vaccine but a significant increase in deaths in the second year of life after receipt of that vaccine. Ottaviani[67] did a detailed case study of one young child who died three hours after receipt of a hexavalent vaccine at 3 months of age. He did a detailed autopsy identifying bilateral hypoplasia of the arcuate nucleus. He concluded that this death could be consistent with the Triple Risk Model or be one of the SIDS

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[62] Goldman, G.S. and N.Z. Miller, *Relative Trends in Hospitalizations and Mortality Among Infants by the Number of Vaccine Doses and Age, based on the Vaccine Adverse Event Reporting System (VAERS): 1990-2010*, 31 Hum. Exp. Toxicol. 1012 (2012), Exhibit 19 at 1016, Table 4.

[63] Traversa, G. et al., *Sudden Unexpected Deaths and Vaccinations During the First Two Years of Life in Italy: A Case Study*, 6 PLoS One 1 (2011), Exhibit 13-U at 4.

[64] Kuhnert R. et al., *Reanalyses of Case Control Studies Examining the Temporal Association Between Sudden Infant Death and Vaccination*, 30 Vaccine 2349 (2012), Exhibit C-20 at 2355.

[65] Zinka, B. et al., *Unexplained Cases of Sudden Infant Death Syndrome Shortly After Hexavalent Vaccination*, 24 Vaccines 5779 (2006), Exhibit 13-S.

[66] Kries, R. et al., *Sudden and Unexpected Deaths After the Administration of Hexavalent Vaccines (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B, Haemophilus Influenza Type B): Is There a Signal?*, 164 Eur. J. Pediatr. 61 (2005), Exhibit 13-R.

[67] Ottoviani, G. et al., *Sudden Infant Death Syndrome (SIDS) Shortly After Hexavalent Vaccination: Another Pathology in Suspected SIDS?*, 448 Virchows Arch. 100 (2006), Exhibit 13-T at 4.

"grey zone" cases in which it is difficult to establish if the pathological findings were sufficient to cause death.

Each of the studies contained considerable acknowledgment of its own methodological deficiencies that may have affected the results. In different papers, these included inclusion without autopsies, small samples, comparing SIDS victims to living children rather than vaccinated SIDS to unvaccinated SIDS, as well as having no control group or having potential underreporting as in VAERS. The Kuhnert paper which analyzed three other case control studies including Venneman, said, "The small number of cases is a problem with the three case control studies, particularly in view of the short time periods under investigation. This problem is illustrated by the very broad confidence intervals of estimates that are only related to the events of the first few days."[68]

Dr. Miller criticized several of the studies for failing to use cases that were verified by autopsy, that the Vennemann study compared a new hexavalent vaccine to older vaccines rather than asking the question as to whether vaccines regardless of new or old could be associated with SIDS, and used data based on the number of vaccines sold rather than administered. Tr. 70-74. He noted that the IOM concluded that the evidence that it reviewed was insufficient to accept or reject causation. Tr. 387. In his report, Dr. Miller explained why it is difficult to do reliable epidemiological studies of SIDS. He said, "[I]f the risk for SIDS is present only in those infants who are already vulnerable because of a pre-existing brainstem abnormality, then no retrospective (or prospective) epidemiological study not grounded in a thorough neuropathological examination of all of the supposed SIDS cases would be likely to identify that putative causal relationship." Exhibit 13 at 5. He observed that J.B. would be one of those not counted as he did not have a complete neuropathological autopsy. *Id.* at 6.

Dr. McCusker criticized some studies as case reports or having no control group. She looked to Kuhnert which incorporated Vennemann to argue that there was no significant finding that SIDS occurred more often than chance. Tr. 228.

The Vaccine Program does not require epidemiological evidence and the studies presented contained multiple methodological flaws, and did not tend to shed much light on the question at issue, that is, whether the death of the child in this case was caused or triggered by the vaccinations received the day before. Thus the studies were read and considered and credited to show that vaccines are generally safe, but were specifically unpersuasive as to whether they are on rare occasions the exogenous factor resulting in the perfect storm in a child with a defective arcuate nucleus or other 5HT structure during the vulnerable period of life. They were also unpersuasive to reject causation as they frequently showed some temporal correlation to the receipt of vaccines even if those correlations were not found to be statistically significant.

[68] Kuhnert et al. (2012), Exhibit C-20 at 2355.

C. Expert Opinions

1. Petitioners' Expert Douglas C. Miller

Dr. Douglas C. Miller earned his bachelor's degree from Williams College and his medical degree from the University of Miami School of Medicine in 1978.[69] He received a Ph.D. in Physiology and Biophysics from the University of Miami in 1980. *Id.* Dr. Miller was a resident at Massachusetts General Hospital from 1980-1984, focusing in the areas of anatomic pathology and neuropathology. *Id.* He currently serves as a clinical professor of pathology and anatomical sciences, as well as the program director of pathology residency, at the University of Missouri School of Medicine. *Id.* at 3. He also serves as an associate medical examiner for Boone, Callaway, and Greene Counties in Missouri. *Id.*; Tr. 10. Dr. Miller has been a full-time faculty member at the medical schools at Robert Wood Johnson in New Jersey, New York University, and the University of Missouri. He has published over 150 articles in medical journals and is the author of a textbook on neuropathology.

i. *Althen* Prong One: Medical Theory

Dr. Miller, consistent with the dominant literature in the field, proposed the Triple Risk Model of SIDS as the framework for his theory of causation.[70] Tr. 19. As explained above, this model first provides that SIDS can occur only when an infant is in a critical developmental period (the first year of life). Tr. 20. Second, SIDS can occur only to an infant who is inherently vulnerable in some way. *Id.* Third, the infant must encounter an exogenous stressor. *Id.*

Dr. Miller explained the normal physiological process for handling carbon dioxide and stimulating breathing. He said if the carbon dioxide levels rise above a normal threshold to an abnormal threshold, a normal brainstem's response – in this age group – is mediated by the arcuate nuclei alone. The excess carbon dioxide stimulates other neuronal systems to alert the cervical spinal cord motor neurons to tell the diaphragm and other muscles of respiration to contract, at the same time signaling up through other mechanisms in the basal forebrain, underneath the lower part of the frontal lobes, to wake up. In general, there is arousal and there is deeper breathing to blow off the carbon dioxide, and if it is position-related, the infant would also move so that homeostasis is restored. Tr. 29. He explained that this process is dependent on serotonin, an excitatory neurotransmitter, which stimulates the cells to which it signals to fire more rapidly to increase breathing or arousal. Tr. 28. That is in contrast to GABA, which is inhibitory and balances the excitatory effect of serotonin. *Id.*

Dr. Miller explained that the majority opinion in the medical community is based principally but not exclusively on work done by Dr. Hannah C. Kinney, in a series of papers that stretch back more than 25 or 30 years and has been verified by other people. She has shown that "the medulla, the lowest part of the brainstem, in infants who have died of SIDS and have been autopsied and have had the appropriate examinations is defective. In particular, it has a defect in

[69] Curriculum Vitae of Dr. Douglas C. Miller, Exhibit 14 at 1.
[70] Kinney, H.C. et al., *Medullary Serotonergic Network Deficiency in the Sudden Infant Death Syndrome: Review of a 15-Year Study of a Single Dataset*, 60 J. Neuropathol. Exp. Neurol. 228 (2001), Exhibit 13-C.

a set of nuclei [or] groups of neurons, which use, as a neuro-transmitter a molecule called serotonin … which is also known as 5-hydroxytryptophan and which is abbreviated as 5-HT." Tr. 19. He further explained that Dr. Kinney and others have shown various deficits in infants, but the ones who die of SIDS have in common deficits in either the number of 5-HT neurons or in receptors for serotonin on those neurons or various other associated abnormalities. All of these suggest that the infants who die of SIDS usually die in their sleep and usually after an episode of apnea – that is, the cessation of breathing with elevated carbon dioxide in the blood to which they fail to respond normally. They fail to respond because the 5-HT system is the system which, in that age group, allows for arousal and increased breathing to respond to that kind of a danger. Since they fail to respond, they do not wake up, they do not breathe, and they die. Tr. 20.

Dr. Miller theorized, consistently with the research of Dr. Kinney and others, that many SIDS infants have "abnormalities of the medullary serotonergic synaptic systems governing respiration and arousal from apnea." *Id.* at 6. He said that "we have data that at least 70 percent of infants who ultimately die of SIDS have a defective 5-HT system which is way over half and thus statistically likely that [J.B.] was one of those." Tr. 62. Dr. Miller said, "It's really a neurochemical question. These molecules (cytokines) are provoked by an immune response, an innate immune response, originally in the periphery, but their effect in terms of SIDS is a neurochemical effect, affecting synaptic transmission and neuronal activity of the 5-HT system and maybe the GABA system in the medulla, and that's a neurochemical synaptic effect." Tr. 61. He stressed that the role of the cytokines in SIDS was in their capacity to modify normal neurologic function rather than being purely immune in nature. He assumed that J.B. was an immunologically normal child, who when given a vaccination would have had an appropriate immune response, including the production of cytokines such as the ones identified by Kashiwagi et al. Therefore, he would expect the level of cytokines to be transiently increased after vaccination. Tr. 62. "These cytokines would have been circulating in his body after vaccination and we have direct evidence that there was some cytokine-central nervous system interaction in that he had fever. Then there is a logical chain of events that says cytokines depressed the 5-HT system in a defective medulla leading to SIDS during sleep." Tr. 62-63.

Dr. Miller stated that research is still identifying all of the exogenous stressors for SIDS. Tr. 44. He opined that one very well-recognized exogenous stressor for SIDS is mild infection. Tr. 45. Some of the estimates indicate that 40 - 50% of SIDS victims have had a very recent or current mild upper respiratory infection (URI) at the time of death. Tr. 45. He said that it is explicit in the literature from Dr. Kinney's laboratory and others that what happens with mild infections is that the response to the infection involves the production of certain cytokines and that those cytokines can act on the central nervous system. He presented a theory: that a mild upper respiratory infection can act as a neurochemical stressor by prompting the upregulation of cytokines, which he theorizes are detrimental in two ways. He said that an infection could cause fever, an extrinsic risk factor, and can cause elevated IL-1β levels, which would further depress a defective medullary 5-HT system. The system would then be incapable of responding to excess carbon dioxide, resulting in death. Tr. 46.

Dr. Miller cited several studies, including ones discussed above by Rognum, Kashiwagi, Kadhim, Brambilla, Stoltenberg, and Froen, that addressed the issue of cytokine stimulation and the function of cytokines entering the central nervous system. From these studies, Dr. Miller concluded that either mild URIs or vaccinations upregulate the production of cytokines, and these inflammatory cytokines, can "shut down" a structurally vulnerable 5-HT system and completely prevent it from restoring an infant's normal breathing. Tr. 35. In other words, the cytokines and the structural defect in the serotonin system acting in concert during a vulnerable period have the cumulative effect of causing SIDS by making the baby incapable of responding to excess carbon dioxide.

Dr. Miller noted that Kashiwagi found similar cytokine profiles in the recently-vaccinated population and those suffering from influenza, and further that the cytokine profiles were similar in post-vaccination babies whether they had a fever or not. Tr. 49. He explained that cells that are injured by infection initially produce an innate immune response. The cells of the innate immune system release cytokines which signal further activation of the adaptive immune system to respond to the foreign antigen. He said that there is a wide range of things that the cytokines produce, but the initial production is certainly peripheral where there is infection. Tr. 50. He testified that there is a whole lot of evidence that cytokines, produced peripherally, interact with the central nervous system and the easiest one to understand is the way fever is produced. He explained that fever is mediated by the central nervous system and specifically by the hypothalamus in the brain. The hypothalamus sets our body temperatures. It causes us to shiver if we are in the cold and need to warm up, or to sweat when we are overheated. Tr. 50-51. He further explained that if the fever was generated in response to an infection outside of the brain, such as in the case of a URI, there would be no inflammation in the brain as the brain is not infected, but there is still an interaction with the hypothalamus in the brain caused by cytokine signaling that causes fever in response to an infection outside of the brain. Tr. 51-52. Dr. Miller stated that he was not aware of any literature describing URI as a *mechanical* exogenous stressor and that in his professional experience conducting autopsies, he had never seen a URI "obstruction of the airway" that would be sufficient on its own to cause death. Tr. 46.

Dr. Miller stated that vaccinations can be an extrinsic risk factor in SIDS, as they prompt the upregulation of cytokines that, among other things, produce fever. Tr. 62-63. He testified that, based on the literature, there is a scientifically-plausible mechanism for vaccinations acting as the extrinsic risk factor in SIDS in much the same way as a mild infection. He explained that when you get a vaccination or a whole group of them at once, as J.B. did, it evokes a response which includes the production of cytokines, and that among those cytokines are IL-6, TNFα, and IL-1β. The physiological studies have shown that these can raise body temperature by producing fever, which is a risk factor, and they can inhibit the activity of 5-HT neurons in the medulla causing prolonged apneas and interference with autoresuscitation. Tr. 54, 62-63. When the vaccines are administered in the presence of the defects in the medulla, during the critical developmental period, they are likely to have a similar effect as mild infection that may cause a failure of the medullary response system and ultimately a death. Tr. 54.

Dr. Miller stated that mild upper respiratory tract infection is widely recognized to be an exogenous stressor under the Triple Risk Model. However, he acknowledged that there is not wide recognition, or a generally accepted theory, that vaccinations are an exogenous stressor. He stated that the Institute of Medicine concluded "the evidence is insufficient to say that there is an effect or there isn't an effect." Tr. 55. The Kinney research team has not studied the relationship between vaccination and SIDS. Tr. 60. Dr. Miller pointed to "multiple reports of similar cases of SIDS following various neonatal or infant vaccinations, mostly stressing the close temporal relationships between vaccination, increased cytokine production, and death from apparent SIDS as seen with this case."[71] He said that these individual cases and small case series show a "suspicious association between the timing of vaccination and the timing of SIDS deaths." Tr. at 55.

Summarizing his theory and review of the literature, Dr, Miller testified that the papers cited, including Kadhim, Kashiwagi, Rognum, Stoltenberg, and Froen, "verify the importance of the 5-HT system and its interactions with the GABA system in the medulla in terms of response to apnea or other respiratory-related insults." Tr. 34. Second, "they showed that there's an altered cytokine profile in SIDS cases versus non-SIDS cases, dying of other things, like drowning or trauma." *Id.* Third is the specific information on IL-1β, in that it inhibits the 5-HT system. *Id.* Therefore, in the context of SIDS, this suggests that if there is an elevated level of IL-1β to which the 5-HT neurons are exposed in an infant who already has too little 5-HT activity because of a defective brainstem, this additional cytokine effect would shut down the system such that it would not respond to other external stressors such as prone sleeping, nicotine, infection or fever. Tr. 34-35.

Dr. Miller addressed this analysis in terms of the cytokine reaction generated by vaccines. He said that we know that when a child gets a vaccine or a whole group of vaccines all at once, as occurred in this case, it evokes a response which includes the production of cytokines; that among those cytokines are IL-6, TNFα, and IL-1β. Those levels go up in the blood. We know that IL-1β can inhibit the activity of the 5-HT neurons in the medulla. If you take an infant who has a defective medulla with a defective 5-HT system already, you put in a stress situation with elevated carbon dioxide or low oxygen, and there is a vaccination which further shuts down the 5-HT system, and you can get a complete failure of response and therefore a death. He concluded that the mechanism is plausible. Tr. 54.

ii. *Althen* Prong Two: Logical Sequence of Cause and Effect

Dr. Miller then applied his theory to J.B.'s specific case. As an initial matter, he agreed with the decision to classify J.B.'s death as SIDS. Exhibit 13 at 1. Under the Triple Risk Model, Dr. Miller opined that J.B. was in the critical developmental period. Tr. 44. Statistically, he was inherently vulnerable. Dr. Miller opined that Kinney et al. have found that a significant proportion – up to 70% – of SIDS infants have abnormalities in the arcuate nuclei and other sections of the medulla. Exhibit 13 at 3. Dr. Miller said that there is also a Japanese study in

[71] Vege & Rognum (2004), Exhibit 13-Q; Kries et al. (2005), Exhibit 13-R; Zinka et al. (2006), Exhibit 13-S; Ottoviani et al. (2006), Exhibit 13-T; Traversa et al. (2011), Exhibit 13-U; Institute of Medicine, *Adverse Effects of Pertussis and Rubella Vaccines* (1991), Exhibit 13-V.

which that number went as high as 90 percent. Tr. 38. He testified that it is statistically most likely that J.B. also had this medullary 5 HT defect based on the Kinney data and other studies, even though it was not confirmed because the medical examiner did not sample that section of the brain. Exhibit 13 at 4-6; Tr. 37-38. Dr. McCusker agreed that "according to the Triple Risk theory, the brain problem must exist [in J.B.'s case]." Tr. 206.

A great many autopsies of SIDS infants outside of the research context do not section all of the necessary areas of the brain or view them histopathologically, which is typical of medical examiner autopsies. Tr. 16. Respondent's expert pathologist, Dr. Harris, acknowledged that based on Dr. Kinney's research, the majority of SIDS babies and up to 70% in some of her studies had an abnormality of the 5-HT system. Tr. 346. However, "[d]etection of these abnormalities requires special immune-histochemical research techniques not generally available for a 'routine' autopsy." *Id.* Dr. Miller testified that even in some autopsies where no structural abnormality was found in Dr. Kinney's research, when the full histochemistry was performed, there were still receptor binding deficits, such as in the IL-6 and gp130 studies. Tr. 41-42. Unfortunately, the types of tools she used including autoradiography and immunohistochemistry are not generally available for autopsies. Tr. 42-43.

Dr. Miller discussed the logical sequence of cause and effect between vaccines administered on September 2, and J.B.'s death on September 3. He opined that the vaccines acted as a critical external stressor in this case. He noted that J.B. was a "healthy infant… developing normally." Exhibit 13 at 4. He was "immunologically normal." Tr. 62. Therefore, after receiving vaccinations, his body mounted an innate immune response including the production of cytokines. Exhibit 13 at 6; Exhibit 16 at 1; Tr. 63. Those cytokines circulated in J.B.'s body, specifically into the central nervous system. Exhibit 13 at 6; Tr. 63. These peripheral cytokines interacted with the hypothalamus to provoke fever the night after the vaccinations, and the following day (before J.B.'s death). Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62-64. "Those cytokines then acted in the brainstem which was already deficient in serotoninergic drive for respiratory effort, leading to an apneic episode from which he did not recover, i.e., SIDS." Exhibit 13 at 6; *see also* Tr. 62 (the cytokines "depress[ed the] 5-HT system in a defective medulla, leading to SIDS during sleep").

He opined that there was "no other demonstrable inciting event" for J.B.'s death. Exhibit 13 at 1. There was no evidence of the fever being related to anything other than J.B.'s vaccinations. Tr. 66. The autopsy did not identify any other infectious processes. Tr. 66.[72]

Dr. Miller was asked whether the pillow in J.B.'s crib increased the risk of SIDS. Tr. 87. Dr. Miller was not sure whether J.B.'s head was on the pillow. *Id.* He said, "If the pillow was by his feet, I don't think it's a risk factor." *Id.* A review of the investigation files indicates that there was no evidence as to whether or not his head was on the pillow. The only relevant evidence was that it was "a little crib pillow-very flat" and that his mother told the police that his nose or mouth were not covered when she found him about ten minutes after replacing his pacifier. Exhibit 7 at 5.

[72] Dr. Miller noted that there was bacterial growth and food particles in J.B.'s lungs and epithelial cells in the upper airways. He opined that this was not evidence of a separate infectious process. He agreed with the medical examiner that these were terminal or resuscitative events. Tr. 17-18; 66; 352-53.

On cross-examination, Dr. Miller stated that J.B. was placed on his back but was found on his side, which demonstrates that he was able to "move around." Tr. 92. However, J.B. did not pass away until "something else intervened." Tr. 85. Based on his theory and the temporal association, Dr. Miller opined that the vaccines were the intervening factor that caused J.B.'s death. Tr. 85; Exhibit 7 at 5. He said that he looks at SIDS cases individually and that it was his diagnosis that the vaccines contributed substantially to the death of J.B. in this case. Tr. 106-08.

iii. *Althen* Prong Three: Timing

With regard to timing, Dr. Miller stated several reports "have noted an elevated risk for SIDS within the first 48 hours following immunization, although this is not statistically significant." Exhibit 13 at 5. He stated that J.B. died within this 48-hour "window of elevated risk" following vaccination. *Id.*

Dr. Miller also stated that the available evidence is that foreign antigens, like those contained in vaccinations, activate the production of cytokines "within hours" and that production "peaks within 2 to at most 4 days." Exhibit 16 at 1. Thus, a vulnerable infant who receives vaccinations is most likely to suffer a fatal event if one is to occur "within the first 48 hours to at most 4 days." *Id.* Dr. Miller opined that J.B.'s death was "well within this vulnerable period." *Id.*

2. Respondent's Expert Dr. Christine McCusker

Dr. Christine McCusker earned a Masters in Molecular Virology in 1988, followed by an M.D. in 1993, at McMaster University, in Hamilton, Ontario. Exhibit D at 1. Her residency training was in pediatrics, at Montreal Children's Hospital, McGill University, from 1993-1996. *Id.* at 2. She was then a clinical fellow in allergy and immunology at McGill University from 1996-1999. *Id.* Dr. McCusker is board certified in pediatrics. *Id.* She is currently the division director of pediatric allergy, immunology, and dermatology at the Montreal Children's Hospital at McGill University Health Center and is the director of the Clinical Immunology Lab. Tr. 122. She has a wet lab that studies developmental immunology, which has peer-reviewed funding. *Id.* She also runs a clinical research program that uses databases to follow patients with primary immunodeficiency. *Id.* In addition, she sees pediatric patients at McGill Children's emergency room and at several allergy, immunology, and general pediatrics clinics. Tr. 124. Dr. McCusker also teaches medical students in the areas of immunology, dermatology, and malignant hematology. *Id.*

i. *Althen* Prong One: Response to Petitioners' Medical Theory

Like petitioners' expert Dr. Miller, Dr. McCusker accepted Dr. Kinney's formulation of the Triple Risk Model. Dr. McCusker agreed with Dr. Miller on the critical development period, and that an infant may be "vulnerable" because of a brain defect, premature birth, male gender, and/ or African American race. Dr. McCusker disagreed with Dr. Miller's opinion that upper respiratory infection, and by extension, vaccines, act as *neurochemical* exogenous stressors within the Triple Risk Model.

Dr. McCusker spent considerable time explaining why upper respiratory infection and other exogenous stressors, such as "being placed or found in a prone/ side-sleep position, found face down, head covered, sleeping on an adult mattress, couch, or playpen, soft bedding, bed-sharing, and signs of upper respiratory tract infection," are *mechanical*. Specifically, each one impedes an infant's ability to exhale carbon dioxide and inhale fresh oxygen, thereby increasing the risk of SIDS. Tr. 127-28.[73]

She opined that the prone sleep position is more widely recognized as an exogenous stressor for SIDS, but that the side-sleep position poses just as much risk. Tr. 131. She stated that breathing depends on "drop[ping] the diaphragm down and creat[ing] a negative airspace, [in which] the air comes rushing in." Tr. 130. An infant's body is not fully developed, so it uses "more than just the diaphragm" and "a lot of abdominal muscle to breathe." *Id.* An infant lying supine with the head back breathes most easily. *Id.* In contrast, an infant in either the prone or side-sleep position has more difficulty dropping the diaphragm and exhaling carbon dioxide. *Id.* Dr. McCusker also opined that the side-sleep position compresses "at least half your rib cage." Tr. 132. She stated that an infant's rib cage is "soft" and "very pliable." Therefore, it does not take much to influence the infant's ability to exchange air. *Id.* She also noted that an infant's breath is much more shallow and rapid than an adult's, and therefore the diffusion of exhaled carbon dioxide is less than in adults and rebreathing is more likely. *Id.* Theoretically, this means that an infant is at greater risk of re-inhaling expelled carbon dioxide. *Id.* Dr. McCusker acknowledged that the Back to Sleep Campaign previously advised parents to avoid all risk factors for SIDS, and that early research emphasized avoiding prone sleeping. *Id.* at 132-33. However, she said more recent studies looking "a little bit more closely" indicate that "prone and side-sleeping have equal risk." Tr. 134. She also stated that an infant learns to roll from the supine position to the side or prone position, but "usually not until somewhere between four and six months." Tr. 134-35. She did acknowledge, however, that the American Academy of Pediatrics does say that once a child is able to roll from his back to his side or to prone, then the parent should not disturb them. They should just have nothing else in the crib that could obstruct breathing. Tr. 135.

She also stated that gastroesophageal reflux is an exogenous stressor. Tr. 137. Specifically, an infant's airway and esophagus are linked at the back of the throat. *Id.* An infant may regurgitate and inhale at the same time, and therefore stop breathing momentarily. *Id.* at 138. If the infant neither swallows nor expels the food, his breathing will become obstructed and he will not recover. *Id.*

Dr. McCusker stated that bundling is an exogenous stressor and suggested several possible reasons why. *Id.* at 135. First, she opined that bundling decreases an infant's arousal, which helps the infant go back to sleep, but may increase the incidence of SIDS. *Id.* at 136. Second, a bundled infant may be less able to roll out of the prone or side-sleeping position. *Id.* Third, bundling may be an exogenous risk factor by leading to hyperthermia. *Id.* It should be noted that there is no evidence of bundling in this case, as J.B.'s father said he placed him on his back with a blanket across the midsection, but there was no indication that he was wrapped or bundled.

[73] Trachtenberg, Kinney, et al. (2012), Exhibit C-11.

Dr. Miller stated that hyperthermia was a term encompassing both high ambient temperature and fever. But Dr. McCusker disagreed. She testified that hyperthermia was high ambient temperature, and *hyperpyrexia* was fever. She stated that older literature listed both hyperthermia and hyperpyrexia as exogenous risk factors for SIDS. Tr. at 201, 287. However, she opined that newer literature, such as an article by Trachtenberg, lists hyperthermia as a risk factor for SIDS, but not fever. Tr. at 201, 287, 290. She agreed with this distinction. She reasoned that an infant experiencing hyperthermia tries to cool himself down. Tr. 289. To do so, the infant takes short, shallow breaths, which increase CO2 levels, which trigger the pathway to SIDS. Tr. 288, 295. She cited an article by Harper and Kinney, which provides that "vasodilation associated with overheating makes compensation for low blood pressure more difficult."[74] Dr. McCusker opined that fever is *not* a risk factor for SIDS. Specifically, she said in fever the body fasciculates or shivers – it makes small muscle movements that create friction, which generates heat inside the body. *Id.* at 184. The body cannot make these movements during deep REM sleep. Therefore, it stays in NREM sleep. *Id.* at 184-85. She opined that an infant generating or maintaining a fever, who does not descend into REM sleep, is less susceptible to SIDS. *Id.* at 202. It should be noted that nowhere in the submitted literature was an explicit distinction made between hyperthermia and hyperpyrexia, including in Trachtenberg or the Harper & Kinney article. Dr. McCusker is correct that in a 1992 article by Dr. Kinney, she mentioned "infection, fever and hyperthermia" as exogenous stressors.[75] Later articles generally reference hyperthermia and overheating. However, in a 2009 article, Dr. Kinney described a SIDS scenario in which in part she describes "an infant may be slightly febrile due to an otherwise trivial upper respiratory tract infection (3) as a consequence, the apnea component of the LCR is inordinately prolonged by mild hyperthermia,"[76] This reference would appear to suggest that the term hyperthermia may be more broadly inclusive.

Unlike Dr. Miller, Dr. McCusker characterized mild upper respiratory infection as a purely mechanical extrinsic risk factor for SIDS. Tr. at 127-28. She opined that an infant is accustomed to breathing through the nose, which enables uninterrupted bottle or breast-feeding. *Id.* at 138-39. When the nose is congested, she said, the infant still exerts significant effort to breathe through the nose, which elevates carbon dioxide. *Id.* at 139. If and when the infant finally resorts to breathing through the mouth, that is less effective and also increases the risk of respiratory distress. *Id.* at 140-43.

Dr. McCusker then spoke about cytokines. She asserted that cytokines serve a variety of positive functions in the healthy human brain. *Id.* at 145-58.[77] Researchers initially theorized that cytokines found in the brain, including IL-6, IL-1β, and tumor necrosis factor-alpha (TNF-alpha), had traveled there through the cerebrospinal fluid, to respond to inflammation in the brain. *Id.* at 151-52. However, research beginning in the late 1990s indicates that the brain itself

[74] Harper & Kinney (2010), Exhibit C-12 at 3.

[75] Filiano & Kinney (1992), Exhibit 13-A at 401.

[76] Kinney et al. (2009), Exhibit 13-H at 539.

[77] Besedovsky, H.O. and A. del Ray, *Central and Peripheral Cytokines Mediate Immune-Brain Connectivity*, 36 Neurochem Res. 1 (2011), Exhibit C-3.

produces cytokines. *Id.* at 152. Dr. McCusker cited articles reporting that inflammatory cytokines such as IL-6 and IL-1β regulate pain sensitivity, memory consolidation, stress, fever, and sleep. *Id.* at 152-56.[78] Ron-Harel wrote, "Pro-inflammatory cytokines are abundantly expressed in healthy brain and are involved in the regulation of many physiological functions such as pain sensitivity, memory consolidation and neural plasticity. Elevation in brain cytokine levels is considered part of the adaptive response to external stimuli. Exposure to acute psychological stressors by induction of adrenalin, noradrenalin and dopamine induces an increase in brain proinflammatory cytokines which modulate the neuroendocrine and behavioral response to the stressor. *Id.* at 3. She also cited an article by Moidunny et al. suggesting that cytokines including IL-6 may play a neuroprotective role in the brain after stroke or head trauma. *Id.* at 157.[79] Moidunny was studying the role of IL-6 in reducing glutamate excitotoxicity in stroke and head trauma with the goal of further research to identify additional pharmacological protection with IL-6 from glutamate neurotoxicity in these patients. Moidunny does not discuss SIDS or the role of peripheral cytokines in this article.

Dr. McCusker also cited to an article by Chen Miller, which discusses the role of Tryptophan Hydroxylase 2 which is a rate limiting enzyme in 5-HT biosynthesis. The article discusses advances in understanding Tryptophan Hydroxylase TPH and TPH2 which are critical for the initiation of the synthesis of 5-HT (serotonin) which modulates the stress response by interacting with the hormonal hypothalamic pituitary adrenal axis and neuronal sympathetic nervous system. The TPH2 mRNA expression is abundant in the raphe nuclei or regions containing raphe nuclei such as the pons and medulla, while it is detectable in a number of other regions including the cortex, hypothalamus, thalamus, hippocampus, amygdala and cerebellum. TPH2 gene expression is sensitive to stressful events including hemorrhage and hypoxia and involves neuronal and hormonal mechanisms. The article hypothesizes about the role of TPH2 and serotonin in response to stimulating events such as hypotensive hemorrhage, hypoxia and adverse events experienced in early life or as an adult, and a possible role in such conditions as PTSD but it was not clear how this paper directly addresses the issue of respiratory depression in SIDS. [80]

Dr. McCusker argued that the various animal studies cited by Dr. Miller were not relevant to cytokines' effect in infant brains *in vivo*. *Id.* at 162-87. First, she stated that the Brambilla article,[81] which showed that IL-1β depressed serotonin in rats' brain tissue, was not

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[78] Ron-Harel, N. et al., *Brain Homeostasis is Maintained by "Danger" Signals Stimulating a Supportive Immune Response Within the Brain's Borders*, Brain Behav. Immun. (2011), Exhibit C-1; Su, Y. et al., *Predator Exposure-Induced Cerebral Interleukins are Modulated Heterogeneously in Behavioral Asymmetry*, 135 Immunol. Let. 158 (2011), Exhibit C-4; Kinney et al. (2011), Exhibit 13-F.

[79] Moidunny, S. et al., *Interleukin-6-Type Cytokines in Neuroprotection and Neuromodulation: Oncostatin M, but not Leukemia Inhibitory Factor, Requires Neuronal Adenosine A1 Receptor Function*, 114 J. Neurochem. 1667 (2010), Exhibit C-2.

[80] Chen, G.L. & G.M. Miller, *Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin-Stress Interaction and Clinical Implications*, 159B Am. J. Med. Genet. B. Neuropsychiatr. Genet. 152 (2012), Exhibit C-15.

[81] Brambilla, D. et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 Eur. J. Neurosci. 1862 (2007), Exhibit 13-M.

relevant to sleeping infants. *Id.* at 185. Specifically, the Brambilla study submerged rats' brain tissue in "super-physiologic doses" of IL-1β for an extended period of time; and kept it isolated in petri dishes, which would not reflect what happens to a vulnerable infant in a "crisis situation." *Id.* at 186-87.

Similarly, Dr. McCusker opined that the Stoltenberg and Froen articles,[82] which reported that very young piglets did not recover from apnea as quickly when they received super-physiological doses of cytokines, had limited significance. *Id.* at 162-63. The articles reported this effect only in piglets younger than fifteen days old; in a previous study, cytokines did not have any effect on older piglets. *Id.* at 163. Dr. McCusker opined that pigs' and infants' respiratory systems develop at similar paces; therefore, piglets younger than fifteen days old could be compared only to infants under one month old. *Id.* at 164. Furthermore, she argued that Froen induced extremely high cytokine levels that would not occur naturally in infants. *Id.* at 171. On rebuttal, Dr. Miller responded to this criticism, by saying that pigs' *brains* are very different from human brains. Pigs are born with much more myelin than adult brains; they are much more mature than our brains. The piglets are walking and do things early in piglet life that humans take up to a year or more to do. Thus, this model is not an irrelevant model for a 4-month-old in terms of brain development. He noted correctly that what Stoltenberg and Froen were looking at was *brain physiolog*y or pathophysiology. They were not looking at respiratory development in terms of pulmonary or bronchial development or vascular or cardiac development. They were looking at the responsive neurons in the brain. Tr. 358.

Dr. McCusker also argued that studies of cytokine levels in human brains were only observational, and did not support Dr. Miller's theory. She stated that the Rognum article[83] found similar IL-6 levels in SIDS infants *with* and *without* minor infections. She argued that if infection upregulates cytokine levels, the data between these two groups should be different. *Id.* at 173-74.

Dr. McCusker opined that cytokines play a protective role. Specifically, they maintain homeostasis in the body. She stated that cytokines carry messages (e.g., that an infant's breathing is disrupted) to receptor cells, which contain gp130 molecules, which are supposed to respond to those messages (e.g., by prompting the infant to arouse or gasp). *Id.* at 174-77. Dr. McCusker noted that the Rognum article reported that SIDS brains showed increased binding of IL-6 to neurons in the arcuate nucleus, but no corresponding increase in expression of gp130 (a "signal transducer" for the 5-HT system).[84] She said that if the lack of a corresponding increase in gp130 is physiologically important, which "is a big if," it would imply that the increased IL-6 would not be doing anything. Tr. 175

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[82] Stoltenberg et al. (1994), Exhibit 13-J; Froen, J.F. et al., *Adverse Effects of Nicotine and Interleukin-1β on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome*, Pediatrics (April 2000), Exhibit 13-K.

[83] Rognum, Kinney et al. (2009), Exhibit 13-N; Kadhim et al. (2010), Exhibit 13-O.

[84] Rognum, Kinney et al. (2009), Exhibit 13-N.

As Dr. Miller mentioned, Rognum suggested that IL-6 may have "aberrant interactions" with the arcuate nucleus, leading to SIDS. However, Rognum also suggested another theory: that the "increased expression of the IL-6R in the arcuate nucleus *may be a compensatory mechanism* as defective arcuate neurons may require excessive IL-6 stimulation in order to respond to altered CO2 levels." *Id.* at 528 (emphasis added). Kinney cited this theory, writing: "The expression of IL-6 is elevated in the arcuate nucleus in SIDS infants, which may reflect a compensatory mechanism whereby defective arcuate 5-HT neurons require excessive cytokine stimulation to respond to infection-induced hypercapnia."[85] Dr. McCusker adopted and elaborated on this theory suggesting that IL-6 mounts a protective response. Tr. 157. She cited an article by Moidunny, which states that some IL-6 cytokines have "neuroprotective properties" and that IL-6 requires gp130 receptor subunits to be activated for signaling.[86] When a stressor – such as inadequate oxygen or hypoxia - occurs, the cytokines bind to the 5-HT system, which expresses gp130 molecules to prompt a response – such as prompting the body to turn over or gasp. Tr. 155-56, 161, 175-77, 241. Dr. McCusker opined that these responses can be "quite rapid, within hours or days." Tr. 180-81. Based on these findings, Dr. McCusker suggested that SIDS infants have potentially protective IL-6 molecules in the brain, but in SIDS infants hey fail to prompt the upregulation of gp130 molecules. Thus the IL-6 is ineffective. Tr. 176

Dr. McCusker stated that neither the Kinney team nor the AAP lists vaccinations as a risk factor for SIDS. *Id.* at 144. Dr. Miller testified to a conversation that he had with Dr. Kinney who told him that she did not want to study vaccines because she did not want to testify and did not want to be involved in vaccine controversies. Tr. 60. Dr. McCusker acknowledged that medical literature has reported a temporal association between vaccination and infant death in certain cases. Specifically, the Ottaviani study reported that a three-month-old white female infant received a hexavalent vaccine, lost consciousness one hour later, did not recover upon resuscitation, and passed away a few hours later.[87] Dr. McCusker highlighted that Ottaviani suggested the case might fall into a "SIDS 'gray zone'" because it was "difficult to establish whether the pathological findings [were] sufficiently severe to have caused the death." *Id.* Dr. McCusker noted that Ottaviani published another study of five infants displaying those same pathological abnormalities; however, that study did not mention vaccinations.[88] Therefore, she suggested that the vaccination in the first Ottaviani case was temporally associated with, but did not cause, that infant's death despite the fact that the author stated that in this case the sudden death in a child with arcuate hypoplasia could have been triggered by the hexavalent vaccine or could have been a gray zone case where it is difficult to determine if the pathological findings were sufficient to cause the death. Tr. at 103. It should be noted that the gray zone study focused on the neuropathology and histopathology of five specific SIDS victims to identify the possible brainstem abnormalities. The victims were chosen for study with no reference to vaccines or other specific causal pattern. The case report involving the child who died three

[85] Kinney et al. (2011), Exhibit 13-F at 195.

[86] Moidunny et al. (2010), Exhibit C-2 at 1668.

[87] Ottoviani et al. (2006), Exhibit 13-T at 101-02.

[88] Ottoviani G. et al., *Sudden Infant Death Syndrome "Gray Zone" Disclosed Only by a Study of the Brainstem on Serial Sections*, 33 J. Perinat. Med. 165 (2005), Exhibit C-16 at 6.

hours after receipt of the hexavalent vaccine was published subsequently to the gray zone study and mentions it as the group's prior work. It does hypothesize that the death could have been triggered by the vaccination or fall into the gray zone category.[89]

Dr. McCusker's comments in her report about the literature submitted by petitioners caused some concern, in that they could be read as misleading. Exhibit C at 7-8. Dr. McCusker stated that in the study by Rognum et al., "although [in SIDS infants] there was increased intensity staining for IL-6R, it was not different from those dying of infectious causes." Exhibit C at 7 (discussing Exhibit 13-N). However, Dr. McCusker did not note that at most the SIDS infants had mild infections, which would not be expected to cause elevated cytokines in the brain, while the other group had severe infections which *would* be expected to cause elevated cytokines in the brain and that "the mean IL-6R intensity grade in the arcuate nucleus was significantly higher in the SIDS group than in the control group."[90] [the control group died of "primarily violent causes."] *Id.* at 521.

Of greater concern was Dr. McCusker's characterization of the article by Kadhim et al. Exhibit C at 7-8 (discussing Exhibit 13-O). She stated: Kadhim et al. "examined IL-2 levels in SIDS versus non-SIDS brains and showed no difference in expression in IL-2 and they hypothesize that IL-2, like the cytokines IL-1β, TNFα, and IL-6, may be expressed in normally functioning brains of infants." Exhibit C at 7-8. Kadhim et al. actually stated; "SIDS victims often have preceding mild infectious/ inflammatory conditions (like coryza/ mild upper respiratory infections, soft stools/ mild gastroenteritis, post-vaccinal fever, etc.)"[91] They compared the brains of SIDS infants to those of infants who died of *severe* infectious/ inflammatory conditions. *Id.* at 123. They found that IL-2 levels were unexpectedly comparable in the two groups. *Id.* Kadhim said, "the comparable (equally intense) expression of IL-2 in SIDS infants was rather unexpected as SIDS victims have no obvious or detectable serious health conditions before death and that autopsies show no obvious cause for their demise. (as per definition). However, this high expression in SIDS would corroborate the tenet that SIDS victims experience hyperimmune reactions with 'exaggerated cytokine response to the often reported preceding mild/trivial infectious/inflammatory conditions. Upregulated cytokines exert serious effects on many biological systems including the turnover, release, and transmission of neurotransmitters; cytokines therefore act as neuro-modulators that could modify neural, neuroimmune, and neuroendocrine functions, and can modify synaptic transmissions." *Id.* at 125. The authors further concluded, "Thus various biological stressors such as infectious inflammatory, ischemic or anoxic, and hyperimmune conditions, and metabolic disorders induce IL-2 which is preferentially expressed in vital brainstem neuronal centers. IL-2 and other subsequently triggered cytokines in downstream immune inflammatory mediators interact with neurotransmitters and/or their receptors and modify their function. The resulting neuronal molecular disequilibrium tips the delicate molecular balance causing dysfunction in those vital

[89] Ottoviani et al. (2006), Exhibit 13-T at 103.

[90] Rognum, Kinney et al. (2009), Exhibit 13-N at 521.

[91] Kadhim et al. (2010), Exhibit 13-O at 122.

brainstem centers in producing disturbed homeostasis with potentially drastic effects on target organs systems and eventual death." *Id.*

Dr. McCusker reviewed the epidemiological papers submitted and noted that an article by Kuhnert found a *decreased* incidence of SIDS in days 1-3 after vaccination, then *increased* incidences of SIDS in days 4-7, 8-14, and 15-21. Tr. 229-35.[92] Furthermore, she stated that other studies did not find *any* temporal association between vaccination and SIDS. First, an article by Jonville-Bera et al. did not find a heightened risk of SIDS in French infants vaccinated at three months old.[93] Second, Toro et al. found that the incidence of SIDS in two-month-old children in Hungary decreased when that country instituted vaccinations at that age. *Id.* at 7.[94] Third, Vennemann et al. did not find an increased risk of SIDS with vaccination.[95] In Dr. McCusker's opinion, "large studies, designed to unmask rare events, have shown no link between vaccination and SIDS and have at least in some studies demonstrated a vaccine protective effect for SIDS." Exhibit C at 7.

At trial, Dr. McCusker added that the Kries study cited by petitioners did not support their case. Specifically, SIDS is defined as a syndrome that only affects children "under one year of age."[96] However, Kries et al. did not find an association between vaccination and death in children under one year old. They found an increased incidence of SIDS only in children vaccinated during the *second* year of life. *Id.* Therefore, she said this study does not support petitioners' theory about vaccination and SIDS. Tr. at 257.

ii. *Althen* Prong Two: Response to Petitioners' Opinion of a Logical Sequence of Cause and Effect

Dr. McCusker stated that there was "no evidence" that vaccinations contributed to J.B.'s death from SIDS on September 3, 2011. Exhibit C at 8; Tr. 126. She did not dispute that J.B. was in the critical development period. She agreed that "according to the triple-risk theory, the brain problem must exist" for an infant to succumb to SIDS. Tr. 206.

She agreed that vaccines "increase cytokine circulation." Tr. 195. She also stated that Kashiwagi et al. showed that 24-48 hours after vaccination, a child will have elevated cytokines, whether or not he has a fever. Tr. 199. "Cytokine elevation in this model is independent of fever." *Id.* Dr. McCusker stated that J.B. had a fever, and because he was generally healthy and had no signs of upper respiratory infection, the fever could be attributed only to his vaccinations. Tr. 204-05. The fever was "an indication that [J.B.] was responding… to the vaccine." Tr. 238.

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[92] Kuhnert et al. (2012), Exhibit C-20.

[93] Jonville-Bera A., et al., *Sudden Unexpected Death in Infants Under 3 Months of Age and Vaccination Status – A Case Control Study*, 51 Br. J. Clin. Pharmacol. 271 (2001), Exhibit C-18.

[94] Toro K. et al., *Change in Immunization Schedule and Sudden Infant Death Syndrome in Hungary*, 42 FEMS Immunol. and Med. Microbiol. 119 (2004), Exhibit C-19.

[95] Vennemann et al. (2007), Exhibit C-17.

[96] Kries et al. (2005), Exhibit 13-R at 1.

She stated that J.B. had a fever on September 3, 2011, but after he was given Advil that morning at approximately 8:00 a.m., his fever resolved. Exhibit C at 4; Tr. 204-05, 237. She also stated that a non-steroidal would last for eight hours. Tr. 192. She stated that "if IL-1β mediated respiratory depression [occurred] in the case of J.B., the Advil he was given would have acted to counter this effect, suggesting that this mechanism was not involved in his death from SIDS." Exhibit C at 5, 8.

Her theory was that J.B. 'was put down for his nap, he rolled over, he started rebreathing, and he died of a sudden infant death due to hypercapnia… independent of any cytokines." Tr. 206. She opined that there were several recognized exogenous stressors in J.B.'s case: formula feeding, side sleeping, soft bedding, and a pillow under his head. Exhibit C at 5; *also* Tr. 128-29. In her report, Dr. McCusker stated that J.B. "was found on his side with his face down on a pillow." Exhibit C at 4 (citing Exhibit 7 at 6). (The sixth page of this exhibit is a confirmation of faxing the record.) However, the preceding page is a handwritten scene investigation form. It states that J.B.'s crib had a "little crib pillow." Exhibit 7 at 5. J.B. was found "on side with head downward." *Id.* The form also indicates that neither J.B.'s nose nor his mouth was covered. *Id.*

At the hearing, Dr. McCusker first testified that J.B.'s "face was downward according to the reports." Tr. 128. On cross-examination, she could not identify where in the record it said that his face was down on a pillow. Tr. 265. She thought "he was found with his head down. There was a pillow in the bed, which is clear from the photos. So, it would be easy to hypothesize that he was at least found face down in the general vicinity of a pillow, and one would wonder what the pillow was doing in the bed if it wasn't for under his head." Tr. 266. She noted that the photos of the crib showed a pillow on one end of the bed and diapers and wipes on the other end. Tr. 266 (discussing Exhibit 9 at 8-9). She opined that J.B.'s head would have been on the end of the bed where the pillow was. Tr. 266-67. Dr. McCusker acknowledged, however, that she did not know whether J.B. was actually found with his head on the pillow. Tr. 267. She also agreed that J.B.'s crib was taken down shortly after his death, after which law enforcement and J.B.'s parents participated in a death scene reenactment. Tr. 267-68. That reenactment does not mention the pillow or any other elements that were in the crib. Tr. 268.

The undersigned asked Dr. McCusker about the "mechanical effect" of the sleep position she assumed that J.B. was found in. Tr. 269. Dr. McCusker stated that side-sleeping, a pillow under the head, "the lack of tight bed sheets," and the "disarray" in the crib all together present "the same risk factors as prone" sleeping. Tr. 269-72. The undersigned commented that these facts were not completely clear from the record. Tr. 272.

iii. *Althen* Prong Three: Response to Petitioners' Timing Argument

Dr. McCusker stated that she understood Dr. Miller's testimony to be that "the upregulation of the serotonin through the TPH2 and 1433 system… would not be an instantaneous event and that it would take time and presumably more than 24 hours' time." Tr. 180. She stated that "the production of increasing cortisol that occurs following a stimulus and

upregulation through IL-6 is actually quite rapid, within hours, not days." Tr. 181.[97] But she also stated that Kashiwagi et al. showed that a child will have elevated cytokine levels in the blood 24-48 hours after vaccination. Tr. 198.

3. Respondent's Expert Dr. Brent Harris

Dr. Brent A. Harris earned a Masters in Biology from Hahnemann University in 1988. Exhibit A at 1. He then earned a M.D. and a Ph.D. in Pharmacology from Georgetown University in 1995. *Id.* He then obtained post-doctoral training at Stanford Medical School, where he was a resident in Anatomic Pathology from 1995-1999, chief resident from 1997-1998, and a neuropathology fellow from 1997-1999. *Id.* Dr. Harris is board certified in anatomic pathology and neuropathology and is a Fellow of the College of American Pathologists. *Id.* He is currently an Attending Pathologist, Associate Professor in Neurology and Pathology, and Director of Neuropathology at Georgetown University Medical Center. *Id.* He also serves as a Neuropathology Consultant for the Chief Medical Examiner, the National Institutes of Health, Howard University Hospital, the Washington, DC Veterans Administration Hospital, and the American International Pathology Laboratory. *Id.*

i. *Althen* Prong One: Response to Petitioners' Theory

Dr. Harris agreed with the other experts that the Triple Risk Model is a generally accepted and reliable model of SIDS. Tr. 345. He could not say whether all extrinsic risk factors are mechanical or whether some of them may be neurochemical. *Id.* at 346. However, he testified that he would want to see conclusive proof before he would list vaccines as a risk factor in a medical report that he wrote. Tr. 348. He was aware of studies finding that vaccinations induce the production of cytokines in the brain, but not of any studies finding that those cytokines have a detrimental effect. Exhibit A at 6.

ii. *Althen* Prong Two: Response to Petitioners' Opinion of a Logical Sequence of Cause and Effect

Dr. Harris agreed with the characterization of J.B.'s death as SIDS and that under the Triple Risk Model, J.B. was in the critical development period. Exhibit A at 6. It cannot be confirmed whether J.B. had a brain defect rendering him "vulnerable" because the autopsy did not sample that section of the brain. Exhibit A at 6.

Dr. Harris opined that if vaccinations are found to be an exogenous stressor, they "certainly cannot be proven in J.B.'s death." Exhibit A at 6. He stated that there were "no pathologic findings in the brain or other organs in this case that indicate a vaccine-related death." Exhibit A at 7; *see also* Tr. 328. J.B.'s brain was found to have metabolic glia, which are not fully understood. Exhibit A at 6-7. Dr. Harris also opined: Induction of cytokines after

[97] This may not be an accurate characterization of Dr. Miller's opinion. A review of the transcript did not find a clear statement from Dr. Miller about the timing of cytokine production. But in his expert report, Dr. Miller actually opined that cytokine production would *begin* "within hours" and would *peak* "within 2 to at most 4 days." *See* section above (citing Exhibit 16 at 1).

vaccination is a recognized physiological response involved in the immune process. The primary immune surveillance cells in the brain are microglia.These cells when activated by circulating molecules or direct invasion in the brain by organisms change their morphology and produce a host of cytokines in response. Over-activation of these cells in J.B.'s brain is a non-specific finding that could be related to the prior day's vaccination and/ or infection." Exhibit A at 6. Dr. Harris testified that the "circulating molecules" that activate microglia can be either lipopolysaccharides from bacteria or "circulating cytokines," although this is not completely understood. Tr. 342.

iii. *Althen* Prong Three: Response to Petitioners' Timing Argument

Dr. Harris agreed with Dr. McCusker's opinion that cytokine signaling "doesn't happen immediately but happens over a period of time." Tr. 343. He did not otherwise address the timing for the cytokine response or whether it fit the case of J.B.

III. ANALYSIS

A. Summary of the Arguments

The parties agree that the sole issue to be resolved is "whether the vaccines that J.B. received on September 2, 2011 caused or substantially contributed to his death." Joint Prehearing Submission at 2. Pursuant to *Althen,* petitioners must show by a preponderance of the evidence a reasonable theory as to how the vaccine could cause the harm at issue, a logical but not scientifically certain explanation of how it did, and show the timing was appropriate given the theory of causation. The Federal Circuit has observed that this preponderance standard enables "the finding of causation in a field bereft of complete and direct proof of how the vaccines affect the human body." *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1280 (Fed. Cir. 2005). The standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." *Id.* (citing *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994) ("to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program")).

To address the issue in the case, several questions must be addressed. The specific questions for decision are whether inflammatory cytokines generated by a mild infection are likely the critical exogenous stressor in many cases of SIDS when mild infection is also present. The second question is whether the same cytokines are stimulated by the innate immune response to vaccines and whether they are likely to be the exogenous stressor in some SIDS cases, particularly, as in this case, when the child was thoroughly examined by a physician the day before he died and found to be completely healthy, and there was no evidence of viral infection by nasal swab at autopsy.

Petitioners' theory is essentially that a high percentage of SIDS infants, almost 50% in most studies, have no history of a serious illness in the days and weeks prior to death, but have a mild infection or fever at the time of death. In most instances, the mild infection was an upper

respiratory infection, although one author listed post-vaccinal fever among the conditions.[98] In this case, J.B., a nearly five-month-old African American boy, who had been born at 36 weeks, died of unknown causes while napping in the early afternoon one day after receiving his scheduled four-month vaccines. He had a well-documented physical examination the prior day, performed by an M.D. pediatrician who had performed a similar examination about five weeks prior. J.B. was documented to be healthy, with no signs or symptoms of illness. He had patent nasal passages and clear lungs, and he was progressing well in terms of growth and milestones. His pediatrician noted that he was able to raise his head, hold it steady and roll over. In the 28-hour period following vaccination, at 4 a.m. and again at 8 a.m., his mother noticed that he had a mild fever and gave him children's Advil. He seemed to be fine and playing normally during the morning, but was fussy and started running a fever again in the early afternoon. Exhibit 8 at 2. His father then put him in his crib for a nap. He was put in the crib on his back, with a blanket over his midsection. He was using a pacifier. There was a small, flat, crib pillow in the bed. The air conditioning in the house was set at 76 degrees. His mother checked on him and replaced his pacifier during his nap. She came back about ten minutes later, noticed that he had rolled onto his side with his head tilted slightly downward, and he was not breathing. There is no evidence that his breathing passages were in any way obstructed or that his face was down in the bed or pillow when his mother found him. She called 911. Police and emergency medical personnel responded within minutes. J.B. was transported to the hospital when he could not be revived on scene. He was pronounced dead at the hospital.

Under the first leg of the Triple Risk Model, petitioners theorize that J.B. likely had a defective or under-developed serotonin system in the arcuate nucleus or other medullary area, which unfortunately was not examined or sectioned at autopsy. He was clearly within the vulnerable risk period for SIDS in that he was between four and five months old and, given his pre-maturity, only about four months based on dates of conception. He had several intrinsic risk factors in that he was born at 36 weeks, he was male and he was African American, all of which groups are overrepresented among SIDS deaths – blacks more than whites and Hispanics, boys more than girls, and preterm babies more than term babies. As noted above, at birth, J.B. had Apgar scores of 8 at one minute and 9 at five minutes. He had grown to 16 pounds and was well within the average ranges for height, weight and head circumference. He appeared to be meeting expected milestones as documented by his pediatrician. He was receiving good medical care and did not appear to be affected by issues associated with poverty, which is often speculated to account for the overrepresentation of African American babies in the SIDS statistics. He was a boy and it has been suggested, as noted above, that boys are more dependent than girls on an effective serotonin system for sensing the accumulation of carbon dioxide and responding appropriately to clear it.

Also, J.B. was put to bed on his back. At J.B.'s two last appointments, Dr. Wright noted that he slept on his back. The available evidence indicates that he rolled onto his side but was not prone. His mother described in the police reenactment that he had turned to his right side and his head was turned slightly downward. Nothing in the notes of the reenactment indicated that the baby's mouth or nose were in or close to the bedding, and in her police interview his mother noted that his nose and mouth were not covered. His father indicated that he had a fever when he was put down for his nap.

[98] Kadhim et al. (2010), Exhibit 13-O at 122.

Thus, petitioners theorize that he did have a fever during the night, early morning and before his nap. Dr. Miller testified that the fever documents the effect of inflammatory cytokines, likely IL-1 and/or IL-6 signaling from the periphery to the hypothalamus to cause the fever. They also theorize that the fever elevates body temperature, which is another risk factor for SIDS. According to petitioners' theory, because J.B. had no evidence of illness or infection prior to vaccination, it is therefore highly likely that the fever was generated by the vaccines, which likely caused a cascade of cytokines to cross the blood brain barrier and further suppress the function of the already underdeveloped medullary serotonin system during sleep. This caused his death to occur within about 28 hours of the administration of the four-month vaccines.

Respondent disagrees, saying that J.B. was premature, an African American boy, and was side sleeping, all of which are risk factors for SIDS. Citing the principle of Occam's Razor, he argues that it is unnecessary to consider anything beside these known risk factors and that the proximate timing to the administration of the vaccines can be explained by coincidence given that the peak time period of the occurrence of SIDS deaths coincides with the timing of the two month and four month vaccine administration schedules. He further argues that there has not been epidemiology to substantiate a causal relationship between vaccines and SIDS. Dr. McCusker argued that the role of mild infection in relation to SIDS deaths is one of obstructing airways rather than one of chemosensitivity, and she discussed her experience of suctioning the noses of infants brought into the emergency room with upper respiratory infections.

Dr. Miller and Dr. Harris agreed that an ideal autopsy would have sectioned the ventral medulla and that that was not done in this case. They also agreed that the type of histological examination that was done by Dr. Kinney and others would be unlikely to be done in a standard autopsy. Tr. 339. They agreed that there is not definitive proof of defective medullary structures.

B. *Althen* Prong One

After extensive review of the literature in the field of SIDS causation and listening to the testimony of the experts in this case, I think it is clear that the Triple Risk Model is broadly accepted as the general structure for understanding SIDS, even if the lack of comprehensive autopsies do not allow the medical profession to say that SIDS always has a deficient medullary serotonin system, as demonstrated in up to 75% of the cases examined by Dr. Kinney and her group.[99] She has said that "the most compelling hypothesis is that SIDS is related to a brainstem abnormality in the neuroregulation of cardiorespiratory control."[100] She further observed, "according to the Triple Risk Model, *only* infants with an underlying brainstem disease process die of SIDS, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS. They do not have the underlying vulnerability." *Id.* at 521. Dr. Miller opined that it is likely that J.B. had this defect based on the data from these studies. Tr. 37. Dr. McCusker agreed, "according to the triple-risk theory that the brain problem must exist." Tr. 206. The "brain problem" described in the triple-risk literature is that in the respiratory control center in the medulla. As such, it is reasonable to conclude that the petitioners have shown by a

[99] Kinney & Thach (2009), Exhibit A-4 at 6.

[100] Kinney et al. (2009), Exhibit 13-H at 519.

preponderance of the evidence that an infant who has died of unknown causes, and in whom autopsy has ruled out other causes, had the inherent brainstem vulnerability. I do conclude that J.B. did.

There is also no disagreement that the Back to Sleep Campaign convincingly demonstrated the danger of prone sleeping. By persuading parents to place babies on their backs to sleep during the vulnerable risk period, the campaign brought about an approximate 50% reduction in the rate of SIDS. Side-sleeping has also been recognized as having an elevated relative risk for SIDS, but the reason for this is not entirely clear. Dr. McCusker stated at some length her understanding of the mechanics of breathing in an infant. Essentially, she explained that the diaphragm drops down creating negative pressure within the lung relative to the atmosphere, at which point air rushes in. She suggested that the stomach muscles which the baby uses to help drop the diaphragm are compressed, as are the soft ribs in infants who are prone or side-sleeping, which reduces the gas exchange. Tr. 129-32. Dr. Miller disagreed with her explanation of respiratory physiology in that he did not find persuasive the notion that side-sleeping in a four-month-old is going to inhibit the ability to have inspiratory motion in the diaphragm, which creates the negative pressure in the lungs. Rather, he said the literature in SIDS has emphasized the pocket of air and re-inhaled carbon dioxide. Tr. 354.

The policy statement by the American Academy of Pediatrics, which was repeatedly referenced by Dr. McCusker but not marked as an exhibit, says that the risk of side-sleeping is similar in magnitude to prone sleeping (2.0 vs. 2.6).[101] The statement appears to focus on the risk of turning if the infant is placed on his side. "The risk of SIDS is exceptionally high for infants who are placed on their sides and found on their stomach. The side sleep position is inherently unstable, and the probability of an infant rolling to the prone position from the side sleep position is significantly greater than rolling prone from the back." *Id.* at 7. Interestingly , the same report addresses the issue of children who are able to roll over, which it notes generally occurs at 4-to-6 months of age, and that as they age it is more likely that they will roll. The Academy recommends, "If the infant can roll from supine to prone and from prone to supine, the infant can then be allowed to remain in the sleep position that he or she assumes." *Id.* at 8.

In this case, J.B. was placed supine and he rolled to his side, but not prone. It would appear from this policy statement that the greatest concern with side sleeping is when the infant is placed on its side and can easily roll to the prone position. The fact that the Academy recommends allowing the baby to remain in the position to which he rolls after being placed supine suggests that it is likely that a baby who can roll probably also has developed the ability to raise and turn his head.

All of the experts in this case appeared to agree that at least the predominant thinking in medicine as to the cause of SIDS is explained by the Triple Risk Model. Although as Dr. Harris testified we do not know with certainty that the medullary serotonergic network deficiency is always present because a great many autopsies, such as the one in this case, are not adequate to

[101] Moon R.Y. et al., American Academy of Pediatrics – Task Force on Sudden Infant Death Syndrome, *SIDS and Other Sleep Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment,* 128 Pediatrics 1030 (2011), available at http://pediatrics.aappublications.org/content/128/5/1030.long.

document that deficiency, it was also recognized that as Dr. Kinney stated in a 2009 paper, "only infants with an underlying brainstem disease process die of SIDS."[102] Dr. McCusker agreed that according to the triple risk theory the brain problem must exist. Tr. 206. There has also not been significant debate about the statistical relevance of the other intrinsic risk factors. The success of the Back to Sleep Campaign in educating the public about the danger of prone sleeping has been remarkable in reducing SIDS deaths by half. But the other half still occur. The question remains as to what extrinsic risk factors come to play at that "fatal intersection of vulnerability, critical period and stressor."[103] The literature strongly suggests that SIDS is likely to be multi-factorial. Some cases are likely to be caused by continued prone sleeping, but others are likely caused by other factors. Mild infections, often described as "trivial" infections, appear to be a factor as they have been reported to be present in nearly 50% of SIDS deaths, raising the question of what it is about mild, otherwise non-life threatening infections that appear to interact with the impaired medullary serotonin system during the vulnerable period to cause the "perfect storm" that results in an unexplained death of a child?

Dr. Miller, relying on multiple pieces of research described in the SIDS literature, opined that it is likely that the cytokine signaling triggered in the immune system by mild infection interacts with the underdeveloped 5-HT system in the brainstem, during sleep when the excitatory function of serotonin is reduced, to further suppress the function of the brainstem to cause a cardio-respiratory crisis. The further issue raised is whether, in the absence of a mild infection, can the multiple vaccines administered together – in this case the day before – trigger the same cytokines as does a mild infection with the same fatal result? Dr. Miller concluded that they do.

Petitioners refer to the significant number of SIDS deaths that document the co-occurrence of mild or trivial infections which appear to stimulate a cytokine response similar to that generated by severe infections with adverse or repressive effects on the 5-HT system for chemosensitive response to hypercarbia, leading to failure to arouse and failure to initiate a gasping reflex and ultimately death. Petitioners are not the first to suggest this theory. Dr. Kinney has written, "A causal role for mild infection in sudden infant death is suggested by reports that in approximately half of SIDS cases, the infants have a seemingly trivial infection around the time of death, as well as mild tracheobronchial inflammation and altered serum immunoglobulin or cytokine levels and the presence of microbial isolates at autopsy. In infants who die unexpectedly of infection, the given organism may precipitate *a lethal cytokine cascade or toxic response*."[104] Another article by her group explained the likely mechanism: "During infection, peripherally produced IL-6 may cross the blood brain barrier and bind to IL-6 receptors on 5-HT neurons that mediate homeostasis in response to the infectious stressor and potentially mediate sickness behavior. …We found ubiquitous expression of IL-6 receptors and gp130 neurons in all regions in the infant medulla, including those effector nuclei critical to respiratory and autonomic control, and those that contain 5-HT source neurons. Serotonergic

[102] Kinney et al. (2009), Exhibit 13-H at 521.

[103] Filiano & Kinney (1994), Exhibit 13-B at 197 [also filed as Exhibit A-2].

[104] Kinney & Thach (2009), Exhibit A-4 at 2 (emphasis added).

neurons in the caudal 5-HT system, including in the raphe obscurus and arcuate nucleus, express IL-6Rs on somata and processes, indicating the site of IL-6/5 HT interaction."[105]

Various authors have identified the presence of IL-1β, IL-6, and IL-2, which are all pro-inflammatory cytokines, in elevated levels in the infant medulla in SIDS. Stoltenberg studied the effects of injection of IL-1β in piglets, and theorizes that in addition to cytokines being transported to the brain by retrograde axonal transport, his findings suggested an equally important alternative route in the immune-stimulation of the brain, inducing hypoxia and sudden infant death. He said that it has been shown that IL-1β is internalized by blood brain barrier endothelial cells, which implies that this cytokine passes through the blood brain barrier at the endothelial rather than the ependymal or blood cerebrospinal fluid part of the brain barrier. He found in his experiments with piglets that IL-1 stimulates the release of β-endorphin and the level of β-endorphin in CSF correlates strongly with the duration of apnea. Further, he found that "IL-1β stimulates GABA-transmission and hence increases the inhibitory postsynaptic function by opening of chloride-delective channels, and this will reduce the activity in the central respiratory neurons and may produce hypoxia."[106] Dr. McCusker referred to an article by Besedovsky for the proposition that cytokines are produced in the brain, suggesting that cytokines active in the brain necessarily originate in the brain. However, on review of the article, Besedovsky also noted that some cytokines such as IL-1 and IL-6 are produced both peripherally and within the brain.[107] He postulated that tripartite synapses possess the cellular and molecular components to function as a "relay system" capable of receiving and integrating peripheral immune signals with central neural signals. *Id.* at 5.

One of the best understood functions of cytokines in the case of infection and vaccination is the triggering of fever. When this occurs, cytokines from the periphery at the site of the infection travel to the brain, in particular to the hypothalamus, which then causes fever. As J.B. had a fever in the day following vaccination after having a completely clear medical examination the day before, Dr. McCusker agreed with Dr. Miller that in order for fever to have occurred there had to be a hypothalamic signal, which is mediated by endogenous pyrogens, i.e. IL-6 or TNFα. Tr. 286. The literature also recognizes IL-1 and others which are known pyrogens as well. She also agreed that in the absence of an infection, the only thing we can attribute the fever to is the vaccine. Tr. 205.

After identifying a plausible mechanism for the means of activation of cytokines in the medullary brainstem from a peripheral source, the next key question is why does mild or trivial infection appear to occur in conjunction with SIDS? It is not the infection itself which causes death, as by its mild nature it is not life threatening. Whether the infection is mild or severe, it triggers the innate immune response, which in turn triggers the release of cytokines. As Dr. McCusker explained, cytokines are small molecules that are released by different cell types originally described in immune cells. They are viewed primarily as communication molecules,

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[105] Kinney et al. (2011), Exhibit 13-F at 191.

[106] Stoltenberg et al. (1994), Exhibit 13-J at 427.

[107] Besedovsky, H.O. and A. del Ray, *Central and Peripheral Cytokines Mediate Immune-Brain Connectivity*, 36 Neurochem Res. 1 (2011), Exhibit C-3 at 1.

because they are released by one cell and bind to another through a series of signaling steps. Tr. 145. Dr. Miller explained that cytokines are messenger molecules that have a lot of different effects which were first identified as products of the innate immune system, but are seen elsewhere as well, including the brain. IL-6 binds with 5-HT and IL-1 has been shown in animals to inhibit 5-HT firing. Tr. 30. There was no disagreement between the experts or in the literature that cytokines are released by the innate immune response to infection, whether it be mild or severe.

The Siljehav-Hofstetter article filed by respondent provides an additional theoretical basis for the role of cytokines in SIDS. The authors found that IL-1β stimulates a prostaglandin (PGE2) with receptors in the rostral ventrolateral medulla. They explained that once stimulated by IL-1β, PGE2 induced depression of this vital brainstem neuronal network, e.g., during an infectious response, that could result in gasping and autoresuscitation failure and ultimately death."[108]

Dr. Miller found further support in the work of Kadhim, who found overexpression of IL-1β in the arcuate nuclei in 17 of 17 SIDS brains studied, but only in 1 of 6 non-SIDS brains.[109] Kadhim noted that cytokines could exert neuromodulatory effects in the ascending reticular activating system, which is involved in the arousal reflex. He noted that IL-1 causes prolonged apneas and depresses respiration and the brain appears to be less effective than the periphery in inducing IL-1 antagonist to terminate IL-1β actions. He hypothesized that the particular pattern of neuronal cytokine he detected might therefore overturn a subtle equilibrium in a molecular chain involving vital brain centers, causing SIDS. *Id.* at 1259.

In a second study involving SIDS brains, Kadhim's group noted that SIDS victims often have preceding mild infections and that cytokines have neuromodulatory effects whereby they can modify neurotransmission. In this study, they compared the brainstems of SIDS victims to those of infants who died of diverse severe pathological conditions, mainly infectious, hemodynamic, metabolic, severe congenital, or other serious conditions. They found that IL-2, another inflammatory cytokine, was preferentially expressed in specific neuronal centers within the brainstem. In this study, they found equally intense immune reactivity within the arcuate and dorsal vagal nuclei in fatally sick infants, as with SIDS victims who had no obvious or detectable serious health condition before death. They hypothesized that a hyperimmune response to mild infection in the SIDS babies may result in a molecular disequilibrium which tips the delicate molecular balance, causing dysfunction in those vital brainstem centers and producing disturbed homeostasis with potentially drastic effects on target organs/systems and eventual death.[110]

[108] Siljehav (2012), Exhibit C-9 at 9897.

[109] Kadhim et al. (2003), Exhibit 13-L at 1256.

[110] Kadhim et al. (2010), Exhibit 13-O at 122-26.

Brambilla also provided some support for this theory by demonstrating in animals that IL-1 inhibited firing of neurons that promoted wakefulness in the dorsal raphe nucleus and enhanced activity of GABAergic neurons which are inhibitory and induce enhancement of NREM sleep.[111]

Rognum further compared brains of SIDS victims to those of babies who died of severe infections and to another group who died from drowning, suffocation, strangulation, or other violent causes. They found that the SIDS babies had higher cytokines in the medullary brainstem than did those who died of violent causes but their levels were not as high as those that died of infectious causes. In a small section of their study, the Rognum group found elevations of IL-6R in the arcuate nucleus in the SIDS and infection groups relative to the controls. However, they found that the gp130, which is necessary for IL-6 to function, did not rise as high above the controls as did the infection group, although it was higher than in those dying violent deaths. This caused them to speculate that the IL-6R might be reactive to an excess carbon dioxide crisis rather than its cause. Thus significant evidence has been produced to show that cytokines are abundantly present in the medullary brainstem of SIDS infants relative to those dying of other causes which strongly suggests a hyperimmune response to mild infection in these children well out of proportion to the mild or trivial infection that they had. The presence of these cytokines also appears likely to suppress the 5-HT response to the accumulate of carbon dioxide in the body and the ultimate failure of the respiratory response system.

The next important question is whether the vaccines can play the same cytokine generating role as mild infection in a child who does not have an infection. If, as his father described, the child developed symptoms such as a fever, crankiness and not being himself, signs of cytokine activation, and had no evidence of infection, could one or more of the seven vaccines he received the day before have generated a cytokine cascade that caused him to be unable to respond to elevated carbon dioxide in his system, whether it was produced by rebreathing or metabolically? Dr. Miller's thesis was that the main role for mild inflammation as a risk factor for SIDS is thought to be in elevating cytokines. He said that is explicit in multiple articles that have been submitted. Then, if vaccines produce the same cytokine responses as very mild upper respiratory infections, which is what is demonstrated by Kashiwagi, it would seem logical to impute both having the same effect on the central nervous system. Tr. 370.

Indeed, Kashiwagi conducted testing with multiple vaccines and studied the cytokine response. He found that there was a more significant response in children who received three or four vaccines at one time than in those who received fewer, and he found that higher IL-1β production was noted in young infants, but decreased at around 2 years or older.[112]

He also examined the cytokine profiles in 61 serum samples obtained from recipients who exhibited febrile illness within 24 hours of being vaccinated and 18 serum samples from recipients without febrile illness. The samples were taken within 48 hours of vaccination in both groups. These were compared to each other and to cytokine profiles of ten normal subjects

[111] Kinney et al. (2009), Exhibit 13-H.

[112] Kashiwagi et al. (2014), Exhibit 17 at 680.

without vaccination. "Higher levels of IL-6, IL-10, IL-12, G-CSF,[113] and IFN-α were detected in both the febrile and non-febrile vaccination subjects in comparison with those in normal subjects." *Id.* at 680.

The Lee and Schulzke studies of multiple vaccine administration to premature infants, referenced above, found an elevation in the rate of apnea, bradycardia, and, in the Lee study, oxygen desaturations (Schulzke did not look at desaturations). Both authors hypothesized that the adverse events may be related to the immune response to the vaccines, particularly as Lee found there was no difference in the rate of adverse events between whole cell pertussis and acellular pertussis.[114] Schulzke noted that the adverse events occurred within 6 to 24 hours of vaccination.[115] While not studying SIDS, these studies focused on premature infants in a controlled environment – a hospital – where the mechanism that is hypothesized to occur in SIDS could be rapidly recognized, addressed, and treated. It seems quite likely that the same sequence occurring post-administration of multiple vaccines may be what occurs in the uncontrolled environment of the home when the child and often the parents are sleeping, or at least not in the same room with the child when the combination of events leading to the fatal sequence occurs.

Dr. Miller's theory, consistent with many of the articles in the literature, is that SIDS is multifactorial. Multiple factors come together at the fatal moment that causes the perfect storm leading to death. He theorizes that the cytokines triggered by the vaccines in the initial innate immune response to the vaccines travel to their receptors in the arcuate nucleus and suppress the serotonin function in a child whose functionality in that area is already impaired by an underdeveloped or defective 5-HT system while he is asleep, which further reduces 5-HT function. The input of the cytokines stimulated by the vaccines causes the lack of response to elevation of carbon dioxide that converts a recoverable event to a fatal one. Whether the vaccine generated cytokines cause additional metabolic activity generating fever and additional production of carbon dioxide, or whether they caused the neurons in the brainstem to be unable to respond to rebreathed or accumulated carbon dioxide, it is probable that they played an important role in causing the death of this infant.

Dr. McCusker disagreed. She argued that the presence of the various intrinsic risk factors together with a flat pillow in the bed and side-sleeping to which the child turned after being placed supine was sufficient to explain the death. She argued that the role of mild infection was that it caused obstruction in the nasal passages in infants who are "obligate nose breathers" (Tr. 138) and mucous in the nose would obstruct the breathing of the child sufficient to cause death. She referred to infants she sees in the emergency room with upper respiratory tract infections who need to be suctioned which then brings down their carbon dioxide level. Tr. 139-40. Dr. Miller disagreed. He stated that he had never seen a SIDS autopsy where the death was

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[113] G-CSF is an abbreviation for granulocyte colony stimulating factor. It is another cytokine which mobilizes and recruits neutrophils to the site of inflammation from the marginal pool. Kashiwagi et al. (2014), Exhibit 17 at 693.

[114] Lee, J. et al., *Frequency of Apnea, Bradycardia, and Desaturations Following First Diphtheria-Tetanus-Pertussis-Inactivated Polio-Haemophilus Influenzae Type B Immunization in Hospitalized Preterm Infants*, 6 BMC Pediatr. 20 (2006), Exhibit 20.

[115] Schulzke (2005), Exhibit 21 at 3.

attributed to nasal passage obstruction by mucous and that he had never seen any literature to support that concept. Tr. 355.

The literature certainly suggests that Dr. McCusker's interpretation of the role of mild infection was too limited in that she ignored the entire concept of brainstem chemosensitivity in response to carbon dioxide accumulation. Dr. Kinney wrote, "Serotonergic neurons at the medullary ventral surface and in the midline (raphe) are now known to be preferentially chemosensitive to CO2 and although they are not the only central chemosensitive neurons they appear to play a critical potentially modulatory role. … A small but important population of 5 HTE neurons is embedded within the human arcuate nucleus suggesting that the putative dysfunction in chemosensitivity related to the arcuate anomaly specifically involved these embedded 5 HT neurons."[116] In an article in the New England Journal of Medicine, Kinney wrote, "the arousal from sleep that is triggered by abnormal levels of carbon dioxide and oxygen is essential for the initiation of protective airway responses. … Arousal involves a progressive activation of specific subcortical to cortical brain structures and consists of ascending and descending components that mediate cortical and subcortical arousal respectively."[117] The importance of the chemosensitive role in the stimulation of breathing, arousal, and ultimately gasping in response to the accumulation of excess carbon dioxide appears critical to all of the triple risk hypotheses. A stuffy nose does not explain the inability of the neurons in the arcuate nucleus to modulate breathing rhythm and respond to excess carbon dioxide by initiating breathing, particularly when there was no evidence of mucous congestion in the nose the day before at the medical exam, in the report of the parents, or at the autopsy. The role of cytokines stimulated by vaccines administered approximately 28 hours before seems much more likely to play a critical role, similar to that of mild infection in causing the ultimate convergence of the multiple factors leading to death. The inhibition of the 5-HT response, beyond its initially impaired level with which the child had lived to that date, seems more likely to be caused by the cytokine response to the multiple vaccines than to a stuffy nose or the side-sleeping position to which he had turned, particularly when there was no evidence of nasal congestion or of the breathing passages being obstructed. Exhibit 7 at 5. In fact the evidence was to the contrary.

Dr. McCusker, citing to the Imeri article[118] on sleep in general, also testified that fever would tend to push the child out of REM sleep and into NREM, which she argued would make him more arousable. A review of the Imeri article, which discusses the immune system and sleep in general, and not specifically in infants, does indeed discuss the role of fever and the generation of shivering in NREM sleep and that during the course of most infections there is an increase in the amount of time spent in NREM sleep and a decrease in the amount of REM sleep. *Id.* However, it also discusses the role of IL-1 and the generation of GABAergic inhibitory cytokines. *Id.* at 205. Imeri also acknowledged the role of peripherally generated cytokines in the regulation of sleep. Imeri concluded that at present we know little about these mechanisms

[116] Kinney et al. (2009), Exhibit 13-H at 522.

[117] Kinney & Thach (2009), Exhibit A-4 at 5.

[118] Imeri L. & M.R. Opp, *How (and Why) the Immune System Makes Us Sleep*, 10 Nat. Rev. Neurosci. 199 (2009), Exhibit C-6 at 201.

by which cytokines inhibit REM sleep and argued that it is important because REM sleep is disrupted in many pathologies that involve altered cytokine concentrations. *Id.*

Dr. Miller hypothesized two roles for fever – overheating and travel of cytokines to the brain in the mechanism of SIDS. Dr. McCusker agreed with cytokine signaling as relevant to the production of fever but disagreed that fever was the equivalent of hyperthermia in the SIDS literature. On the witness stand she drew a sharp distinction between environmental hyperthermia and overheating secondary to fever, which she called hyperpyrexia. The literature was unclear on this point. But the significant importance of fever to this case was in demonstrating the travel of peripheral cytokines stimulated by the vaccines across the blood brain barrier to the hypothalamus. Fever is the most obvious manifestation of the signaling of cytokines from the peripheral location of the vaccinations to the brain. The SIDS literature suggests that production of inflammatory cytokines IL-6, IL-10, IL-12, and IFNγ in response to DPT, Hib, and PCV7 were detected in both febrile and non-febrile groups, with febrile illness appearing 12-16 hours post vaccination.[119] NREM sleep is also implicated in SIDS. A distinctive feature of 5-HT neurons is that they exhibit differential firing rates according to the level of arousal, with increased firing during waking, decreased firing during NREM, and almost complete absence of firing during REM. Given the relationship of the firing of raphe 5-HT neurons to arousal, the medullary 5-HT system is postulated to modulate and integrate homeostatic function according to the level of arousal.[120] Thus, particularly in the deeper levels of NREM sleep, the 5-HT system is also functioning at lower levels, potentially contributing to the multi-factorial causal picture.

After review of all of the above, I have concluded that petitioners have presented a reasonable and reliable theory of vaccine causation involving the role of inflammatory cytokines acting as an extrinsic stressor in a baby with a brainstem deficit during the vulnerable time period. It is particularly important to note that the literature indicates that SIDS is likely caused by a multi-factorial process. Dr. Kinney wrote in the New England Journal of Medicine in 2009, "Current evidence suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has defective cardiorespiratory or arousal defense systems during a critical developmental period when immature defense mechanisms are not fully integrated. Thus our current understanding of the pathogenesis of SIDS reflects the simultaneous juxtaposition of multiple events that, when taken individually, are far less powerful than the result of their chance combination."[121] In another 2009 article she wrote; "We now conceptualize SIDS as the biologic version of the perfect storm, in which the simultaneous and chance combination of multiple events is far more powerful than any individual event alone."[122]

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[119] Kashiwagi et al. (2014), Exhibit 17 at 680.

[120] Kinney, H.C., *Brainstem Mechanisms Underlying the Sudden Infant Death Syndrome: Evidence from Human Pathologic Studies*, 51 Dev. Psychobiol. 223 (2009), Exhibit 13-E at 226.

[121] Kinney & Thach (2009), Exhibit A-4 at 7.

[122] Kinney et al. (2009), Exhibit 13-H at 539.

I have concluded that the petitioners have demonstrated by a preponderance of the evidence that the vaccines can and likely did play a critical role in this child's death by stimulating the production of inflammatory cytokines that suppressed the respiratory response system and caused the vulnerable infant to be unable to respond in the normal way to the accumulation of carbon dioxide in his system. Accordingly, petitioners have satisfied the requirement of *Althen* Prong One by presenting a reasonable explanation of how the vaccine could cause or substantially contribute to the child's death.

C. *Althen* Prong Two

Althen Prong Two requires the demonstration of a logical cause and effect as to how the vaccine caused the harm, in this case the sudden unexplained death of J.B. Under *Althen* Prong Two, petitioners must prove that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Capizzano,* 440 F.3d at 1324 (quoting *Althen,* 418 F.3d at 1278).

Dr. Miller testified that it was his diagnosis that J.B. died of SIDS and that the vaccines were a substantial contributing factor to his death. Tr. 126. Having accepted the theory of a causal role of vaccine stimulated cytokines as an exogenous factor converging with the first two prongs of the Triple Risk Model, the question of logical cause and effect requires a review of the likely mechanism and comparing it to the operative facts of the case. Kashiwagi in particular found that cytokines began to be produced 6 hours after stimulation and increased until 24 hours, showing the same level thereafter. Higher levels of IL-1B, IL-6, G-CSF, and TNFα were produced in that study by the concurrent stimulation of three vaccines than by one alone.[123] J.B. received seven vaccines at his 4 to 5 month well baby visit with his pediatrician on September 2, 2011. He was carefully examined and documented to be in entirely good health the day before. Overnight, he developed a mild fever, consistent with cytokine signaling from the vaccination site to the brain. In the early afternoon of September 3, he died during his nap.

Dr. Miller discussed the logical sequence of cause and effect explaining how he believed the vaccines acted as an exogenous stressor which caused J.B. to succumb to SIDS. He noted that J.B. was a "healthy infant… developing normally." Exhibit 13 at 4. He was "immunologically normal." Tr. 61. Therefore, after receiving vaccinations, his body mounted an innate immune response including the production of cytokines. Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62. Those cytokines circulated in J.B.'s body, going to the central nervous system. Exhibit 13 at 6; Tr. 62. These peripheral cytokines interacted with the hypothalamus to provoke fever the night after the vaccinations and during the following day (before J.B.'s death). Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62-64. "Those cytokines then acted in the brainstem which was already deficient in serotoninergic drive for respiratory effort, leading to an apneic episode from which he did not recover, i.e., SIDS." Exhibit 13 at 6; *see also* Tr. 62 (the cytokines "depress[ed the] 5-HT system in a defective medulla, leading to SIDS during sleep").

[123] Exhibit 17 at 679.

He opined that there was "no other demonstrable inciting event" for J.B.'s death. Exhibit 13 at 1. There was no evidence of the fever being related to anything other than J.B.'s vaccinations. Tr. 66. The autopsy did not identify any other infectious processes. Tr. 66.[124]

On cross-examination, Dr. Miller stated that J.B. was placed on his back but was found on his side, which demonstrates that he was able to "move around." Tr. 92. However, J.B. did not pass away until "something else intervened." Tr. 85. Based on his theory and the temporal association, Dr. Miller opined that the vaccines were the intervening factor that caused J.B.'s death. Tr. 85.

An innate immune response to either mild infection or to a vaccine is likely to be fast and begins the process of immune attack of a foreign antigen. Part of that response is the triggering of cytokines to signal further response in the immune system. The triggering of the innate immune system by vaccination is necessary and fundamental to producing the adaptive response and immune memory which vaccines are designed to produce. After review and consideration of all of the testimony and the literature submitted, I have concluded that Dr. Miller has presented a reasonable and persuasive theory that the cytokine cascade triggered by the innate response to the vaccine antigens is similar to the cytokine response to a mild infection, and that the inflammatory cytokines had an immune modulatory effect on J.B.'s impaired medullary 5-HT system causing a prolonged apneic event resulting in his death. As such, the progression from vaccination to an unexplained death within approximately 28 hours is logical.

This logical progression is also consistent with reports of at least mildly elevated SIDS deaths in some studies such as Traversa, which found a 2.0 relationship in the first 7 days.[125] Goldman reported a statistically significant increase in deaths when 5 to 8 vaccines were administered simultaneously as opposed to 1 to 4.[126] Ottaviani[127] and Zinka[128] reported on SIDS deaths within 48 hours of receiving vaccinations. Other studies, such as Kuhnert[129], found neither a protective effect nor elevated risk, but Kuhnert noted that the small number of cases is a problem with the three case control studies he reviewed, particularly in view of the short time periods under investigation. According to Kuhnert, this problem was illustrated by the very broad confidence intervals of estimates that were related to the first few days. *Id.* at 2355.

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[124] Dr. Miller noted that there were bacterial growth and food particles in J.B.'s lungs and epithelial cells in the upper airways. He opined that this was not evidence of a separate infectious process. He agreed with the medical examiner that these were terminal or resuscitative sequelae. Tr. 17-18; 66; 352-53.

[125] Traversa et al. (2011), Exhibit 13-U at 8.

[126] Goldman & Miller (2012), Exhibit 19 at 1016.

[127]Ottoviani et al. (2006), Exhibit 13-T.

[128] Zinka et al. (2006), Exhibit 13-S.

[129] Kuhnert et al. (2012), Exhibit C-20.

The statistical prevalence of boys, African Americans and premature babies among the victims of SIDS also seems to be clear and causes their inclusion as intrinsic risk factors. I think it is reasonable to question in this case whether the influence of prematurity would still be a likely factor, given that he had nearly reached the age of five months and appeared to be developing very well. It is also reasonable to question whether the statistical prevalence of African Americans should be a significant factor, as it is often speculated that this may be a function of socioeconomic status and poor medical care. This child appeared to have been living in a two-parent household, with attentive parents, was well-nourished, and was receiving good medical care. The role of his male gender may well have been important, as Dr. Kinney has reported a greater reduction in 5-HT-1A in the medullary raphe in males compared to females dying of SIDS.[130]

Given that Dr. Miller's thesis and that of much of the literature for the Triple Risk Model is that SIDS results from the convergence of multiple factors, it seems likely that his male gender may well have been a contributing intrinsic factor that may have amplified the effect of the cytokine response to the vaccines on the day that he died. But, his gender, his race, and his prematurity – all intrinsic factors – do not explain his death without the interaction with a critical extrinsic factor, which I have concluded was likely the cytokines triggered by the vaccines which depressed his 5-HT system sufficiently that he did not respond when carbon dioxide became elevated in his system.

The evidence for J.B.'s death occurring as a result of his having turned to his side without a causal input from another significant extrinsic factor such as the vaccine stimulated cytokines suppressing his response system is weak in this case. As noted above, the Academy of Pediatrics recommends leaving a child in the assumed position when he has rolled from his back presumably because it is also likely that he can push up and lift his head by the time he can roll. This capability was documented in J.B's case by his pediatrician. Although there was a flat pillow and a light blanket in the bed, J.B.'s mother told the police investigators that his head was not covered and that his head was turned downward only slightly. The scene investigation noted her report that J.B.'s mouth and nose were not covered. Exhibit 7 at 5. It was described that he had been put to sleep in the middle of the bed. Thus, there is no evidence in this case that the baby's breathing passages were obstructed or that he was breathing into an air pocket. The possibility of rebreathing carbon dioxide in that position cannot be ruled out, but seems less likely based upon this evidence derived from the extensive interviews and the site re-enactment performed by the responding police. Thus, even if the side- sleeping position did cause some rebreathing of carbon dioxide, I have concluded from the evidence that it is most likely that the cytokines stimulated by the vaccines caused suppression of the already impaired medullary serotonin system with the consequent failure to chemically sense elevated carbon dioxide, which caused the ultimate failure to arouse and to breathe normally thus substantially contributing to the death of J.B

The emphasis of the Triple Risk Model on prone sleeping has had a powerful impact in reducing SIDS deaths by approximately 50%. But there remains a significant number of SIDS deaths each year, some of which are likely related to continued prone-sleeping and some to side-sleeping. But the co-occurrence of mild infection in the statistics in nearly 50% of cases raises a

[130] Kinney et al. (2009), Exhibit 13-H at 532.

significant issue about the operative extrinsic risk factor or factors in the remaining cases, including many that are found supine. In this case, an apparently perfectly healthy child was found dead a day after vaccination, having had a mild fever in the interim without evidence of infection. He was not prone sleeping but had turned to his side, with no evidence that his breathing passages were in any way impaired. Significant literature introduced demonstrates that the triggering of inflammatory cytokines in response to vaccines is similar to that raised in response to mild infection. J.B.'s post-vaccinal fever provided confirmation of responsive cytokine activity. The cause and effect between the vaccines, the cytokines triggered by the vaccines, and their co-occurrence with other intrinsic and/or extrinsic risk factors in the presence of a defective or underdeveloped brainstem seems likely to have produced the perfect storm that resulted in J.B.'s death. Thus, I am persuaded that petitioners have proved prong two.

D. *Althen* Prong Three

Under *Althen* prong three, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan*, 539 F.3d at 1352. The acceptable temporal association will vary according to the particular medical theory advanced in the case. *See Pafford*, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. *See, e.g.*, *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

Dr. Miller stated that the available evidence is that foreign antigens, like those contained in vaccinations, activate the production of cytokines "within hours" and that production "peaks within 2 to at most 4 days." Exhibit 16 at 1. Thus, a vulnerable infant who receives vaccinations is most likely to suffer a fatal event if one is to occur "within the first 48 hours to at most 4 days." Exhibit 13 at 5. Dr. Miller opined that J.B.'s death was "well within this vulnerable period." *Id.*

In this case, the timing of the innate immune response to the multiple scheduled vaccinations that J.B. received on September 2, to his death the following afternoon appears entirely appropriate for an innate immune response in the vulnerable risk period for SIDS. It is also consistent with reports of at least mildly elevated SIDS deaths in some studies and reports of deaths that occur within the first several days after the vaccination. In this case, one day post-vaccination is appropriate timing, in that inflammatory cytokines stimulated during the innate immune response to the vaccine antigens are likely to be active in close proximity to the stimulating event. As Dr. Miller stated, an adverse event that can be caused by the inflammatory cytokine response to vaccine antigens would be likely to occur within a few days of the vaccination. The cytokine response has been shown by Kashiwagi[131] to occur within 6 to 24 hours of the vaccination, and the very essence of the innate immune response is one that occurs rapidly after the invasion by a foreign antigen. As noted above, that rapid innate immune response is necessary to initiate the ultimate adaptive immune response necessary to achieve the

[131] Kashiwagi et al. (2014), Exhibit 17 at 679.

design purpose of vaccination. The close temporal relationship of the child's death to the receipt of seven vaccines is reasonable and consistent with the theory of neuro-modulation in the arcuate nucleus by the cytokine response to the vaccines. Accordingly, I am persuaded that prong three of *Althen* has been satisfied.

IV. CONCLUSION

In this case, I have concluded that petitioners have presented sufficient evidence and testimony to entitle them to compensation in the Vaccine Program. I have not concluded that vaccines present a substantial risk of SIDS. In fact, the evidence is to the contrary. The vast majority of vaccine recipients do not succumb to SIDS. Under the multi-factorial analysis of the Triple Risk Model, it is theorized that the ultimate fatal event may occur when multiple factors converge during this vulnerable period to cause death when one stressor acting alone may not have. As Dr. Kinney wrote, "Current evidence suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has defective cardiorespiratory or arousal defense systems during a critical developmental period when immature defense mechanisms are not fully integrated. The convergence of these factors appears to be far more powerful than any one taken individually."[132] Thus, even if J.B. were rebreathing some carbon dioxide on this occasion, it was likely the combination with the cytokines that caused depression of the 5-HT system that caused his death by blunting the normal chemosensitive response to excess carbon dioxide. The multi-factorial analysis, including vaccines as an extrinsic risk factor, meets the *Shyface* standard that the vaccine need not be the sole or even predominant factor but must be a "but for cause" and a substantial factor in causing the death. *Shyface*, 165 F.3d at 1352. In this case, I have concluded, after review of the evidence, that it is more likely than not that the vaccines played a substantial causal role in the death of J.B. without the effect of which he would not have died. The role of inflammatory cytokines as neuro-modulators in the infant medulla has been well described and is likely the reason for a significant number of SIDS deaths occurring in conjunction with mild infection. I have concluded that it is more likely than not that the vaccine-stimulated cytokines had the same effect in this vulnerable infant during sleep.

Accordingly, petitioners are entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master

[132] Kinney et al. (2009), Exhibit 13-H at 539.

THE BLOG 10/17/2016 06:35 pm ET | **Updated** Dec 06, 2017

SPIDER Bites CDC

By Carey Gillam

Concerns about the inner workings of the U.S. Centers for Disease Control and Prevention (CDC) have been mounting in recent months amid disclosures of cozy corporate alliances. Now a group of more than a dozen senior scientists have reportedly lodged an ethics complaint alleging the federal agency is being influenced by corporate and political interests in ways that short-change taxpayers.

A group calling itself CDC Scientists Preserving Integrity, Diligence and Ethics in Research, or CDC SPIDER, put a list of complaints in writing in a letter to the CDC Chief of Staff and provided a copy of the letter to the public watchdog organization U.S. Right to Know (USRTK). The members of the group have elected to file the complaint anonymously for fear of retribution.

"It appears that our mission is being influenced and shaped by outside parties and rogue interests... and Congressional intent for our agency is being circumvented by some of our leaders. What concerns us most, is that it is becoming the norm and not the rare exception," the letter states. "These questionable and unethical practices threaten to undermine our credibility and reputation as a trusted leader in public health."

The complaint cites among other things a "cover up" of the poor performance of a women's health program called the Well-Integrated Screening and Evaluation for Woman Across the Nation, or WISEWOMAN. The program provides standard preventive services to help 40- to 64-year-old women reduce their risks for heart disease, and promote healthy lifestyles. CDC currently funds 21 WISEWOMAN programs through states and tribal organizations. The complaint alleges there was a coordinated effort within the CDC to misrepresent data given to Congress so that it appeared the program was involving more women than it actually was.

"Definitions were changed and data 'cooked' to make the results look better than they were," the complaint states. "An 'internal review' that involved staff across CDC occurred and its findings were essentially suppressed so media and/or Congressional staff would not become aware of the problems."
The letter mentions that Congresswoman Rosa DeLauro, a Democrat from Connecticut, who has been a proponent of the program, has made inquiries to CDC regarding the data. A spokesman for her office, confirmed as much.

The complaint also alleges that staff resources that are supposed to be dedicated to domestic programs for Americans are instead being directed to work on global health and research issues.

And the complaint cites as "troubling" the ties between soft drink giant Coca-Cola Co., an advocacy group backed by Coca-Cola, and two high-ranking CDC officials - Dr. Barbara Bowman who directed the CDC's Division for Heart Disease and Stroke Prevention until retiring in June, and Dr. Michael Pratt, senior Advisor for Global Health in the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) at the CDC.

Bowman, retired after revelations of what the complaint called an "irregular" relationship with Coca-Cola and the nonprofit corporate interest group set up by Coca-Cola called the International Life Sciences Institute (ILSI). Email communications obtained through Freedom of Information Act (FOIA) requests by USRTK revealed that in her CDC role, Bowman had been communicating regularly with - and offering guidance to - a leading Coca-Cola advocate seeking to influence world health authorities on sugar and beverage policy matters.

Emails also suggested that Pratt has a history of promoting and helping lead research funded by Coca-Cola while being employed by the CDC. Pratt also has been working closely with ILSI, which advocates for the agenda of beverage and food industries, emails obtained through FOIA showed. Several research papers co-written by Pratt were at least partly funded by Coca-Cola, and Pratt has received industry funding to attend industry-sponsored events and conferences.

Last month, Pratt took a position as Director of the University of California San Diego Institute for Public Health. Next month, ILSI is partnering with the UCSD to hold a forum related to "energy balance behavior," planned for November 30 to December 1 of this year. One of the moderators is another CDC scientist, Janet Fulton, Chief of the CDC's Physical Activity and Health Branch. Pratt is on annual leave from the CDC during his stint in San Diego, according to the CDC.

The forum fits into the messaging of "energy balance" that Coca-Cola has been pushing. Consumption of sugar-laden foods and beverages is not to blame for obesity or other health problems; a lack of exercise is the primary culprit, the theory goes.

Experts in the nutrition arena have said that the relationships are troubling because the mission of the CDC is protecting public health, and yet certain CDC officials appear to be close with an industry that, studies say, is linked to about 180,000 deaths per year worldwide, including 25,000 in the United States. The CDC is supposed to be addressing rising obesity rates among children, not advancing beverage industry interests.

CDC spokeswoman Kathy Harben would not address what the agency might be doing, if anything, in response to the SPIDER complaint, but she said the agency makes use of a "full range of federal ethics statutes, regulations, and policies" that apply to all federal employees."

"CDC takes seriously its responsibility to comply with the ethics rules, inform employees about them, and take steps to make it right any time we learn that employees aren't in compliance," Harben said. "We provide regular training to and communicate with staff on how to comply with ethics requirements and avoid violations."

The SPIDER group complaint ends with a plea for CDC management to address the allegations; to "do the right thing."

Let's hope someone is listening.

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THE HILL

The CDC is being influenced by corporate and political interests

BY CAREY GILLAM, CONTRIBUTOR - 10/17/16 06:00 PM EDT

Concerns about the inner workings of the U.S. Centers for Disease Control and Prevention (CDC) have been mounting in recent months amid disclosures of cozy corporate alliances. Now a group of more than a dozen senior scientists have reportedly lodged an ethics complaint alleging the federal agency is being influenced by corporate and political interests in ways that shortchange taxpayers.

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Carey Gillam is a veteran journalist, formerly with Reuters, who directs research for U.S. Right to Know, a nonprofit consumer education group focused on food safety and policy matters.

The views expressed by contributors are their own and not the views of The Hill.

TAGS **U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION** **CDC** **US RIGHT TO KNOW**

Format: Abstract

Full text links

PLoS One. 2009 May 29;4(5):e5738. doi: 10.1371/journal.pone.0005738.

How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data.

Fanelli D[1].

Author information

Abstract

The frequency with which scientists fabricate and falsify data, or commit other forms of scientific misconduct is a matter of controversy. Many surveys have asked scientists directly whether they have committed or know of a colleague who committed research misconduct, but their results appeared difficult to compare and synthesize. This is the first meta-analysis of these surveys. To standardize outcomes, the number of respondents who recalled at least one incident of misconduct was calculated for each question, and the analysis was limited to behaviours that distort scientific knowledge: fabrication, falsification, "cooking" of data, etc... Survey questions on plagiarism and other forms of professional misconduct were excluded. The final sample consisted of 21 surveys that were included in the systematic review, and 18 in the meta-analysis. A pooled weighted average of 1.97% (N = 7, 95%CI: 0.86-4.45) of scientists admitted to have fabricated, falsified or modified data or results at least once--a serious form of misconduct by any standard--and up to 33.7% admitted other questionable research practices. In surveys asking about the behaviour of colleagues, admission rates were 14.12% (N = 12, 95% CI: 9.91-19.72) for falsification, and up to 72% for other questionable research practices. Meta-regression showed that self reports surveys, surveys using the words "falsification" or "fabrication", and mailed surveys yielded lower percentages of misconduct. When these factors were controlled for, misconduct was reported more frequently by medical/pharmacological researchers than others. Considering that these surveys ask sensitive questions and have other limitations, it appears likely that this is a conservative estimate of the true prevalence of scientific misconduct.

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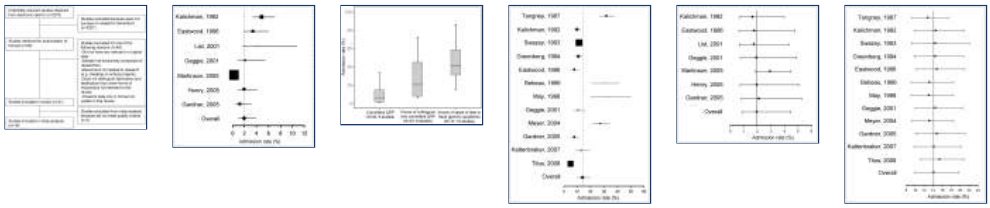

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The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias

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Key findings

- The Cochrane human papillomavirus (HPV) vaccine review missed nearly half of the eligible trials.
- The review was influenced by reporting bias and biased trial designs.
- Authors of Cochrane reviews should make every effort to identify all trials and the trials' limitations.

In May 2018, the Cochrane Collaboration published its review of the human papillomavirus (HPV) vaccines.[1] The review primarily assessed the vaccines' effect on precursors to cervical cancer. Cochrane has high standards for its reviews[2]; however, there were important limitations in its HPV vaccine review, which we address in this paper.

The Cochrane review missed nearly half of the eligible trials

The Cochrane review conducted trial searches up until June 2017 and included 26 randomised trials with 73 428 women.[1] In January 2018, we published an index of the study programmes of the HPV vaccines that included 206 comparative studies.[3] As of June 2017, about one-third of the 206 studies were not published and half of the completed studies listed on ClinicalTrials.gov had no results posted.[3] Although we sent our index to the Cochrane group handling the Cochrane review, the review stated that, 'nearly all end-of-study reports have been published in the peer-reviewed literature'. When we applied the Cochrane review's inclusion criteria to the 206 studies, we identified 46 completed and eligible trials. The number of randomised participants could be assessed for 42 of the 46 trials and was 121 704. With nearly half of the trials and half of the participants missing, the Cochrane authors' conclusion, 'that the risk of reporting bias may be small', was inappropriate. Fifteen of the 20 additional trials were listed on ClinicalTrials.gov; the Cochrane authors would therefore have identified more trials if they had searched ClinicalTrials.gov in more depth and searched additional trial registers (we searched 45 trial registers[3]).

The Cochrane authors stated that they 'did not include the nine-valent vaccine [Gardasil 9] ... since the randomised trials ... did not incorporate an arm with a non-HPV vaccine control'. This is not correct. The only saline placebo trial of approved HPV vaccines is a Gardasil 9 trial (V503-006; NCT01047345) that was published in 2015.[4] Its participants had previously been vaccinated with four-valent Gardasil, but according to the Cochrane review protocol,[5] this was not an exclusion criterion. Since many countries are shifting to Gardasil 9,[6] it is unfortunate that the Gardasil 9 trial was not included in the Cochrane review.

No included trial in the Cochrane review used a placebo comparator

All 26 trials included in the Cochrane review used active comparators: adjuvants (aluminium hydroxide ($Al[OH]_3$) or amorphous aluminium hydroxyphosphate sulfate [AAHS]) or hepatitis vaccines.

Adjuvants are not regulated separately from their vaccine antigens. According to the Food and Drug Administration (FDA), adjuvants are unreliable comparators.[7] One HPV vaccine manufacturer (GlaxoSmithKline that produces Cervarix) states that its aluminium-based comparator induces harms: 'higher incidences of myalgia might namely be attributable to the higher content of aluminium in the HPV vaccine (450 µg $Al[OH]_3$) than the content of aluminium in the HAV [hepatitis A] vaccine (225 µg $Al[OH]_3$)'.[8] The comparator hepatitis vaccines also used the HPV vaccines' aluminium-based adjuvant.

The Cochrane authors mistakenly used the term placebo to describe the active comparators. They acknowledged that 'The comparison of the risks of adverse events was compromised by the use of different products (adjuvants and hepatitis vaccines) administered to participants in the control group'. Nevertheless, this statement can easily be overlooked, as it comes after 7500 words about other issues in the discussion and under the heading 'Potential biases in the review process'. Active comparators was not a bias in the review process but a bias in the design of the HPV vaccine trials.

The use of active comparators probably increased the occurrence of harms in the comparator groups and thereby masked harms caused by the HPV vaccines. It is noteworthy that many women were excluded from the trials if they had received the adjuvants before or had a history of immunological or nervous system disorders; for example, in the PATRICIA trial with 18 644 women[9] and the FUTURE II trial with 12 167 women.[10] These exclusion criteria lowered the external validity of the trials and suggest that the vaccine manufacturers were worried about harms caused by the adjuvants. The criteria are not listed as warnings on the package inserts of the HPV

vaccines,[11–13] which may have led to more vaccine-related harms in clinical practice than in the trials.

The included HPV vaccine trials used composite surrogate outcomes for cervical cancer

In line with World Health Organization (WHO) recommendations,[14] the Cochrane review was based on composite surrogate outcomes: 'cervical intraepithelial neoplasia grade 2 and above [CIN2+], CIN grade 3 and above [CIN3+] and adenocarcinoma in situ [AIS]'.[1] The use of such outcomes seemed reasonable for a preliminary assessment of HPV vaccine benefits, but the outcomes can be difficult to interpret. If there were clinically important differences in the severity of the cervical lesions in the two compared groups, they may not have been apparent in the composite outcomes of CIN2+ and CIN3+. The Cochrane authors did not describe any cervical cancers in the 26 trials, although cancers did occur in the trials; for example, in the ClinicalTrials.gov entry for the VIVIANE trial, one case of 'Adenocarcinoma of the cervix' and one case of 'Cervix cancer metastatic' are listed in the HPV vaccine group (see 'Results: Serious Adverse Events').[15] Furthermore, the relationship between CIN2 and cervical cancer is not clear-cut. Most CIN2 lesions in women below age 30 regress spontaneously; an active surveillance approach has therefore been recommended for this group.[16] The Cochrane review's 26 trials mainly included women below age 30 and used frequent cervical screening (often every six months) that did not reflect real-life practice (often every three to five years[6]).

The Cochrane review incompletely assessed serious and systemic adverse events

The Cochrane authors reported that they made a 'Particular effort' to assess serious adverse events and performed a sensitivity analysis that gave them 'confidence that published and registry or website-sourced data are similar for the same study'.[1] This seems unlikely. As an example, the PATRICIA trial publication only included two thirds (1400/2028) of the serious adverse events listed on ClinicalTrials.gov. The Cochrane authors included 701 vs 699 serious adverse events (1400) from the PATRICIA trial publication (see the Cochrane reviews' 'Figure 10, Analysis 7.6.2') and 835 vs 829 serious adverse events from its ClinicalTrials.gov entry (see 'Comparison 7, Analysis 6: 7.6.2'; both analyses were called '7.6.2'). We found 1046 vs 982 serious adverse events (2028) when we summarised the data from ClinicalTrials.gov (see 'Results: Serious Adverse Events').[17]

The Cochrane authors concluded with 'high certainty' that the risk of serious adverse events was similar in the HPV vaccine groups and the comparator groups. However, the authors failed to mention that several of the included trials did not report serious adverse events for the whole trial period. For example, FUTURE I,[18] FUTURE II[10] and FUTURE III,[19] which in total included 21 441 women with up to four years follow-up, only reported serious adverse events occurring within 14 days postvaccination. Furthermore, the Cochrane authors did not explain what the serious adverse events consisted of or whether some of them were more common in the HPV vaccine groups.

The Cochrane authors found more deaths in the HPV vaccine groups than in the comparator groups. The death rate was significantly increased in women above age 25 (risk ratio [RR] 2.36, 95% confidence interval [CI] 1.10 to 5.03; no absolute numbers were provided for this subgroup analysis, but the total numbers of deaths were 51 in the HPV vaccine groups and 39 in the comparator groups). The Cochrane authors suggested that this was a chance occurrence since there was no pattern in the causes of death or in the time between vaccine administration and date of death. However, as the Cochrane review only included randomised trials, the authors cannot rule out that the increase could be caused by the HPV vaccines. A death may be coded in a way that does not raise suspicion that the vaccine caused it; for example, a 'traumatic head injury' or 'drowning' could have been caused by a 'syncope', which is a recognised harm.[11–13] As of May 2018, WHO's pharmacovigilance database—VigiBase, managed by the Uppsala Monitoring Centre (UMC)—contained 499 deaths reported as related to HPV vaccination.[20]

The Cochrane authors concluded that, 'Systemic events with general mild symptoms were similarly frequent in vaccinated recipients and placebo or control vaccine recipients'. Their Analysis 7.5 showed a non-significant increase in systemic events: RR 1.02 (95% CI 0.98 to 1.07) with a total of 9137 vs 9054 events. The Cochrane authors did not include all of their trials that were eligible for systemic events in Analysis 7.5; for example, the PATRICIA trial was not included. On ClinicalTrials.gov, PATRICIA has 7129 vs 6557 systemic events listed under 'Results: Other Adverse Events (General disorders)', which in itself is a significantly increased risk: RR 1.09 (95% CI 1.07 to 1.11).[17]

The Cochrane authors 'planned requesting data from data owners, to fill in gaps with available unpublished data', but 'due to constraints in time and other resources' they were unable to do so.[1] Considering that seven years passed from the publication of the Cochrane protocol in 2011[5] to the Cochrane review in 2018,[1] lack of time seems a poor excuse for not trying to obtain unpublished trial documents and data. More importantly, harms cannot be assessed reliably in published trial documents—especially in journal publications of industry-funded trials where even serious harms often are missing.[21] One reason may be the space restrictions that most medical journals have. As an example, the journal publication for the PATRICIA trial is 14 pages long[9] while its publicly available corresponding clinical study report is over 7000 pages long,[22] although it is an interim report that has been shortened. Clinical study reports are usually confidential documents, but they can be requested from the European Medicines Agency (EMA) and ClinicalStudyDataRequest.com (CSDR).

Despite the mentioned examples of reporting bias, the Cochrane authors judged all trials at low risk of reporting bias (see the Cochrane review's 'Figure 4: 'Risk of bias' summary').

The Cochrane review did not assess HPV vaccine-related safety signals

The Cochrane authors referred to many observational studies in their discussion that found no safety signals of harms associated with the HPV vaccines.[1] They cited WHO's Global Advisory Committee on Vaccine Safety (GACVS) that expressed 'concerns about unjustified claims of harms'. The Cochrane authors did not mention a study from 2017 by the WHO UMC that found serious harms following HPV vaccination overlapping with two syndromes: postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS).[23] The WHO UMC provided part of the rationale for EMA's investigation of POTS and CRPS in 2016.[24] As of May 2018, the WHO UMC VigiBase contained 526 cases of POTS and 168 cases of CRPS reported related to HPV vaccination.[20]

The Cochrane authors did not investigate whether the included trial data reported cases of POTS, CRPS or other safety signals. Instead, the authors cited EMA, which concluded that 'No causal relation could be established' between POTS or CRPS and the

HPV vaccines.[1] EMA's conclusion was based on the HPV vaccine manufacturers' own unverified assessments[24] that only included half of the eligible trials.[3] Furthermore, the HPV vaccine manufacturers search strategies for POTS and CRPS were inadequate and led to cases being overlooked.[25] As an example, in 2014, the Danish Medicines Agency (DMA) asked the HPV vaccine co-manufacturer Sanofi-Pasteur-MSD to search for specific POTS-related symptoms in its database (including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting). The manufacturer only searched for 'postural dizziness', 'orthostatic intolerance' and 'palpitations and dizziness'. The Danish Medicines Agency discovered this because only three of 26 Danish reports of POTS showed up in Sanofi's searches.[25] As another example, EMA identified six possible cases of POTS and CRPS related to Gardasil 9 that Merck had not identified.[26]

Industry trial funding and other conflicts of interest

The Cochrane authors assessed the impact of industry funding 'by meta-regression. No significant effects were observed'.[1] They stated that, 'All but one of the trials was funded by the vaccine manufacturers', which is not correct. According to ClinicalTrials.gov, this particular trial ('CVT' or 'Costa Rica trial'[1]) was sponsored by GlaxoSmithKline.[27] Therefore, all included trials were funded by the HPV vaccine manufacturers and the meta-regression was meaningless.

The Cochrane Collaboration aims to be free from conflicts of interest related to the manufacturers of the reviewed products.[28] Most of the 14 Cochrane authors on the first published protocol for the Cochrane review had major conflicts of interest related to the HPV vaccine manufacturers.[29] The Cochrane review only has four authors; three of whom had such conflicts of interest a decade ago. The review's first author currently leads EMA's 'post-marketing surveillance of HPV vaccination effects in non-Nordic member states of the European Union', which is funded by Sanofi-Pasteur-MSD that was the co-manufacturer of Gardasil.

Cochrane's public relations of the review were uncritical

The announcement of the Cochrane review on Cochrane.org under 'News' included a 'Science Media Centre roundup of third-party expert reaction to this review'.[30] Six experts were cited—all from the UK, although the Cochrane Collaboration is an international organisation. Two of the experts had financial conflicts of interest with the HPV vaccine manufactures. A third expert was responsible for vaccinations in Public Health England (PHE) that promotes the HPV vaccines. The experts highlighted the 'intensive and rigorous Cochrane analysis', 'that the HPV vaccine is the most effective way for young girls to protect themselves against cervical cancer' and that 'the vaccine causes no serious side-effects'. No expert criticised the review. In our view, this is not balanced and people with conflicts of interest in relation to the manufacturers should not be quoted in relation to a Cochrane review. Richard Smith—the former editor of the British Medical Journal (BMJ)—described medical journals as an extension of the marketing arm of the drug industry.[31] We are concerned that some observers may see Cochrane reviews in the same light when Cochrane publishes such public relation messages.

Conclusion

Part of the Cochrane Collaboration's motto is 'Trusted evidence'. We do not find the Cochrane HPV vaccine review to be 'Trusted evidence', as it was influenced by reporting bias and biased trial designs. We believe that the Cochrane review does not meet the standards for Cochrane reviews or the needs of the citizens or healthcare providers that consult Cochrane reviews to make 'Informed decisions', which also is part of Cochrane's motto. We recommend that authors of Cochrane reviews make every effort to identify all trials and their limitations and conduct reviews accordingly.

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Contributors LJ: wrote the first draft. LJ, PCG and TJ: contributed to the conception, drafting, critical revision for important intellectual content and the final approval of the article.

Competing interests LJ and PCG have no conflicts of interest to declare. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011–2013, TJ acted as an expert witness in a litigation case related to the antiviral oseltamivir, in two litigation cases on potential vaccine related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997–1999), GSK (2001–2002), Sanofi-Synthelabo (2003), and IMS Health (2013) and in 2014 was retained as a scientific adviser to a legal team acting on oseltamivir. TJ was a member of three advisory boards for Boerhinger Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022).

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Lawrence Solomon
Columnist

THE BLOG

Don't Believe Everything You Read About Flu Deaths

The CDC's decision to play up flu deaths dates back a decade, when it realized the public wasn't following its advice on the flu vaccine. During the 2003 flu season "the manufacturers were telling us that they weren't receiving a lot of orders for vaccine,"Dr. Glen Nowak, associate director for communications at CDC's National Immunization Program, told National Public Radio.

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Flu results in "about 250,000 to 500,000 yearly deaths" worldwide, Wikipedia tells us. "The typical estimate is 36,000 [deaths] a year in the United States," reports NBC, citing the Centers for Disease Control. "Somewhere between 4,000 and 8,000 Canadians a year die of influenza and its related complications, according to the Public Health Agency of Canada," the *Globe and Mail* says, adding that "Those numbers are controversial because they are estimates."

"Controversial" is an understatement, and not just in Canada, and not just because the numbers are estimates. The numbers differ wildly from the sober tallies recorded on death certificates -- by law every certificate must show a cause -- and reported by the official agencies that collect and keep vital statistics.

According to the National Vital Statistics System in the U.S., for example, annual flu deaths in 2010 amounted to just 500 per year -- fewer than deaths from ulcers (2,977), hernias (1,832) and pregnancy and childbirth (825), and a far cry from the big killers such as heart disease (597,689) and cancers (574,743). The story is similar in Canada, where unlikely killers likewise dwarf Statistics Canada's count of flu deaths.

Even that 500 figure for the U.S. could be too high, according to analyses in authoritative journals such as the American Journal of Public Health and the British Medical Journal. Only about 15-20 per cent of people who come down with flu-like symptoms have the influenza virus -- the other 80-85 per cent actually caught rhinovirus or other germs that are indistinguishable from the true flu without laboratory tests, which are rarely done. In 2001, a year in which death certificates listed 257 Americans as having died of flu, only 18 were positively identified as true flus. The other 239 were simply assumed to be flus and most likely had few true flus among them.

"U.S. data on influenza deaths are a mess," states a 2005 article in the British Medical Journal entitled "Are U.S. flu death figures more PR than science?" This article takes issue with the 36,000 flu-death figure commonly claimed, and with describing "influenza/pneumonia" as the seventh leading cause of death in the U.S.

"But why are flu and pneumonia bundled together?" the article asks. "Is the relationship so strong or unique to warrant characterizing them as a single cause of death?"

The article's answer is no. Most pneumonia deaths are unrelated to influenza. For example, "stomach acid suppressing drugs are associated with a higher risk of

community-acquired pneumonia, but such drugs and pneumonia are not compiled as a single statistic," explained Dr. David Rosenthal, director of Harvard University Health Services. "People don't necessarily die, per se, of the [flu] virus -- the viraemia. What they die of is a secondary pneumonia."

Pneumonia, according to the American Lung Association, has more than 30 different causes, influenza being but one of them. The CDC itself acknowledges the slim relationship, saying "only a small proportion of deaths... only 8.5 per cent of all pneumonia and influenza deaths [are] influenza-related."

Because death certificates belie claims of numerous flu deaths, CDC enlisted computer models to arrive at its 36,000 flu-death estimate. But even here it needed to bend conventional medical terminology to arrive at compelling death numbers.

"Cause-of-death statistics are based solely on the underlying cause of death [internationally defined] as 'the disease or injury which initiated the train of events leading directly to death,'" explains the National Center for Health Statistics. Because the flu was rarely an "underlying cause of death," the CDC created the sound-alike term, "influenza-associated death."

Using this new, loose definition, CDC's computer models could tally people who died of a heart ailment or other causes after having the flu. As William Thompson of the CDC's National Immunization Program admitted, influenza-associated mortality is "a statistical association ... I don't know that we would say that it's the underlying cause of death."

The CDC's decision to play up flu deaths dates back a decade, when it realized the public wasn't following its advice on the flu vaccine. During the 2003 flu season "the manufacturers were telling us that they weren't receiving a lot of orders for vaccine,"Dr. Glen Nowak, associate director for communications at CDC's National Immunization Program, told National Public Radio. "It really did look like we needed to do something to encourage people to get a flu shot."

The CDC's response was its "Seven-Step 'Recipe' for Generating Interest in, and Demand for, Flu (or any other) Vaccination," a slide show Nowak presented at the 2004 National Influenza Vaccine Summit.

Here is the "Recipe that fosters influenza vaccine interest and demand," in the truncated language that appears on his slides: "Medical experts and public health authorities [should] publicly (e.g. via media) state concern and alarm (and predict dire outcomes) - and urge influenza vaccination." This recipe, his slide show indicated, would result in "Significant media interest and attention ... in terms that motivate behavior (e.g. as 'very severe,' 'more severe than last or past years,' 'deadly')." Other emotive recommendations included fostering "the perception that many people are susceptible to a bad case of influenza" and "Visible/tangible examples of the seriousness of the illness (e.g., pictures of children, families of those affected coming forward) and people getting vaccinated (the first to motivate, the latter to reinforce)."

The CDC unabashedly decided to create a mass market for the flu vaccine by enlisting the media into panicking the public. An obedient and unquestioning media obliged by hyping the numbers, and 10 years later it is obliging still.

Editorial

Mistaken identity: seasonal influenza versus influenza-like illness

Readers of *Clinical Evidence* who are interested in influenza will have been struck by the disparity between policy recommendations and the clinical evidence of the performance of inactivated influenza vaccines.[1][2] For example, there are few RCTs assessing the effectiveness of inactivated vaccines in children and the elderly. Only five RCTs have been carried out in elderly people, of which only one was carried out in the past 2 decades using vaccines available today.[3] Although the evidence is more robust in healthy adults, and partly supports the use of vaccines, this is the population who are universally considered to need them least.[1][2]

The reasons for the contradictions between policy and evidence, and the dearth of corroborating evidence on vaccine performance, are complex and include: the relative rarity of influenza; the current confusion between influenza-like illness and influenza (a simplistic aetiopathogenic model hide-bound by Henle-Koch's postulates of one germ, one disease, one solution); the inability of vaccines to protect populations from an ever-mutating agent; and the difficulty of conducting meaningful prospective studies to assess vaccine efficacy. In addition, the powerful image of influenza depicted by the media is not proportional to the actual threat. The "monster at your door" fame of influenza helps to create preventive expectations that are unachievable with today's technology and with only partial reading of the evidence. For example, we know that in the past 2 decades influenza vaccine studies have risen in prominence in the scientific media, possibly as a result of pharmaceutical sponsorship and the need of larger journals to boost their revenue by selling bulk reprints and subscriptions to offset the decline in print-based returns.[4][5] This rise in prominence is, however, in contrast to the threat from influenza. In the US, the influenza-related mortality rate of the past 20 years has not increased, but plateaued.

Here, I examine the evidence for and the impact of the first two factors listed above — the incidence of influenza, and the masking of its rarity by the systematic failure to distinguish between influenza (a disease) and influenza-like illness (a syndrome, caused also in minor part by influenza viruses).

The causal relationship between the two is scarcely investigated and is frequently overlooked, perhaps because of technical difficulties in quantifying the incidence of "seasonal" influenza and its complications. I must confess that I realised the importance of incidence only after having carried out scores of Cochrane reviews and updates on influenza vaccines and antivirals. I started from the end (the interventions) instead of concentrating on the beginning (the epidemiology of influenza and the other respiratory viruses).

The incidence statistic for influenza, which is often taken for granted, is estimated from virological testing of symptomatic people (so-called viral circulation). What is often poorly understood is that the patient presenting to a physician typically has a syndrome (influenza-like illness, or ILI) that can be caused by various agents. Only a proportion of these syndromes is caused by influenza A and B viruses, but differential diagnosis on clinical grounds alone is not possible.[6][7] Google's near real-time instrument, Flu Trends, provides an excellent example of the confusion generated from following the inaccurate equation "influenza = ILI".[7] Users of Flu Trends think they are following the spread of influenza, while in reality the site depicts the spread of ILI.

To determine (not estimate) the incidence of influenza at any one time, virological testing of a truly random sample of people with ILI is needed. At the same time, testing for all other major causal agents should be carried out, but this is not typically done. In addition, it is not known, or cannot be estimated accurately, how many people have ILI at a given time, which further complicates calculation of incidence. The consequence of this is biased estimates of incidence, where attention is focused on testing for influenza viruses in non-randomly identified people with ILI. Ignorance of the presence of other causal agents has made us blind to the complex ecology of respiratory viruses. How can systematic reviews obviate such tunnel vision?

At present, the only method of determining influenza incidence with a high level of accuracy is to use the control arms of influenza vaccines and antiviral studies. From these, reliable denominators (i.e., number of people with ILI) and numerators (i.e., number of people with influenza and its complications) can be calculated. This is simpler than it sounds. The Cochrane Vaccines Field group has a database of all identifiable studies from 1948 to 2007 that assess the effectiveness of inactivated influenza vaccines and report clinical outcomes (as opposed to surrogate outcomes, such as antibody responses). These are the studies that populate our Cochrane reviews and their updates. The database also comprises studies excluded from the reviews, provided they are comparative and report clinical outcomes. Data available in these studies are collected during the active follow-up of formal studies (often prospectively), in which participant controls with ILI are typically tested (figure 1). As such, they are the optimum data available on influenza incidence. However, high loss to follow-up detracts from the reliability of the data. The data depicted in figure 1 come from the control arms of 95 vaccine comparative studies published between 1965 and 2005 that report, between them, several million observations on incidence.

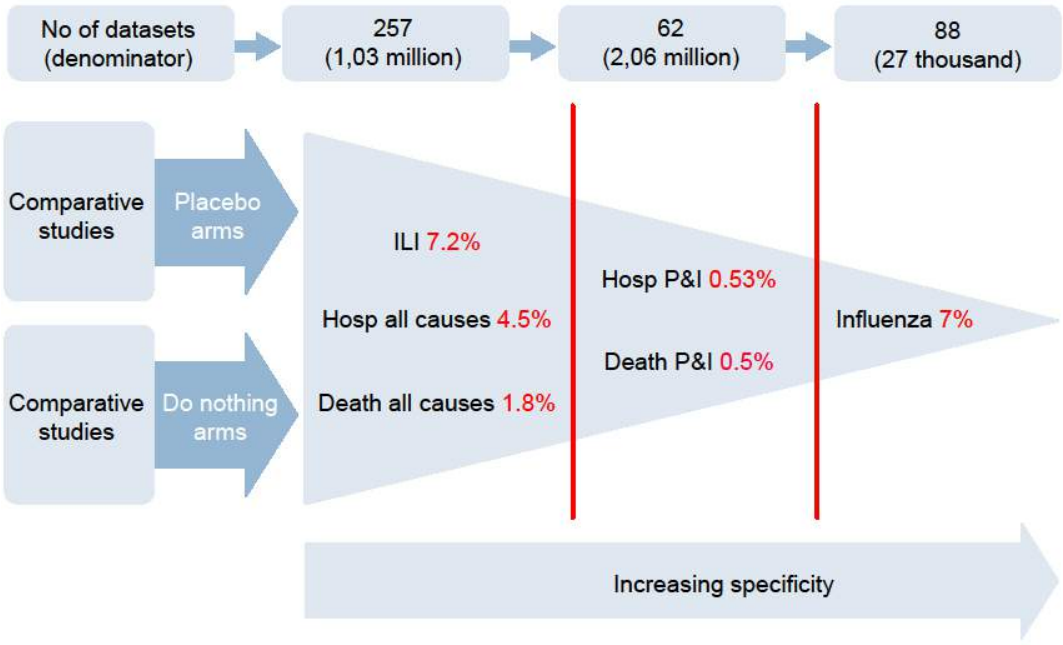

Figure 1. Graphic representation of funnel data in the general population. ILI, influenza-like illness; P&I, pneumonia and influenza (includes ICD 9 codes 480–488).

The availability of a considerable body of data, as figure 1 illustrates, does not always generate a strong evidence base on which to judge efficacy. In the case of inactivated influenza vaccines, the key issue in interpreting the data is over-reliance on non-specific outcomes, such as death from all causes, which may have little to do with influenza-related death. Studies with such non-specific outcomes have been purported to show the effectiveness of influenza vaccines, but actually they only introduce confounding. The funnel in figure 1 exemplifies the richness of data on non-specific outcomes, and the paucity of data on laboratory confirmed influenza A or B. However, this is only part of the story, as data from control arms of comparative vaccine studies seldom look for other viral agents among the samples. Control arms show what is certainly influenza (as is their objective), but do not identify other agents. One of the subliminal effects of this is that observers focus exclusively on one agent, ignoring the rest.

In addition, the data allow a best guess as to how prevalent influenza is, but not its complications. Based on studies in the Cochrane database, incidence of influenza is estimated at around 7%. However, the control arms of the 95 studies identified evaluate people with ILI. Therefore, 7% is not the absolute incidence of influenza in the general population, but is rather the portion of ILI that is caused by influenza, making the incidence of influenza itself in the general population much smaller (approximately 0.5%). Studies of influenza vaccines do not serve well for apportioning slices of the ILI "pie" to non-influenza agents, as they seek only influenza. To do this, we must turn to pie studies, which are a systematic assembling of data from the few studies that followed a defined population, and swabbed ILI symptomatic people for all major agents.

A brief review of pie studies published in the past decade and available in the Cochrane database paints a remarkably similar picture to that of control arms, with an incidence of influenza of 0.5% to 1% of ILIs. Figure 2 shows how the systematically assembled evidence from control arms fits with that from pie studies. Surprisingly, most ILIs cannot be attributed to a specific causal agent. Although many other conclusions can be drawn from observations of pie slices, our aim here is to discuss why influenza inactivated vaccine performance is poor, and why most studies rely on non-specific outcomes, such as death from all causes, and hospitalisations for pneumonia and influenza (which are not usually based on virological testing). One possible answer is that seasonal influenza is a relatively rare and benign condition, with an incidence not exceeding 1% in the general population during autumn and winter months.

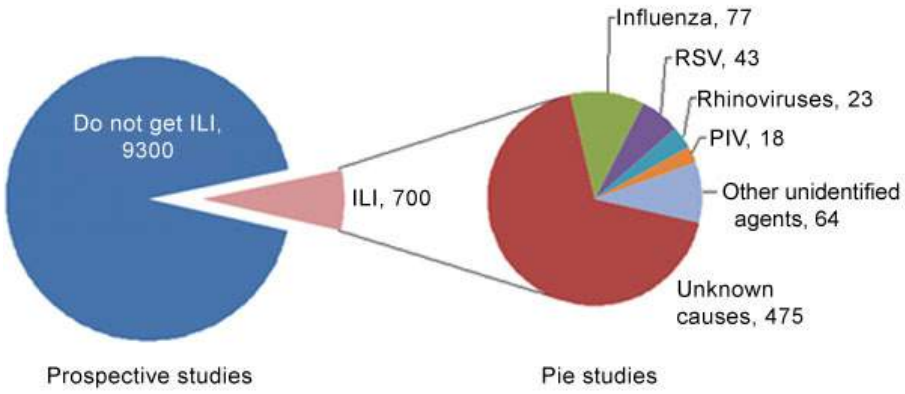

Figure 2. Incidence of influenza-like illnesses (ILI) per 10,000 people (calculated from prospective studies), with breakdown by agent, based on information in pie studies.

Vaccine effectiveness (expressed as a percentage) is calculated by subtracting the ratio of incidence in vaccinated and unvaccinated populations from 1. Therefore, if the incidence in the unvaccinated population is low, then the ratio will be close to 1 and effectiveness will be low. So, vaccines seem to be less effective in illnesses with low incidence. A systematic approach to best evidence completes the picture, and explains what is observed in trials and other comparative studies. In summary, evidence presented here points to influenza being a relatively rare cause of ILI and a relatively rare disease. It follows that vaccines may not be appropriate preventive interventions for either influenza or ILI.

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Why have three long-running Cochrane Reviews on influenza vaccines been stabilised?

Three Cochrane Reviews focussing on the prevention of influenza in healthy adults, healthy children, and in the elderly are long-running reviews under the same senior author team. The protocol for the oldest review was first published 20 years ago.

Over the years the reviews have progressively accumulated evidence leading to ever greater stability in their conclusions. 'Stable' is a publication flag that usually indicates that the results are unlikely to change with the inclusion of new studies, such is the certainty of the results. The influenza vaccine reviews present us with a partly different situation. Readers will notice important outcomes where we have little or no data. They may also see that for some measures of influenza and 'influenza-like illness' (ILI), we have low-certainty evidence. We have reached a point where the evidence is not showing anything different to what it has done for a number of years. We know with varying degrees of certainty about vaccination effects on influenza and ILI, but the gap in our understanding of how vaccines affect the consequences of influenza persist. For each review, the impact of single studies is documented in the summary table 1 "Studies included in the various versions of this review and their impact on our conclusions". This month the three reviews (https://www.cochrane.org/news/featured-review-three-updated-cochrane-reviews-assessing-effectiveness-influenza-vaccines) appear in their latest updated and stabilised format.[1,2,3] Whilst we do not believe that periodic updating will complete the picture, our decision to stabilise is conditional. The three reviews will not be updated again unless certain criteria are met.

First, a new trial that meets inclusion criteria becomes available. Few trials of interest have been conducted recently, as a comparison with an inactive control is considered by some to be unethical. In the elderly, the latest completed trial dates from nearly two decades ago. Our searches have failed to find relevant ongoing trials.

A second condition is the introduction of a new generation of vaccines, based on new technology. This is possible given that several new technologies are being developed, such as vaccines containing fragments of the haemagglutinin antigen "stalk" on the viral surface (so called stalk-specific vaccines).[4]

The third condition is more complex: the development and testing of a new causal paradigm for ILI and influenza. Currently, massive worldwide machinery is needed to produce new vaccines every year to address viral antigenic changes, and to address the poor persistence of the antibody response in individuals. However, the vaccination selection and production programmes are based on aetiological assumptions which are neither explanatory nor predictive, as shown in our reviews. Overall the largest dataset to have accumulated to date is from trials conducted in the population least likely to benefit from vaccines but most likely to produce immunity: healthy adults. In healthy adult trials a high serological response is matched by a very small clinical effect (71 healthy adults need to be vaccinated to prevent one of them experiencing influenza). This weak effect cannot be explained simply by the mismatch of vaccine antigens with wild virus ones. A larger effect is observed in children over the age of two (five children need to be vaccinated to prevent one case of influenza, although there is huge uncertainty around these estimates). There is little evidence on prevention of complications, transmission, or time off work. Other reviews have drawn similar conclusions.[5]

During stabilisation we updated the randomised evidence, but for the first time have decided against updating the large observational evidence base. The observational dataset still appears in the reviews, but only as a historical record of earlier versions. Observational studies were included in the reviews over a decade ago in the hope they could provide long-term and rare harms data and improve the external validity of the trial evidence. They turned out to be of such low quality that their conclusions were inconclusive or unreliable. The most important example is the case-negative study to assess influenza vaccine effectiveness *post hoc* (i.e. after an influenza season) by harvesting data from a surveillance programme. This study design, which is similar to a case-control study, selects influenza cases (cases of ILI which have tested positive for influenza) and controls (cases of ILI which have tested negative) and calculates the relevant odds ratio (OR) of exposure to that season's vaccine. An estimate of vaccine effectiveness is derived from this OR using a standard formula (vaccine effectiveness = 1 - OR%). However, despite their institutional popularity,[6,7] case-negative designs have limited public health significance because the design does not test field effectiveness, but, rather, laboratory efficacy of the vaccine (the capacity of the vaccine to generate a negative polymerase chain reaction (PCR) result). Both cases and controls are symptomatic, so any prevention is solely focused on PCR negativity. In addition, no useful public health absolute measures of effect can be derived (such as absolute risk reduction (ARR) and its reciprocal number needed to vaccinate to prevent one case (NNV)) because the background rates of infection and viral circulation are not part of the calculation of the estimates of effect. There are also problems with the mathematical assumptions made in this design (for details see the reviews). Case-negative studies are an illustration of the narrow and retrospective focus on influenza viruses at the expense of overall ILI - the

illness cluster of interest to patients and their clinicians. Retrospective calculation of relative estimates of laboratory efficacy can be of interest for future decisions on composition of vaccines, but their relevance to everyday decisions seems questionable.

The underlying assumption that influenza vaccination does not affect the risk of non-influenza is contradicted by a recent report from the follow up of a trial by Cowling et al.[8] In 115 participants, those who received trivalent influenza vaccines had higher risk of acute respiratory infection associated with confirmed non-influenza respiratory virus infection (RR, 4.40; 95% CI, 1.31–14.8) compared to placebo recipients. The agents were mainly rhinoviruses and coxsackie/echoviruses; ILI episodes occurred shortly after a peak of influenza activity.

Current yearly registration of candidate influenza vaccines is based on their ability to trigger a good antibody response. But antibody responses are poor predictors of field protection. This is another example of the use of surrogate outcomes in biomedicine, where effects on clinically important outcomes remain unmeasured or unproven from randomised trials: complications and death by influenza.

The simple answer is that we do not understand what the target is. What is the threat of influenza, and what can we ever expect of the vaccines?

The WHO Global Influenza Programme (http://www.who.int/influenza/surveillance_monitoring/en/) (GIP) with its backbone Global Influenza Surveillance and Response System (http://www.who.int/influenza/gisrs_laboratory/en/) (GISRS) is a complex network of 143 national reference centres and specialist laboratories in 113 states carrying out surveillance of circulating influenza viruses. GISRS was devised and developed to guide annual influenza vaccine production, and the emphasis is mainly on influenza viruses, their variants, and emerging strains.

However there is no reliable system to monitor and quantify the epidemiology and impact of ILI, the syndrome that presents clinically. Few states produce reliable data on the number of physician contacts or hospitalised cases due to ILI, and none tie these data to the proportion of ILI caused by influenza. We do not know for certain what the impact of ILI is, nor the impact of the proportion of ILI caused by influenza. Prospective studies apportioning positivity to the scores of viruses probably causing ILI are rare, as interest is focused on influenza. The standard quoted figure of 36,000 yearly deaths in the US is based on the “respiratory and circulatory deaths” category including all types of pneumonia, including secondary to meconium ingestion or bacterial causes. More recently, the US Centers for Disease Control and Prevention (CDC) have proposed estimates of impact ranging between 3,000 and 49,000 yearly deaths. When actual death certificates are tallied, influenza deaths on average are little more than 1,000 yearly (http://dspace.mit.edu/handle/1721.1/69811) . So, the actual threat is unknown (but likely to be small) and so is the estimation of the impact of vaccination.

The uncertainty over the aetiology of ILI, its capricious nature and the weak correlation between immunity and protection, point to possible causal or concurrent factors in the genesis of both ILI and influenza. In other words, virus positivity may only be one of the factors necessary for a case of influenza or ILI to manifest itself.

We await to see whether anyone has the interest or the courage to develop effective ways to control upper respiratory viral syndromes. Meanwhile our reviews will remain as a testimonial to the scientific failure of industry and governments to address the most important clinical outcomes for patients.

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Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations

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Abstract

IMPORTANCE—The Advisory Committee on Immunization Practices (ACIP) recommends the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine for pregnant women during each pregnancy, regardless of prior immunization status. However, safety data on repeated Tdap vaccination in pregnancy is lacking.

OBJECTIVE—To determine whether receipt of Tdap vaccine during pregnancy administered in close intervals from prior tetanus-containing vaccinations is associated with acute adverse events in mothers and adverse birth outcomes in neonates.

DESIGN, SETTING, AND PARTICIPANTS—A retrospective cohort study in 29 155 pregnant women aged 14 through 49 years from January 1,2007, through November 15,2013, using data from 7 Vaccine Safety Datalink sites in California, Colorado, Minnesota, Oregon, Washington, and Wisconsin.

EXPOSURES—Women who received Tdap in pregnancy following a prior tetanus-containing vaccine less than 2 years before, 2 to 5 years before, and more than 5 years before.

MAIN OUTCOMES AND MEASURES—Acute adverse events (fever, allergy, and local reactions) and adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) were evaluated. Women who were vaccinated with Tdap in pregnancy and had a prior tetanus-containing vaccine more than 5 years before served as controls.

RESULTS—There were no statistically significant differences in rates of medically attended acute adverse events or adverse birth outcomes related to timing since prior tetanus-containing vaccination. *

*Check METHODS, Study Design, and EXCLUSIONS. Page 5.

	Time Since Prior Tetanus-Containing Vaccination, y		
Outcome	**<2**	**2–5**	**>5 (Control)**
Local reactions, rate/10 000 women	4.2	7.0	11.2
Adjusted risk ratio (95% CI)	0.49 (0.11–2.20)	0.77 (0.31–1.95)	1 [Reference]
P value	.35	.59	
Preterm delivery, %	6.6	6.4	6.8
Adjusted risk ratio (95% CI)	1.15 (0.98–1.34)	1.06 (0.94–1.19)	1 [Reference]
P value	.08	.33	
Small for gestational age, %	9.0	8.7	9.1
Adjusted risk ratio (95% CI)	0.99 (0.87–1.13)	0.96 (0.87–1.06)	1 [Reference]
P value	.88	.45	

CONCLUSIONS AND RELEVANCE—Among women who received Tdap vaccination during pregnancy, there was no increased risk of acute adverse events or adverse birth outcomes for those who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before. These findings suggest that relatively recent receipt of a prior tetanus-containing vaccination does not increase risk after Tdap vaccination in pregnancy. *

*Check METHODS, Study Design, and EXCLUSIONS. Page 5.

Pertussis (whooping cough) is a vaccine-preventable illness that has been increasing in incidence over the past decade in the United States.[1–3] Neonates and infants are at increased risk of pertussis-related hospitalization and death compared with older children and adults. Many public health strategies have been recommended to decrease the burden of pertussis in neonates and infants.[4–6] Most recently, in 2012, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended tetanus, diphtheria, and acellular pertussis (Tdap) vaccination for all pregnant women during each pregnancy regardless of prior immunization status.[6]

However, few published studies have evaluated the safety of Tdap vaccine in pregnant women.[7–11] In these studies, Tdap vaccination during pregnancy has not been associated with an increased risk of spontaneous abortion, stillbirth, preterm delivery, low birth weight, neonatal complications, or congenital anomalies compared with unvaccinated pregnant controls. Additionally, 1 retrospective study showed that pregnant women vaccinated with Tdap who had received a prior Tdap vaccine within 5 years had no difference in neonatal outcomes compared with women receiving their first Tdap vaccine in pregnancy.[11]

Most safety studies on administering repeated doses of tetanus-containing vaccines are limited to nonpregnant individuals.[12–14] These studies have shown that intervals less than 5 years between tetanus-containing vaccines can be associated with increased local reactions and fever. Although these studies did not find an increased risk of Arthus reactions (severe dermal inflammation, endothelial damage, and vascular necrosis), this has been a concern with shortened intervals between tetanus vaccine doses.[12–14]

This study focused on determining whether there is association between receipt of Tdap vaccine during pregnancy administered in close intervals from prior tetanus-containing vaccinations and acute adverse events in mothers and adverse birth outcomes in neonates.

Methods

Study Population

The study protocol was reviewed and approved by institutional review boards at Emory University, the CDC, and the 7 Vaccine Safety Datalink (VSD) sites and was determined exempt from requiring participant consent. The study cohort included pregnant women enrolled in the VSD (Figure). The VSD is a collaborative project between the CDC and 9 integrated health care organizations.[15] The VSD includes data on more than 9 million individuals annually (approximately 3% of the US population), with an annual birth cohort of approximately 90 000. Data are collected from standardized files prepared at each site that contain individual demographic, enrollment, immunization, hospitalization, emergency department visits, and outpatient visits. For this study, 7 VSD sites contributed data: Group Health Cooperative (Washington), Kaiser Permanente Northwest (Oregon and Washington), Kaiser Permanente Northern California, Southern California Kaiser Permanente, HealthPartners (Minnesota), Marshfield Clinic (Wisconsin), and Kaiser Permanente Colorado. These sites were chosen because they contribute pregnancy data on a yearly basis. Although the majority of the VSD data comes from the 2 California sites, and thus the western United States, the demographic characteristics of the VSD population have been shown to be generally comparable with that of the entire US population.[16]

Study Design

We conducted a retrospective cohort study among pregnant women vaccinated with Tdap by evaluating medically attended acute adverse events (occurring in outpatient, inpatient, and emergency department settings) in mothers and adverse birth outcomes in their neonates. We compared adverse events between women receiving a prior tetanus-containing vaccine less than 2 years before and 2 to 5 years before with women who had received a prior tetanus-containing vaccine more than 5 years before (controls). We chose these comparisons based on intervals used in prior studies comparing acute adverse events following multiple tetanus-containing vaccines in nonpregnant individuals.[12–14] Prior vaccination status was irrespective of pregnancy status at the time of vaccination.

We identified pregnancies ending between January 1,2007, and November 15, 2013, in automated data using a validated pregnancy algorithm[17] that has been used in prior VSD pregnancy studies.[18,19] This pregnancy episode algorithm uses claims, administrative, and

birth data from the electronic medical record to identify pregnancies, pregnancy outcomes, and gestational age at pregnancy outcome, and has been shown to be accurate within 28 days in confirming the estimated pregnancy start date for 99% of live births and in confirming the pregnancy outcome date for 96% of live births.[17]

We included women aged 14 through 49 years who received Tdap vaccine during pregnancy and had continuous insurance coverage from 6 months prior to pregnancy to 6 weeks postpartum with no more than a 30-day gap in enrollment. We excluded women who had no documentation of prior tetanus-containing vaccines, women who received live vaccines during pregnancy, and women with a multiple gestation pregnancy. We also excluded pregnancies with non-live birth outcomes (stillborn, spontaneous abortion, therapeutic abortion, trophoblastic disease, and ectopic pregnancy) because we did not have the resources to access medical records to confirm the timing of these outcomes in relation to vaccination, which could result in inaccurate findings. Finally, we excluded all women who received non-Tdap tetanus-containing vaccines during pregnancy (ie, tetanus diphtheria [Td]).

We identified vaccinations using electronic medical record and insurance claims data that are captured in the standardized VSD vaccine file. We defined a vaccine administered during pregnancy as one given from 7 days after the woman's last menstrual period through 7 days before the date the pregnancy ended. We used these cutoffs to avoid misclassification of vaccines that might have been given prior to pregnancy or postpartum.[10,19]

Outcome Measures

We compared *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes for fever, local reactions (limb pain, limb swelling, cellulitis, lymphadenitis, and Arthus reaction), and allergic reactions (allergy, urti-caria, and anaphylaxis) occurring in intervals of 0 through 3 days and 0 through 7 days following Tdap vaccine, excluding duplicate diagnoses that had been given in the previous 30 days to capture incident cases associated with a health care visit. The day of vaccination was considered day 0, and we excluded any diagnoses on day 0 occurring in the outpatient setting, as they were likely present before the vaccination. As some allergic reactions may occur on day 0 in the outpatient setting, we performed a sensitivity analysis including diagnoses of allergic reactions in the outpatient setting on the day of vaccination. We compared the risk of incident cases of Guillain-Barré syndrome in the inpatient setting, using a 1-through 42-day time window following vaccination. We also examined the following adverse birth outcomes: preterm delivery (defined as gestational age <37 weeks), low birth weight (birth weight <2500 g), and small for gestational age (weight <10th percentile for gestational age and sex).[20]

Statistical Methods

We compared baseline characteristics between the 3 groups of pregnant women who received Tdap vaccine. We used χ^2 tests to compare categorical variables, and analysis of variance to compare continuous variables. We identified all adverse events using *ICD-9-CM* codes. We used log-binomial regression analysis to calculate the relative risks (RRs) for both

rare and non-rare events. Akaike Information Criterion measurements are included as assessments of model fit (eTable1 in the Supplement). We adjusted for differences in gestational age at time of vaccination and VSD site (Kaiser Permanente Northern California, Southern California Kaiser Permanente, or other site) when comparing acute events. When comparing birth outcomes, we also adjusted for maternal age, length of enrollment (in months) in the health plan prior to pregnancy, risk factors for pregnancy adverse events, pregnancy complications, and prenatal care utilization, because these are likely to independently affect birth outcomes. Prenatal care utilization was assessed using the Kotelchuck Adequacy of Prenatal Care Utilization Index, which takes into account the number of prenatal care visits from the time of the first prenatal care visit until delivery.[21] Comorbidities (asthma, diabetes, hypertension, and cardiovascular disease) and pregnancy complications were identified using *ICD-9-CM* codes. Only records that contained information on the neonate (ie, weight and gestational age) were used when analyzing birth outcomes. In addition, only vaccinations given prior to 37 weeks of gestation were included, so as to not bias the results for preterm delivery and low birth weight. All analyses were performed using SAS (SAS Institute), version 9.3.

We performed a priori power calculations based on an expected sample size of 24 000 women and determined that we had 80% or higher power to detect an RR greater than 2 for all of our birth outcomes. However, analyses for medically attended acute adverse outcomes, which are rare, were under-powered. To detect an RR greater than 2 for local reactions, 10 000 participants would be needed in each cohort; for fever, 37 000 participants; and for allergic reactions, 75 000 participants. We considered results to be statistically significant at an a error less than .05 using 2-tailed tests.

Results

From January 1, 2007, through November 15,2013, there were a total of 633 542 singleton pregnancies recorded in the VSD sites (Figure). After applying exclusion criteria, we identified 61 311 pregnancies in which a single Tdap vaccine was given. We excluded 32 156 pregnancies (52%) because there was no prior history of a tetanus-containing vaccine documented. Our final analytic data set included 29 155 pregnancies. Of these pregnancies, 4812 women (17%) had a prior tetanus-containing vaccine less than 2 years before, 9999 women (34%) 2 to 5 years before, and 14 344 women (49%) more than 5 years before (controls).

Among the 29 155 pregnancies ending from 2007 through 2013, the majority of Tdap vaccinations were administered from 2010 through 2013 (98.1%), and most were administered in 2013 (54.0%). In the overall cohort, Tdap was most often administered in the third trimester (67.4%). Fewer women received the vaccine in the second trimester (27.5%) and the first trimester (5.1%). Maternal age, length of enrollment, and gestational age at Tdap vaccination were significantly different in the 3 study groups ($P = <.001$) (Table 1). In addition, most pregnant women who received a prior tetanus-containing vaccine less than 2 years before (94%) and 2 to 5 years before (85%) their current Tdap vaccine had previously received Tdap (as opposed to a non-Tdap tetanus-containing vaccine) vs only 17% of controls ($P < .001$).

Acute Outcomes

Overall, acute adverse events after vaccination were rare (eTables 2–3 in the Supplement). There were no statistically significant differences in fever, allergic reactions, or local reactions among women who had received their prior tetanus-containing vaccine less than 2 years before and 2 to 5 years before compared with controls (Table 2). Fever beginning 0 through 3 days after vaccination occurred at a rate (per 10 000 women) of 2.1 in those who received Tdap and had a prior tetanus-containing vaccine less than 2 years before compared with 3.5 among controls (adjusted RR, 0.66 [95% CI, 0.07–5.77]; $P = .70$). Allergic reactions beginning 0 through 3 days after vaccination occurred at a rate (per 10 000 women) of 2.1 in women who received Tdap and had a prior tetanus-containing vaccine less than 2 years before (adjusted RR, 1.55 [95% CI, 0.13–18.45]; $P = .73$) and 1.0 in those receiving it 2 to 5 years before (adjusted RR, 0.71 [95% CI, 0.06–8.13]; $P = .78$) compared with 1.4 among controls. Local reactions beginning 0 through 3 days after vaccination occurred at a rate (per 10 000 women) of 4.2 in women who received Tdap and had a prior tetanus-containing vaccine less than 2 years before (adjusted RR, 0.49 [95% CI, 0.112.20]; $P = .35$) and 7.0 in those receiving it 2 to 5 years before (adjusted RR, 0.77 [95% CI, 0.31–1.95]; $P = .59$) compared with 11.2 among controls. There was no increased risk of allergic reactions based on the sensitivity analysis including outpatient diagnoses occurring on day 0 (eTable 4 in the Supplement). There were no cases of anaphylaxis, Arthus reactions, or Guillain-Barré syndrome following vaccination.

Birth Outcomes

There were no statistically significant differences in adverse birth outcomes among women who had received their prior tetanus-containing vaccine less than 2 years before and 2 to 5 years before compared with controls (Table 3). Preterm delivery occurred in 6.6% of women who received Tdap and had a prior tetanus-containing vaccine less than 2 years before (adjusted RR, 1.15 [95% CI, 0.98–1.34]; $P = .08$) and 6.4% of those receiving it 2 to 5 years before (adjusted RR, 1.06 [95% CI, 0.94–1.19]; $P = .33$) compared with 6.8% of controls. Low-birth-weight delivery occurred in 4.7% of women who received Tdap and had a prior tetanus-containing vaccine less than 2 years before (adjusted RR, 1.10 [95% CI, 0.92–1.32]; $P = .31$) and4.7% of those receiving it2to5 years before (adjusted RR, 1.03 [95% CI, 0.89–1.18]; $P = .72$) compared with 5.1% of controls. Small for gestational age delivery occurred in 9.0% of women who received Tdap and had a prior tetanus-containing vaccine less than 2 years before (adjusted RR, 0.99 [95% CI, 0.87–1.13]; $P = .88$) and 8.7% of those receiving it2to5 years before (adjusted RR, 0.96 [95% CI, 0.87–1.06]; $P = .45$) compared with 9.1% of controls.

Discussion

To our knowledge, this is the first study to evaluate medically attended acute adverse outcomes in mothers following Tdap vaccine in pregnancy looking specifically at intervals since receipt of prior tetanus-containing vaccinations. We did not find any differences in acute events in the mothers or adverse birth outcomes in neonates when comparing women who were vaccinated with Tdap during pregnancy regardless of the length of time since a prior tetanus-containing vaccine. Our findings should reassure patients and clinicians who

might be hesitant to give Tdap vaccine to pregnant women who recently received a Tdap or other tetanus-containing vaccination.

Our findings are similar to another retrospective cohort study evaluating women receiving Tdap in pregnancy who had a prior pregnancy with Tdap vaccine administered within 5 years compared with multiparous women with no prior Tdap vaccine in pregnancy.[11] This study found no difference in gestational age at delivery, stillbirth, major malformations, neonatal care admissions, ventilation requirements, and neonatal death, whereas ours focused on preterm delivery, small for gestational age, and low birth weight.* The prior study did note a small increase in average birth weight of neonates of women receiving multiple Tdap vaccines. Our study did not compare actual birth weights, but rather compared the presence of low-birth-weight (<2500 g) delivery, and did not find a statistically significant difference. *This was a much smaller study and did not consider the fact that pregnant women in the group declining Tdap vaccination may have chosen to do so because they had high risk pregnancies. "...the cohort of women who declined vaccination suggests that Tdap vaccine nonacceptance may identify a high-risk group..." Our findings contrast with some studies in other populations that suggest an increased risk of adverse events when tetanus-containing vaccines are given at short intervals, most of which evaluated differences in solicited adverse events.[12–14] In 2006, a clinical trial of 7156 children found that Tdap vaccine was well tolerated when given at intervals as short as 18 months since prior tetanus-containing vaccines; however, there was an increase in solicited injection site swelling and erythema in participants who received a tetanus-containing vaccine more recently.[12] A VSD retrospective cohort study of 436 828 Td vaccinations demonstrated that medically attended local reactions, including cellulitis, were more common among persons who received a Td-containing vaccine within the last 5 years compared with a longer interval.[13] Another study assessed safety in 4524 Tdap-vaccinated health care workers during a pertussis outbreak in New England.[14] Overall, there was no difference in the rates of solicited moderate or severe injection site reactions, but there was an increase in redness, swelling, and subjective fever among patients who had received their prior Td-containing vaccine less than 2 years earlier. Among 20 pregnant women included in that study, only 1 person reported severe swelling and 2 reported feeling feverish without documented fever. All symptoms in these pregnant women resolved without treatment, and all neonates were born at term with normal newborn evaluations. None of the pregnant women had received a prior tetanus-containing vaccine 2 years before their Tdap vaccination.

One explanation of the apparent paucity of acute adverse events with short tetanus vaccination intervals in our study could be related to shifts in immunological responses that occur during pregnancy.[22] These include shifts in humoraland cellular-mediated immunity and natural killer cells that occur to protect the fetus from harm. Among other changes, there may be less inflammation that occurs in response to vaccinations, which may result in fewer adverse events following multiple tetanus-containing vaccinations given in close proximity. Another explanation could be that we relied exclusively on medically attended adverse events, which are rare, whereas the majority of prior studies included solicited adverse events. Therefore, milder reactions that do not come to medical care might not have been included.

Our study has some limitations. We had limited power for the acute adverse events analysis. However, the rates of acute adverse events were generally not more common in pregnant women who had more recent tetanus-containing vaccinations. We also excluded women with no prior documented tetanus-containing vaccination, which comprised 52% of the Tdap-vaccinated cohort, to reduce misclassification. Although it is unlikely that these women never received a tetanus-containing vaccine in the past, this exclusion allowed for more conservative estimates of risk as the cohorts were not diluted with women that were potentially previously unvaccinated. There is the potential for some confounding due to differences in the type of vaccine received because the majority of the women in our study who were vaccinated with tetanus-containing vaccines less than 2 years before received Tdap and those vaccinated more than 5 years before had previously received Td. Additionally, we did not review medical charts to validate the adverse events, which would correct for any potential overestimation of the rates of acute reactions following Tdap in pregnancy. Although this is important, we would expect any resulting misclassification bias to be nondifferential, and not to affect our overall results. Finally, the VSD population is an insured population, and these findings may not be generalizable to the entire US population. However, demographic characteristics of the VSD population, including race, ethnicity, income, and education, have been shown to be generally comparable with the population of the United States.[16]

Future studies are needed to determine if there are differences in other important adverse pregnancy outcomes, such as stillbirth and spontaneous abortion, when Tdap is given in pregnancy in close intervals from prior tetanus-containing vaccines.

Conclusions

Among women who received Tdap vaccination during pregnancy, there was no increased risk of acute adverse events or adverse birth outcomes for those who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before. These findings suggest that relatively recent receipt of a prior tetanus-containing vaccination does not increase risk after Tdap vaccination in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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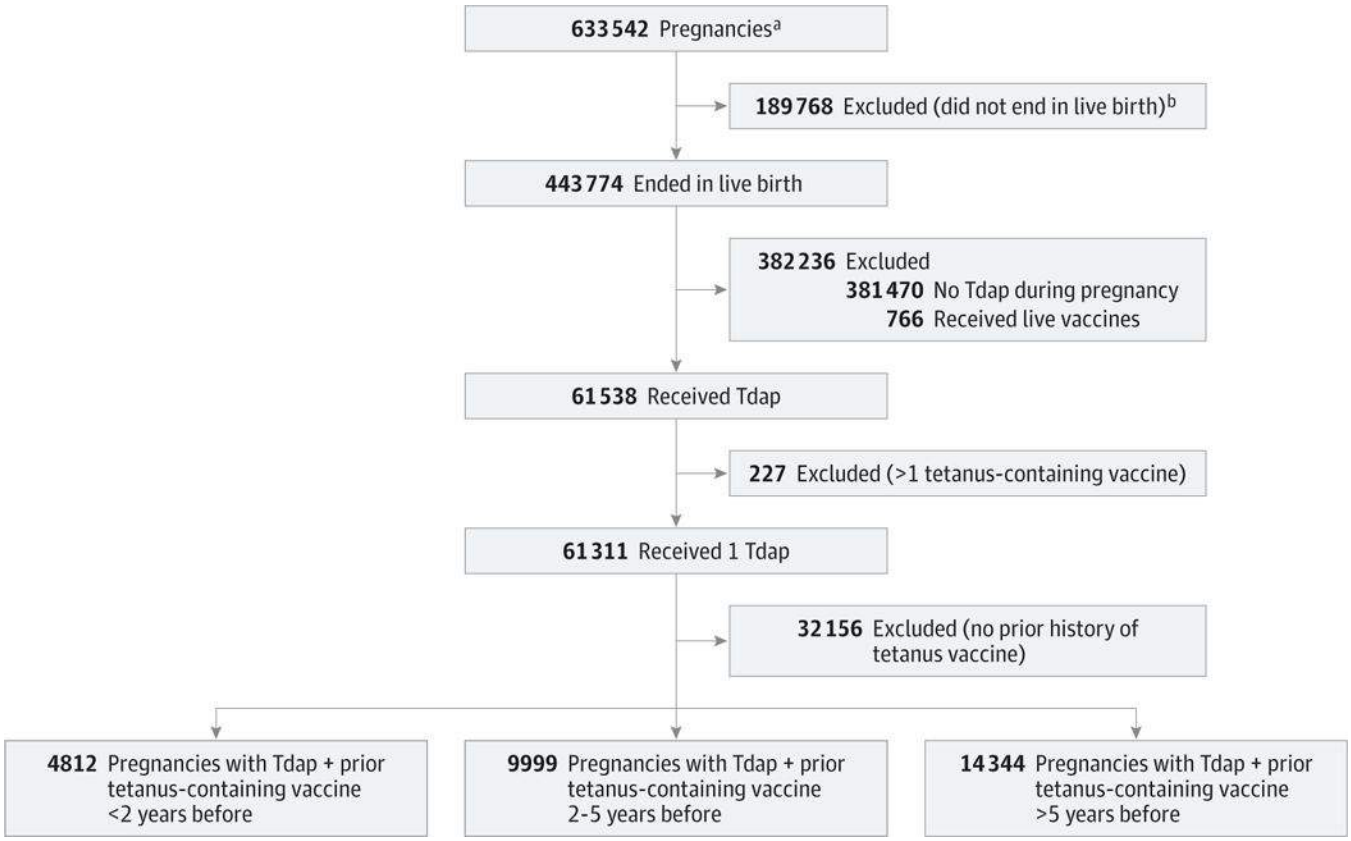

Figure. Tdap Vaccinations Received During Pregnancy From January 1, 2007, Through November 15, 2013, Recorded in 7 Vaccine Safety Datalink Sites

Tdap indicates tetanus, diphtheria, and acellular pertussis.

[a] Singleton pregnancies.

[b] Not live birth includes stillbirth, spontaneous abortion, therapeutic abortion, trophoblastic disease, ectopic pregnancy, and unknown outcomes.

Table 1.

Selected Demographic Characteristics of Pregnant Women Who Received Tdap During Pregnancy by Vaccination Status Recorded in the Vaccine Safety Datalink Sites From January 1, 2007, Through November 15, 2013

Variable	No. (%) Time Since Prior Tetanus-Containing Vaccination, y <2 (n = 4812)	2–5 (n = 9999)	>5 (Control) (n = 14 344)	*P* Value
Maternal age, mean (range), y	30.5 (15–49)	30.7 (14–49)	28.8 (14–48)	<.001
Enrollment prior to pregnancy, mean (range), mo	49.8 (6.0–99.9)	62.4 (6.0–100.5)	63.9 (6.0–99.8)	<.001
Gestational age at Tdap, mean (range), wk	30 (1–39)	30 (1–41)	27 (1–40)	<.001
Adequate prenatal care[a]	3629 (75)	7324 (73)	10 542 (73)	.01
Other vaccines in pregnancy	3012 (63)	6179 (62)	8996 (63)	.33
Maternal comorbidity[b]	1383 (29)	2956 (30)	4394 (31)	.03
Pregnancy complication[c]	2514(52)	5230 (52)	7565 (53)	.74
Prior tetanus vaccine Tdap[d]	4542 (94)	8511 (85)	2477 (17)	<.001

Abbreviation: Tdap, tetanus, diphtheria, and acellular pertussis.

[a]Adequate or adequate plus prenatal care based on Kotelchuck Adequacy of Prenatal Care Utilization Index.

[b]Presence of hypertension in pregnancy, diabetes, cardiovascular disease, or asthma.

[c]Includes any of the following diagnoses: fetal abnormality affecting maternal management, fetal or placental problems affecting maternal management, polyhydramnios, oligohydramnios, premature rupture of membranes, amnionitis, antepartum hemorrhage, placental abruption, placenta previa, or antepartum complications.

[d]Compared with non-Tdap tetanus vaccines (ie, tetanus diphtheria; tetanus toxoid; diphtheria and tetanus toxoids and acellular pertussis, etc).

Table 2.

Acute Outcomes Following Tdap Vaccination in Pregnancy By Interval Since Prior Tetanus-Containing Vaccination

	Time Since Prior Tetanus-Containing Vaccination, y						Relative Risk (95% CI)			
	<2 (n = 4812)		2–5 (n = 9999)		>5 (Control) (n = 14 344)		<2 y vs Control		2–5 y vs Control	
Outcome	No. of Patients	Rate[a]	No. of Patients	Rate[a]	No. of Patients	Rate[a]	Unadjusted[b]	Adjusted[b,c]	Unadjusted[d]	Adjusted[c,d]
Fever										
0–3 d	1	2.1	0	0	5	3.5	0.60 (0.07–5.10)	0.66 (0.07–5.77)		
0–7 d	3	6.2	1	1.0	6	4.2	1.49 (0.37–5.96)	1.61 (0.39–6.66)	0.24 (0.03–1.99)	0.21 (0.03–1.80)
Allergic Reaction										
0–3 d	1	2.1	1	1.0	2	1.4	1.49 (0.14–16.4)	1.55 (0.13–18.45)	0.72 (0.07–7.91)	0.71 (0.06–8.13)
0–7 d	2	4.2	4	4.0	5	3.5	1.19 (0.23–6.14)	1.32 (0.24–7.17)	1.15 (0.31–4.27)	1.23 (0.32–4.80)
Local Reaction										
0–3 d	2	4.2	7	7.0	16	11.2	0.37 (0.09–1.62)	0.49 (0.11–2.20)	0.63 (0.26–1.53)	0.77 (0.31–1.95)
0–7 d	6	12.5	17	17.0	22	15.3	0.81 (0.33–2.00)	1.01 (0.40–2.56)	1.11 (0.59–2.09)	1.28 (0.66–2.47)

Abbreviation: Tdap, tetanus, diphtheria, and acellular pertussis.

[a] Rate per10 000 women.

[b] Tdap + prior tetanus less than 2years before compared with Tdap + prior tetanus more than 5years before.

[c] Adjusting for Vaccine Safety Datalink site and gestational age at vaccination in weeks.

[d] Tdap + prior tetanus 2 to 5years before compared with Tdap + prior tetanus more than 5 years before.

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Table 3.

Adverse Birth Outcomes Following Tdap Vaccination in Pregnancy by Interval Since Prior Tetanus-Containing Vaccination

	No. (%)			Relative Risk (95% CI)			
	Time Since Prior Tetanus-Containing Vaccination, y			<2 y vs Control		2–5 y vs Contro	
Outcome	<2 (n = 3313)	2–5 (n = 7226)	>5 (Control) (n = 10 633)	Unadjusted[a]	Adjusted[a,b]	Unadjusted[c]	Adjusted[b,c]
Preterm delivery[d]	218 (6.6)	460 (6.4)	723 (6.8)	0.97 (0.84–1.12)	1.15 (0.98–1.34)	0.94 (0.84–1.05)	1.06 (0.94–1.19)
Low birth weight[e]	156 (4.7)	342 (4.7)	543 (5.1)	0.92 (0.78–1.10)	1.10 (0.92–1.32)	0.93 (0.81–1.06)	1.03 (0.89–1.18)
Small for gestational age[f]	298 (9.0)	629 (8.7)	996 (9.1)	0.99 (0.87–1.12)	0.99 (0.87–1.13)	0.96 (0.87–1.05)	0.96 (0.87–1.06)

Abbreviation: Tdap, tetanus, diphtheria, and acellular pertussis.

[a] Tdap + prior tetanus less than 2 years before compared with Tdap + prior tetanus more than 5 years before.

[b] Adjusting for gestational age at Tdap vaccination in weeks, Vaccine Safety Datalink site, length of enrollment (in months), prenatal care utilization index, maternal comorbidity, pregnancy complication, and maternal age.

[c] Tdap + prior tetanus 2 to 5 years before compared with Tdap + prior tetanus more than 5 years before.

[d] Gestational age of less than 37 weeks.

[e] Birth weight of less than 2500 g.

[f] Weight of less than the 10th percentile for gestational age and sex.

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Infant Hospitalizations and Mortality After Maternal Vaccination

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Abstract

BACKGROUND: The Advisory Committee on Immunization Practices currently recommends pregnant women receive influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines. There are limited studies of the long-term safety in infants for vaccines administered during pregnancy. We evaluate whether maternal receipt of influenza and Tdap vaccines increases the risk of infant hospitalization or death in the first 6 months of life.

METHODS: We included singleton, live birth pregnancies in the Vaccine Safety Datalink between 2004 and 2014. Outcomes were infant hospitalizations and mortality in the first 6 months of life. We performed a case-control study matching case patients and controls 1:1 and used

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

conditional logistic regression to estimate odds ratios for maternal exposure to influenza and/or Tdap vaccines in pregnancy.

RESULTS: There were 413 034 live births in our population. Of these, 25 222 infants had hospitalizations and 157 infants died in the first 6 months of life. We found no association between infant hospitalization and maternal influenza (adjusted odds ratio: 1.00; 95% confidence interval [CI]: 0.96–1.04) or Tdap (adjusted odds ratio: 0.94; 95% CI: 0.88–1.01) vaccinations. We found no association between infant mortality and maternal influenza (adjusted odds ratio: 0.96; 95% CI: 0.54–1.69) or Tdap (adjusted odds ratio: 0.44; 95% CI: 0.17–1.13) vaccinations.

CONCLUSIONS: We found no association between vaccination during pregnancy and risk of infant hospitalization or death in the first 6 months of life. These findings support the safety of current recommendations for influenza and Tdap vaccination during pregnancy.*

*Methods:

This study removed all cases of:
- Hospitalization or death of the infant during pregnancy or birth.
- Pre-term birth before 34 weeks.
- Birth defects in infants.
- Perinatal complications.

Study also does not compare outcomes to outcomes of unvaccinated infants.

The Advisory Committee on Immunization Practices currently recommends 2 vaccines to be given during each pregnancy; influenza vaccine has been recommended at any time during pregnancy since 2004 to prevent maternal influenza disease and complications[1] and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine has been recommended during each pregnancy since 2012, with a preference for administration between 27 and 36 weeks' gestation, to protect infants from pertussis disease.[2] Given the relative proximity of an immunization administered during pregnancy to a potential infant hospitalization or death, an observed temporal association with maternal influenza or Tdap vaccine during pregnancy and infant death or hospitalization may raise concerns about a possible causal relationship.

Both pertussis and influenza infections are associated with hospitalizations and fatalities in infants, and severity is highest before infants are eligible for the respective vaccines. Approximately half of infants <4 months of age with pertussis require hospitalization, and the majority of deaths from pertussis occur in these infants.[3] In 2014, the US pertussis case rate in infants <6 months of age was 169 per 100 000 infants.[4] Furthermore, there were 8 deaths in infants <3 months of age and 1 death in infants 3 to 11 months of age out of 13 total deaths from pertussis in all age groups in 2014. Similarly, infants are at high risk of hospitalization and death from influenza. The US influenza hospitalization rate ranges from 1.8 to 7.2 per 1000 in infants <6 months of age.[5] For the 2013–2014 influenza season, there were 96 laboratory-confirmed, influenza-associated pediatric deaths, 18 of which occurred in children aged <6 months.[6] Maternal immunization with influenza and Tdap vaccines allows for passive antibody transfer and protection to infants for the respective diseases when they are most vulnerable.[1,2,7]

In 2015, the infant (≤12 months) mortality rate in the United States was 589.5 per 100 000 live births,[8] and the leading causes of infant deaths were (1) congenital malformations, deformations, and chromosomal abnormalities; (2) disorders related to low birth weight and short gestation; and (3) sudden infant death syndrome. In 2010, the leading causes of hospitalizations in infants ≤12 months were (1) acute bronchitis (238 per 10 000 population), (2) jaundice (104 per 10 000 population), and (3) pneumonia (56 per 10 000 population).[9] Although there have been reassuring safety data for influenza and Tdap vaccines in which maternal acute events, pregnancy complications, and birth outcomes were

evaluated,[10–19] there have been limited safety studies beyond the immediate neonatal period.[20–24] Vaccine safety continues to be a primary reason why providers and patients choose not to vaccinate during pregnancy.[25–27] Although the biologic plausibility is unclear for the association of maternal vaccination and infant hospitalization or death, there may be concerns of long-term effects on infants after any pregnancy exposure. In this study, we evaluate whether maternal receipt of influenza and Tdap vaccines increases the risk of hospitalization or death in US infants in the first 6 months of life.

METHODS

Study Population

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention and 8 integrated health care systems (sites) and includes vaccination and health care data on ~10 million persons per year.[28] In addition, the VSD includes data on ~ 125 000 pregnant women annually.

We used data on pregnant women from 5 VSD sites with available data that comprise over 90% of the VSD population: Kaiser Permanente Northern California (Oakland, CA), Kaiser Permanente Southern California (Pasadena, CA), Kaiser Permanente Colorado (Denver, CO), Marshfield Clinic Research Foundation (Marshfield, WI), and Kaiser Permanente Northwest (Portland, OR).

We used the validated VSD Pregnancy Episode Algorithm to identify pregnant women.[29] The Pregnancy Episode Algorithm uses comprehensive electronic medical record and administrative databases (including diagnosis and procedure codes, laboratory tests, pharmacy records, and imaging procedures) to identify pregnancies, pregnancy outcomes, and pregnancy start and end dates, and it is able to link pregnant women to their infants. We included women from the VSD with pregnancies ending in a live birth between January 1, 2004, and June 30, 2014. We required pregnant women to be enrolled at a VSD site for the duration of the pregnancy episode and to have at least 1 prenatal care visit. To increase completeness of data, infants of these pregnant women were required to have a birth record and to have VSD site enrollment until 6 months of life or until the time of death. We excluded pregnancies in which a live vaccine was administered because live vaccines are contraindicated in pregnancy. We also excluded infants of multiple gestation pregnancies, infants born before 34 weeks' gestation, and infants with major birth defects because these infants are at a higher risk of hospitalization and death. Furthermore, we excluded all infants who died during their delivery hospitalization because cause of death in these infants is often a perinatal complication (such as placental abruption) that would likely be unrelated to maternal vaccination.* Additionally, infants who die during the birth hospitalization may be less likely to be enrolled in the VSD and captured in our data. We also excluded infants with external causes of death (*International Classification of Diseases, 10th Revision* [ICD-10] codes S00-T98 and V00-Y98) and infants with external causes of hospitalizations (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 800–999, E800-E999) due to injury and poisonings because these are unlikely to result from a maternal vaccination. ICD-10 coding was not available for hospitalization diagnoses in the United States during the time of this study.

They are admitting that the Vaccine Safety Datalink is not capturing data on infants who die during the birth hospitalization.

*No research to support this statement.

Case-Control Matching

Among infants meeting inclusion criteria, those infants with hospitalizations or deaths within the first 6 months of life were included in this analysis. Respiratory hospitalization case patients were a subset of hospitalization case patients defined by any respiratory ICD-9 code (033, 460–488, 491–496, 510–519) associated with a hospitalization in the first 6 months of life. For infants with >1 hospitalization, the first hospitalization was selected for each category (ie, first all-cause hospitalization, first respiratory hospitalization). Furthermore, an infant could be included as a death case patient and hospitalization case patient if the infant was hospitalized and later died. In the VSD, deaths are identified from state death records, electronic medical records, and administrative sources, and there is approximately a 1-year lag from the time of death to the availability of state death records. Because of lag time in the death data, we evaluated deaths occurring from January 1, 2004, to December 31, 2013, and hospitalizations from January 1, 2004, to December 31, 2014. Matched controls for the infant mortality analysis were selected among infants in the study who survived the first 6 months of life. Matched controls for the infant hospitalization and respiratory hospitalization analyses were selected from infants without death or hospitalization in the first 6 months of life. All infant controls were required to have at least 1 diphtheria-tetanus-acellular pertussis (DTaP) vaccine recorded between 6 weeks and 6 months of age to ensure infants were accessing the health care system. We matched case patients and controls 1:1 using optimal matching.[30] Case patients and controls were matched on the basis of VSD site, birth month and year (within 1 month), and gestational age groups of late preterm (34–36 weeks), term (37–41 weeks), and postterm (42–44 weeks). With our optimal matching, we successfully found controls for 100% of our case patients by using these parameters.

Vaccinations

The exposure of interest was maternal vaccination with any influenza and/or Tdap vaccines during pregnancy. A vaccine during pregnancy was defined as one given from 7 days after the pregnancy start date to 7 days before the pregnancy end date. These time windows were chosen to avoid including exposures to vaccinations given before or immediately after pregnancy. We stratified vaccine exposures as any influenza vaccine (with or without Tdap), any Tdap vaccine (with or without influenza), and both influenza and Tdap vaccines in the same pregnancy. In our evaluation of maternal influenza vaccine, we also repeated our analysis limiting outcomes to events occurring during the influenza season (October through May), to ascertain any protective findings that may be more evident when influenza virus is circulating. We also did a sensitivity analysis stratifying our exposure by influenza vaccine only and Tdap vaccine only to see if our results would differ by limiting our exposure groups.

Statistical Analysis

We measured rates of influenza and Tdap maternal vaccination in our study cohort from 2004 to 2013. We also measured trends of infant deaths and hospitalizations during this same time period to look for any ecological associations between maternal vaccination and our infant outcomes. For our main analysis, we performed a conditional logistic regression

analysis to estimate the odds of maternal vaccination in matched case patients and controls. In our analysis, we determined a priori to include the following potential confounders from electronic VSD data sources[28]: Kotelchuck Adequacy of Prenatal Care Index,[31] race and ethnicity (non-Hispanic African American or American Indian versus other races and ethnicities), maternal age, pregnancy complications and maternal comorbidities (hemorrhage, hypertensive disorders, renal disease, diabetes, thyroid disease, cardiovascular disease, epilepsy), smoking during pregnancy (yes, no, or unknown), infant DTaP exposure before outcome (or index date in matched controls), duration of birth hospitalization in days, and gestational age at delivery in weeks.

We also reviewed medical records of infants with respiratory related deaths (ICD-10 codes: A37, J00–J99). We reviewed clinical information relating to a potential influenza- or pertussis-related cause of death and laboratory data in the 2-week period preceding death. For influenza laboratory data, we looked for positive influenza A or B rapid antigen, polymerase chain reaction (PCR), viral culture, and direct fluorescent antibody test results in all respiratory death case patients. For pertussis, we looked for positive *Bordetella pertussis* PCR and culture test results for any death case patient with the ICD-10 code A37 (whooping cough).

We determined a priori that with an expected average exposure rate of 15% for both vaccines throughout the study period,[32–34] we would need at least 840 case patients to have 80% power to detect an odds ratio of 1.5. The protocol for this study was approved by the Centers for Disease Control and Prevention Institutional Review Board and institutional review boards at each of the participating VSD sites. All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

During our study period, we identified 500 447 pregnancies ending in a live birth that met enrollment criteria. We excluded 87 413 (17.5%) because of maternal or infant factors (Fig 1). Of the remaining 413 034 infants, 25 222 infants had 1 or more hospitalizations and 157 infants died. Of the hospitalized infants, 4644 (18.4%) had a respiratory cause for their hospitalization; 105 (2.2%) of these infants had an influenza ICD-9 code (487, 488), and 137 (3%) had a pertussis ICD-9 code (033.0, 033.9). Of the deaths, 14 (9%) had a respiratory cause of death; however, none of these deaths were considered to have been caused by influenza or pertussis infections on the basis of our laboratory and medical record review. Of the 157 infants that died, the age at death ranged from 1 to 180 days with a mean of 61 days and a median of 51 days. The most common causes of death were unknown causes (32%), sudden infant death syndrome (21%), and certain conditions originating in the perinatal period (17%).

We analyzed overall trends of influenza and/or pertussis vaccination in pregnancy and trends of infant hospitalization and mortality in our study population from 2004 to 2013 (Fig 2). From 2004, there was an increase in maternal influenza vaccination, which became more dramatic in 2009 after the H1N1 influenza pandemic. Maternal Tdap vaccination increased starting in 2010 when California recommended pregnant women to receive Tdap in

pregnancy in response to the 2010 statewide pertussis epidemic.[35] There was another increase in Tdap vaccination in 2012 after the most recent Advisory Committee on Immunization Practices recommendation to administer Tdap vaccination in every pregnancy.[2] We observed no increase in the infant hospitalization rate or infant mortality rate during the same time period.

We matched case patients with eligible controls and compared characteristics between these groups (Table 1, Supplemental Table 3). Infants who were hospitalized were more likely to have mothers with pregnancy complications, less likely to be delivered by cesarean delivery, and less likely to be of African American non-Hispanic or American Indian race. Mean maternal age, gestational age at delivery, and length of birth hospitalization were statistically significantly different between the groups but not clinically different. Infants who died were similar to matched controls.

In our adjusted analysis, we found no significant association between infant hospitalization or death in the first 6 months of life and receipt of maternal influenza and/ or Tdap vaccines and no significant association between infant hospitalization from respiratory causes and maternal influenza vaccine (Table 2). However, the odds of maternal Tdap vaccination was significantly lower among infants with hospitalizations because of respiratory causes (adjusted odds ratio: 0.79; 95% confidence interval [CI]: 0.67–0.94; $P = .007$) compared with controls without hospitalization. Furthermore, when evaluating infant hospitalizations and death occurring during periods of influenza virus circulation (October through May) and peak influenza virus circulation (November through February), we found no association with maternal influenza vaccine exposure (data not shown). When limiting our exposure groups to women receiving influenza vaccine without Tdap vaccine and Tdap vaccine without influenza vaccine, our results were similar to our main analysis (Supplemental Table 4).

DiSCUSSiON

In our study of maternal influenza and Tdap vaccines, we found no increased risk of infant all-cause hospitalizations, hospitalizations from respiratory causes, or all-cause mortality in the first 6 months of life. Our study helps strengthen the growing evidence of long-term safety of vaccination in pregnancy for infants.

Our findings are similar to other studies that have evaluated infant mortality and morbidity after maternal vaccination in pregnancy, most of which have evaluated the safety of adjuvanted H1N1 influenza-containing vaccines. Studies of short-term infant mortality in the first 7 days of life,[20] growth and development and health care visits for infections in the first year of life,[23] early neonatal or childhood death,[22] and childhood hospitalization rates,[21] have not found an increased risk of these outcomes in children of women who received adjuvanted H1N1 influenza–containing vaccines in pregnancy. Unlike these previous studies, however, our study included women who received any type of influenza vaccine, none of which contain adjuvants in the United States, and we found similar results.

Our findings are also consistent with studies in which researchers have evaluated infant mortality and morbidity after Tdap vaccination in pregnancy. These researchers have

evaluated neonatal mortality,[10,36] NICU admissions,[37] length of hospitalization, ventilation requirement, intraventricular hemorrhage, transient tachypnea of the newborn, neonatal sepsis, pneumonia, respiratory distress syndrome, and convulsions.[36,38] There were no differences in outcomes between infants of Tdap-vaccinated and unvaccinated mothers in these studies. Our study included a longer follow-up period than these previous studies and still showed no increased risk of infant mortality or hospitalization after maternal Tdap vaccination.

Other long-term outcomes that have previously been studied after maternal Tdap vaccination include childhood development scores at 13 months of life,[13] infant growth up to 5 to 7 months of age,[24] and complex chronic conditions at 12 months of age.[17] The researchers for these studies did not find an increased risk of these infant outcomes after maternal Tdap vaccination during pregnancy. Our study managed a larger number of infants and had similar findings to these studies, further demonstrating long-term safety in infants of Tdap vaccine exposure in pregnancy.

We did find a protective association between maternal Tdap during pregnancy and infant respiratory hospitalizations, which is consistent with results of other published studies that have looked at infant pertussis as an outcome.[7,39–42] However, only 3% of infants hospitalized for respiratory causes had a pertussis ICD-9 code. This could indicate that infants with pertussis are not being appropriately diagnosed and tested.[43] It is also possible that other factors (eg, the healthy adherer effect[44] and other differences in people who choose vaccination and those who do not) are contributing to this finding.

This study does have some limitations. The VSD captures data on an insured population, which could translate to better health outcomes than the general population. Additionally, VSD has a high rate of women with adequate prenatal care on the basis of the Kotelchuck index, which can translate to better infant outcomes.[31] A recent study has revealed that despite being a fully insured population, the VSD is comparable to the total US population on many important demographic factors.[45] Moreover, the VSD population size is large, and even groups that typically comprise a smaller proportion of insured populations (ie, lower income populations) still have a substantial (>2 million individuals) presence in the VSD. There may have been bias related to requiring controls to have a DTaP vaccine record to be included in the study. We did this to ensure we had access to health care utilization data to avoid misclassifying case patients as controls. To look for bias, we repeated our analysis of hospitalizations requiring case patients to have a DTaP vaccine (98.0% of case patients) and found similar results to our main findings. We looked at broad safety outcomes (hospitalizations, respiratory hospitalizations, and deaths) and may not capture true increases in a specific outcome, if such an association was present. We relied on vaccination data from our VSD electronic data files and may not have captured vaccines in pregnancy occurring outside the health care system. However, previous internal work looking at influenza vaccination in pregnancy revealed that the VSD vaccine files are over 98% complete in capturing these data (J. Donahue, DVM, PhD, unpublished observations). We did not evaluate the risks of infant hospitalizations and mortality in multiple gestation infants, very preterm infants, and those with major birth defects because these infants are at a much higher risk of the outcomes we studied; therefore, our results are not generalizable to these

populations. Finally, we were sufficiently powered for our outcomes of hospitalizations and hospitalizations from respiratory causes but underpowered for the outcome of death.

This is the first study in which infant hospitalizations and mortality in the first 6 months of life after maternal influenza vaccine and Tdap vaccines are evaluated. In this large case-control study, we found no increased risk of infant hospitalization and death after vaccination in pregnancy.

Our findings support the safety of influenza and pertussis vaccinations during pregnancy for infants of vaccinated mothers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

CI	confidence interval
DTaP	diphtheria-tetanus-acellular pertussis
ICD-9	*International Classification of Diseases, Ninth Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
PCR	polymerase chain reaction
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
VSD	Vaccine Safety Datalink

Biography

Dr Sukumaran conceptualized and designed the study, participated in data collection, conducted the analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Ms McCarthy participated in the conceptualization and design of the study, designed the data collection instruments, collected data, participated in the analysis, and reviewed and revised the manuscript; Mr Weintraub participated in the conceptualization and design of the study, participated in the analysis, and critically reviewed the manuscript; Drs Kharbanda, Vazquez-Benitez, Lipkind, Jackson, Klein, Naleway, McClure, Hechter, Kawai, and Glanz contributed to the acquisition and interpretation of data and reviewed and revised the manuscript; all authors critically reviewed the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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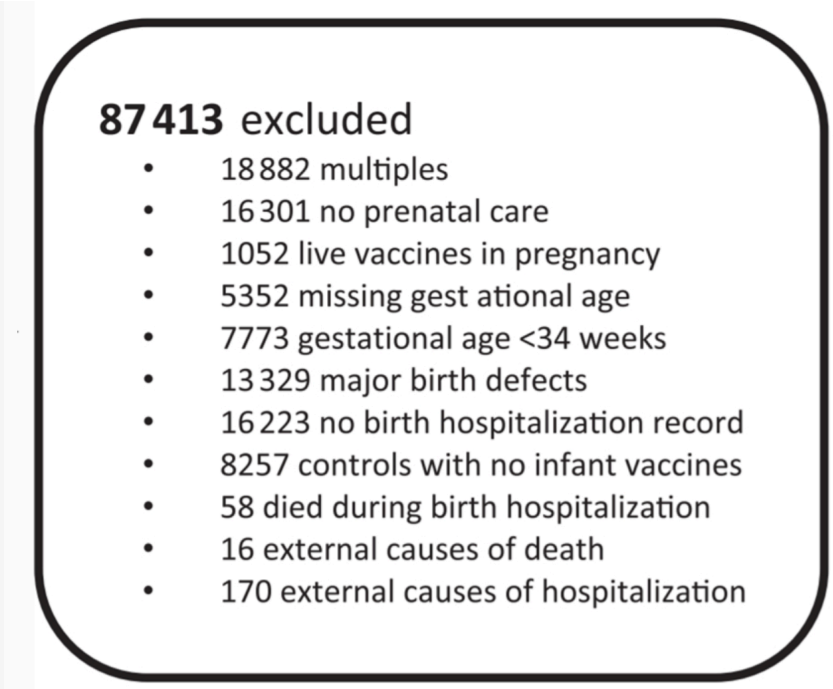

WHAT'S KNOWN ON THIS SUBJECT:

Influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines are recommended in pregnancy. Although there is evidence that these vaccines are safe in pregnant women, there are limited long-term data on infants born to mothers vaccinated during pregnancy.

WHAT THIS STUDY ADDS:

Influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnancy are not associated with an increased risk of hospitalization or death in infants. Our findings contribute to the knowledge of the long-term safety of vaccination during pregnancy.

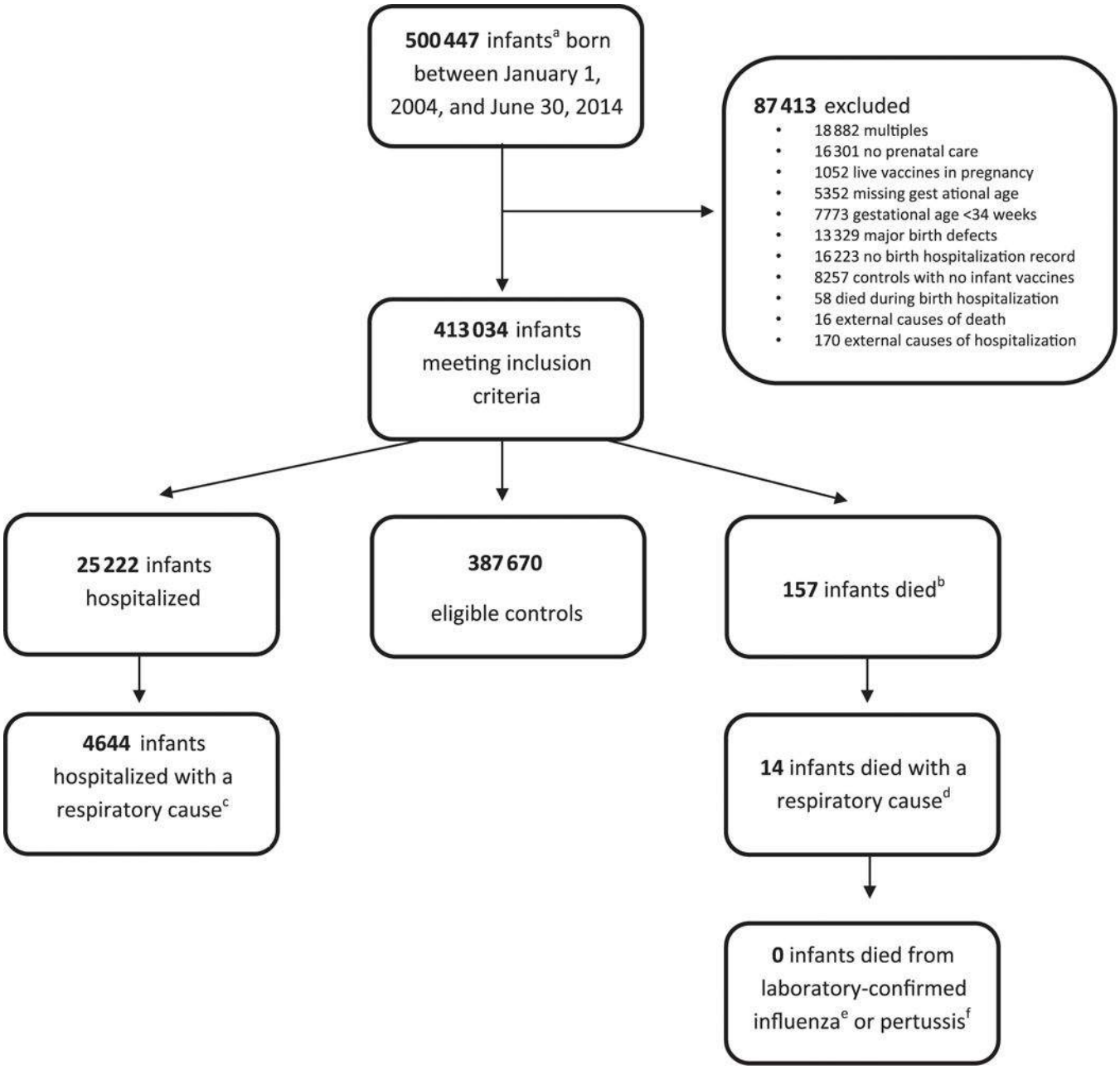

FIGURE 1.

Study population of infants with hospitalization or death in the first 6 months of life in the VSD, 2004–2014. [a] Infants with continuous enrollment in the VSD until 6 months of age or until the time of death whose mothers were enrolled for the duration of their pregnancy. [b] Fifteen infants were hospitalization and death case patients. [c] Defined as ICD-9 codes: 033, 460–488, 491–496, 510–519. [d] Defined as ICD-10 codes: A37, J00–J99. [e] Positive influenza A or B antigen, viral culture, PCR, or direct fluorescent antibody test results within 14 days of hospitalization. [f] Positive *B pertussis* PCR or culture test results within 14 days of hospitalization.

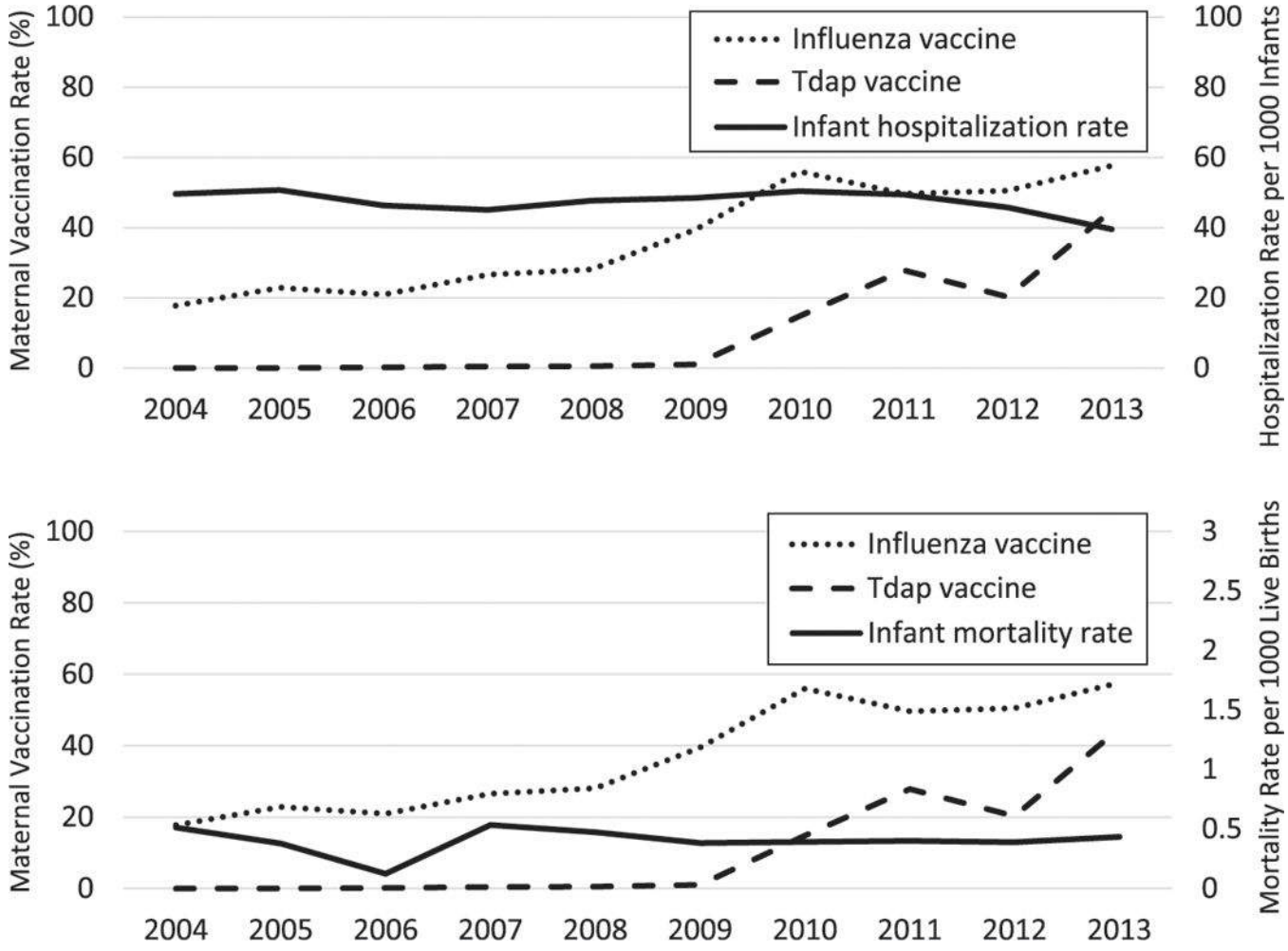

FIGURE 2.

Rates of maternal influenza and Tdap vaccination, infant hospitalization, and infant mortality in the VSD, 2004–2013.

TABLE 1

Characteristics of Matched Case Patients and Controls for Infant Hospitalizations and Mortality in the First 6 Months of Life in the VSD, 2004–2014

	Hospitalization Case Patients (n = 25 222)	Matched Controls (n = 25 222)	P^a	Death Case Patients (n = 157)	Matched Controls (n = 157)	P
Mean age at event in d (range)	36 (1–183)	—	—	61 (1–180)	—	—
Mean gestational age at delivery in wk (range)	39 (34–43)	39 (34–43)	<.0001	39 (34–41)	39 (34–41)	.88
Mean maternal age in y (range)	31 (13–54)	31 (13–55)	.0005	30 (15–41)	30 (16–41)	.23
Mean length of delivery hospitalization in d (range)	2.2 (0–103)	2.2 (0–110)	<.0001	3.5 (0–41)	2.2 (0–18)	.43
Smoking during pregnancy, %	8.9	9.2	.39	15	10	.35
Pregnancy complications, %[b]	31.0	28.7	<.0001	34	27	.14
Cesarean delivery, %	23.6	27.9	<.0001	36	31	.52
Adequate prenatal care by Kotelchuck index, %[31]	94.2	93.9	.30	92	92	.92
African American non-Hispanic or American Indian race, %	5.9	7.2	<.0001	10	6	.14

—, not applicable.

[a] P values calculated by χ^2 tests for categorical variables and Wilcoxon median 2-sample tests for continuous variables.

[b] Pregnancy complications include hemorrhage, hypertensive disorders, renal disease, diabetes, thyroid disease, cardiovascular disease, and epilepsy.

TABLE 2

Matched Case-Control Analysis of Infant Hospitalizations and Death in the First 6 Months of Life in the VSD After Maternal Vaccination, 2004–2014

	1:1 Matched Analysis of Hospitalizations (*n* = 50 444)			1:1 Matched Analysis of Respiratory Hospitalizations (*n* = 9288)			1:1 Matched Analysis of Deaths (*n* = 314)		
Vaccine in pregnancy	Influenza[a]	Tdap[b]	Both[c]	Influenza	Tdap	Both	Influenza	Tdap	Both
Case patients exposed, %	38.7	12.8	8.6	38.4	9.9	7.1	32	6	3
Controls exposed, %	39.3	13.4	9.0	38.1	11.4	7.4	37	12	8
Crude OR (95% CI)	0.97 (0.93–1.01)	0.91 (0.85–0.97)	0.94 (0.87–1.01)	1.02 (0.93–1.12)	0.79 (0.67–0.93)	0.93 (0.78–1.13)	0.81 (0.49–1.31)	0.41 (0.17–0.99)	0.25 (0.07–0.89)
aOR[d] (95% CI)	1.00 (0.96–1.04)	0.94 (0.88–1.01)	0.97 (0.90–1.05)	1.08 (0.97–1.19)	0.79 (0.67–0.94)	0.97 (0.80–1.17)	0.96 (0.54–1.69)	0.44 (0.17–1.13)	0.32 (0.08–1.24)
P[e]	.93	.09	.44	.15	.007	.73	.87	.09	.10

aOR, adjusted odds ratio; OR odds ratio.

[a]Influenza vaccine in pregnancy given with or without Tdap vaccine.

[b]Tdap vaccine in pregnancy given with or without influenza vaccine.

[c]Both influenza and Tdap vaccines given in the same pregnancy.

[d]Adjusting for pregnancy complications, adequacy of prenatal care, smoking during pregnancy, race, maternal age, infant DTaP receipt before event, length of birth hospitalization in days, and gestational age at delivery in weeks.

[e]*P* values correspond to the aOR.

The Present Status of Polio Vaccines.

Author(s) : RATNER, H., Moderator; COX, H. R.; GREENBERG, B. G.; KLEINMAN, H.; MEIER, P., Panelists

Journal article : Illinois Medical Journal 1960 Vol.118 No.2 pp.19 pp.

Abstract : A panel discussion on the present status of poliovaccines was held in Chicago on May 26th, 1960. 2 of the panellists, Dr. Ratner and Professor Meier, have been critics of Salk poliovaceine since its inception. Professor Greenberg and Dr. Kleinman have been concerned with the evaluation of poliovaceine effectiveness and Dr. Cox is responsible for the development of attenuated polio-virus vaccine. Kleinman has also been concerned with field trials of Lederle attenuated poliovaceine. The burden of the argunient is that killed poliovaceine has been a failure and that a change to a living vaccine should be made.

Ratner notes that poliomyelitis incidence has increased from the 1957 level in 1958 and 1959, and that substantial numbers of cases occur in the triply vaccinated. Greenberg points out some fallacies in the assessment of poliovaceine effectiveness. First, the requirements have altered to increase safety but it is thought that polio-vaccine potency decreases following the introduction of a second filtration step. [In the reviewer's experience of making killed vaccine it is clear that the quality of the filtration vitally affects safety but that with suitable precautions no potency need be lost.] The report of the Poliomyelitis Surveillance Unit of December 7th, 1955, is severely criticized because the numbers of children were taken from the 1950 census and no allowance was made for increases in the population. Also, children were considered as vaccinated regardless of whether they were vaccinated early or late in the year. This diminishes the rate in the vaccinated owing to swelling the vaccinated population with those who were vaccinated late in the year after having escaped clinical infection earlier. Differences in diagnostic criteria for non-paralytic and paralytic cases introduced as a result of the 1954 killed polio-vaccine trial are thought to be the major cause of the fall in incidence of reported poliomyelitis m 1957. [Most analyses of killed poliovaceine effectiveness allowing for these factors have showed it to be at least 80% effective.

Kleinman, who had previously estimated killed polio-vaccine to be very effective, is now dubious because of the increase in numbers of paralytic poliomyelitis. He confesses himself unable to decide whether the vaccine is or is not effective.

Meier reiterates his early fears about killed poliovaceine safety and the adequacy of the tests. He is uneasy about the propaganda effort to promote killed polio-vaccine. Experts, he contends, have doubts but in the newspapers the killed vaccine is represented as safe and very effective.

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Meier reiterates his early fears about killed poliovaceine safety and the adequacy of the tests. He is uneasy about the propaganda effort to promote killed polio-vaccine. Experts, he contends, have doubts but in the newspapers the killed vaccine is represented as safe and very effective.
Cox and Kleinman describe the development and use of attenuated poliovaceine mainly in Latin America and Minnesota. They believe the vaccine to be safe and effective in producing antibodies and therefore most likely to be effective in preventing poliomyelitis.
Ratner, summing up, concludes that, if killed polio vaccine is safe and highly effective, licensing of living vaccine is not urgent. The panel's view is that this proposition is not proven and that a living vaccine is an urgent necessity.
[The failure of killed poliovaceine has mainly been due to failure to achieve satisfactory acceptance of the vaccine. It is hoped that this problem will be overcome by an oral vaccine. One argument used in favour of living vaccine is the uniform satisfactory results with living vaccines in the veterinary field. A review by PRIER, *J. Amer. Vet. Med. Ass.*, 1960, v. 137, 577, is not quite so enthusiastic.] *A. J. Beale.*

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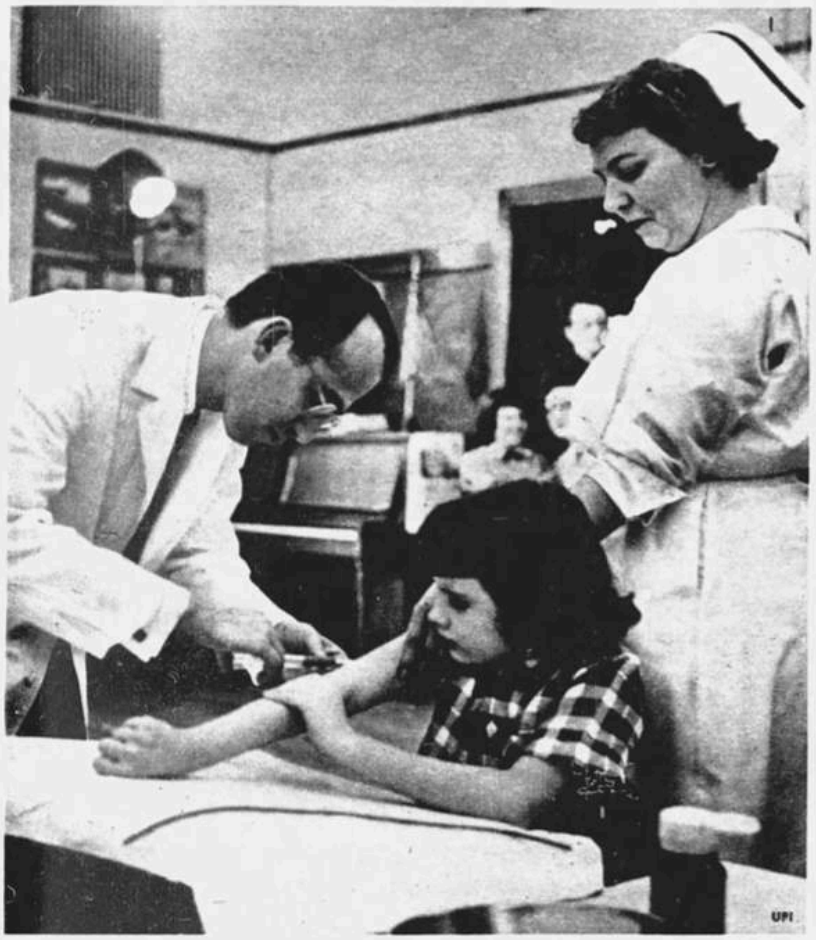


Dr. Jonas E. Salk injects a volunteer with his vaccine in 1954 field trials. Controversial from the first, the Salk vaccine is still a topic hotly debated.

The Truth About

Do Salk Shots Really Prevent Polio? Should We Keep Using Salk Inoculations? How Good Are the New Oral Vaccines? Here Are the Facts

By Joan Beck

BEHIND GLOWING reports of the Salk polio vaccine's success and even rosier predictions about the new, live, oral Sabin vaccine rages a storm of medical controversy that seldom reaches the ears of parents.

Many serious criticisms have been leveled at the Salk vaccine. These are now being acknowledged—at least indirectly—in announcements praising and promoting the new oral vaccines.

Yet all is not yet sweetness and accord among developers of the live, oral vaccines, either. At least three different types have been developed and—according to their producers—proved safe and effective in tests, chiefly in foreign countries, but also in the United States.

One of these new oral vaccines, developed by Dr. Albert Sabin with National Foundation research funds, has been OK'd by the United States public health service for manufacture. But there are problems remaining to be solved in its production and, according to a committee of experts headed by Dr. Roderick Murray of the National Institute of Health, dangers to be considered in its use by the general public (altho it has been given to a reported 77 million Russians and to at least 300,000 Americans. Russian Prof. Mikhail Chumakov, who directed a two year program of inoculation with the Sabin vaccine, says he is convinced polio epidemics have been eliminated in the Soviet Union). Licensing is not expected until this spring. Quantities of the vaccine are not expected to be available for community-wide use until November.

"Both 'live' (Sabin) and 'killed' (Salk) polio-virus vaccines will be needed to combat poliomyelitis in the near future, United States public health officials declared at the A. M. A. clinical meeting," the Journal of the American Medical association reported in December, 1960. "The new oral poliomyelitis vaccine developed by Dr. Albert Sabin and approved for future use in this country will not be the complete solution as far as can be predicted now, the public health service experts said."

Evaluating the true effectiveness of the Salk vaccine and the new oral vaccines has been difficult for several reasons. Polio is a relatively rare disease in the United States. Because so few persons get it in its paralyzing form, success of an immunizing agent is hard to determine.

The definition of polio also has changed in the last six or seven years. Several diseases which were often diagnosed as polio are now classified as aseptic meningitis or illnesses caused by one of the Coxsackie or Echo viruses. The number of polio cases in 1961 cannot accurately be compared with those in, say 1952, because the criteria for diagnosis have changed.

Even the Salk vaccine itself is not a constant, standard product. Since the first field trials of 1954, the vaccine has been changed several times. The first alterations were aimed at increasing the vaccine's safety by changing the method of killing the polio virus and by adding an extra filtration step. Newer changes are intended to increase the vaccine's effectiveness. The success of the Salk vaccine necessarily varies, depending upon which Salk vaccine is being considered.

Ever since the public was first informed about the Salk vaccine in the Francis report of April 12, 1955, the National Foundation has praised its effectiveness and urged parents to have themselves and their children vaccinated. Altho some physicians remained skeptical about the original theories behind the vaccine, about the techniques used in its evaluation, and about its success in combating polio, these objections seldom reached the general public. With the resurgence of paralytic polio in 1958 and 1959, the criticisms increased.

These views were summed up by five experts in a panel discussion on the "Present Status of Polio Vaccines" presented before the Illinois State Medical society in Chicago, in May, 1960, and published in the August and September issues of the Illinois Medical Journal. To make parents aware of the controversy about the Salk vaccine and the problems involved in developing an effective oral vaccine against polio, here is a report of that discussion:

Moderator of the panel was Herbert Ratner, M. D., director of public health in Oak Park, and associate clinical professor of preventive medicine and public health, Stritch School of Medicine, Chicago.

Dr. Ratner noted the upward trend in polio, particularly in the paralytic form, in the United States during 1958 and 1959. He quoted Dr. Alexander Langmuir, in charge of polio surveillance for the United States public health service, as saying this resurgence is "cause for immediate concern."

"In the fall of 1955, Dr. Langmuir had predicted that by 1957 there would be less than 100 cases of paralytic polio in the United States," commented Dr. Ratner. "Four years and 300 million doses of Salk vaccine later, we had in 1959 approximately 6,000 cases of paralytic polio, 1,000 of which were in persons who had received three and more shots of Salk vaccine. Salk vaccine hasn't lived up to expectations."

Dr. Sabin says the number of cases in 1960 was less than in 1959, but that 23 per cent are now occurring in persons who have had three or more doses of Salk vaccine.

Dr. Ratner next reviewed some basic facts about polio. Paralytic polio occurs in cycles and was in a natural decline when the Salk vaccine was introduced in 1955, he pointed out.

Prior to the introduction of the Salk vaccine, the National Foundation defined an epidemic as 20 or more cases of polio per year, per 100,000 population. Now, an epidemic is defined as 35 cases per year per 100,000. This change has resulted in a statistical —but not necessarily a real—drop in polio epidemics.

For every case of known paralytic polio, there are about a thousand "subclinical polio infections," so mild they pass unnoticed, Dr. Ratner explained. These mild cases account for the high degree of natural immunity in adults. You can have a polio infection in the intestines without having paralytic polio or nonparalytic polio with enough symptoms to be diagnosed.

The theory of the Salk vaccine, made with killed polio virus, is that it will produce enough antibodies

the Polio Vaccines

Dr. Herald R. Cox has another oral vaccine.

Dr. Hilary. Koprowski . . . he wants fair play.

circulating in the blood to neutralize poliovirus before it can reach the central nervous system. But "one of the major disappointments of the killed vaccine" is that these circulating antibodies do not protect an individual against getting a polio infection in the intestines, nor its breakthru into the circulatory system, said Dr. Ratner. Protection against paralytic polio depends upon the presence of enough circulating antibodies to offset the virus, he explained.

Discussing the "very misleading way" in which the Salk vaccine data has been handled, was Bernard G. Greenberg, Ph. D., head of the department of biostatistics of the University of North Carolina, school of public health, and former chairman of the committee on evaluation and standards of the American Public Health association.

"There has been a rise during the last two years in the incidence rates of paralytic poliomyelitis in the United States," stressed Dr. Greenberg. "The rate in 1958 was about 50 per cent higher than that for 1957, and in 1959 about 80 per cent higher than that in 1958. If 1959 is compared with the low year of 1957, the increase is about 170 per cent.

"As a result of this trend in paralytic poliomyelitis, various officials in the public health service, official health agencies, and one large voluntary health organization have been utilizing the press, radio, and television and other media to sound an alarm bell in an heroic effort to persuade more Americans to take advantage of the vaccination procedures available to them," said Dr. Greenberg.

"Altho such a program might be desirable until live virus vaccines are available to us on more than an experimental basis, the misinformation and unjustified conclusions about the cause of this rise in incidence give concern to those interested in a sound program based on logic and fact rather than personal opinion and prejudice.

"One of the most obvious pieces of misinformation being delivered to the American public is that the 50 per cent rise in paralytic poliomyelitis in 1958 and the real accelerated increase in 1959 have been caused by persons failing to be vaccinated. This represents a certain amount of double talk and an unwillingness to face facts and to evaluate the true effectiveness of the Salk vaccine," said Dr. Greenberg.

The number of persons over 2 years of age in 1960 who have not been vaccinated cannot be more and must be considerably less than the number who had no vaccination in 1957, Dr. Greenberg pointed out. Then how can it be claimed that it is the large number of unvaccinated persons who are causing the increase in polio, when there were a larger number of unvaccinated individuals in 1957 when the vaccine was given credit for reducing rates of the disease.

"A scientific examination of the data and the manner in which the data was manipulated will reveal that the true effectiveness of the present Salk vaccine is unknown and greatly overrated," Dr. Greenberg stressed.

Why was there such a tremendous reduction in reported rates of paralytic polio in 1955, 1956, and 1957? Much of this highly publicized decrease was a statistical illusion, said Dr. Greenberg.

Prior to 1954, any physician who reported a case of paralytic poliomyelitis was doing his patient a favor because funds were available to help pay his medical expenses. At that time, most health departments used a definition of paralytic poliomyelitis which specified "partial or complete paralysis of one or more muscle groups, detected on two examinations at least 24 hours apart." Laboratory confirmation and the presence of residual paralysis were not required.

In 1955, these criteria were changed. Now, unless there is paralysis lasting at least 60 days after the onset of the disease, it is not diagnosed as paralytic polio.

During this period, too, "Coxsackie virus infections and aseptic meningitis have been distinguished from paralytic poliomyelitis," explained Dr. Greenberg. "Prior to 1954, large numbers of these cases undoubtedly were mislabeled as paralytic polio."

Thus, because the definition of the disease was changed and two similar diseases virtually ruled out, the number of cases of polio reported was sure to decrease in the 1955-57 period, vaccine or not. Then, too, physicians are reluctant today to diagnose paralytic poliomyelitis in a vaccinated child without thoro laboratory tests, thus eliminating most of the false positive cases commonly reported in the pre-1954 period.

"As a result of these changes in both diagnosis and diagnostic methods, the rates of paralytic poliomyelitis plummeted from the early 1950s to a low in 1957," said Dr. Greenberg. The recent increase in the disease, despite improved diagnostic methods, he believes, is due to a long term, increasing trend in the occurrence of polio.

"Without doubt, the increasing trend has been reduced to some extent by the Salk vaccine," explained Dr. Greenberg. "Nevertheless, the Salk vaccine has limited effectiveness in its ability further to reduce this trend. . . . Any future substantial reduction in this trend will require a more potent vaccine, not simply vaccinating more people.

"Today it may be a serious mistake to be ultra-conservative in accepting the various new live vaccines under the impression that there is no hurry because an almost equivalent immunizer exists in the Salk vaccine. A delay in accepting and promoting better vaccines will be a costly one. There must be immediate pressure applied to determine whether or not the new vaccines are more effective, so that we do not cling, for sentimental or personal reasons, to an older vaccine whose true effectiveness is today unknown."

The most accurate way we have of determining the effectiveness of vaccine (except by direct exposure to the disease) is to measure the levels of neutralizing antibodies in the blood, explained Herald R. Cox, Sc. D., director of virus research at Lederle Laboratories and president elect of the Society of American Bacteriologists. We do not know, he said, the exact level of antibodies necessary to protect against paralytic polio.

Herman Kleinman, M. D., an epidemiologist from the Minnesota department of health, pointed out that in antibody studies on children who have received three or more doses of Salk vaccine, he has found more than half do not have antibodies to two of the three types of polio strains used in the Salk vaccine. Twenty per cent lack antibodies to a third type.

"This is a very disturbing fact," said Dr. Kleinman. "If polio antibodies mean anything in respect to protection, then I am forced to conclude that much of the Salk vaccine we have been using is useless."

Dr. Kleinman also commented on the "changing concept of polio" and said physicians were reluctant to diagnose the disease without overwhelming evidence. He called the insistence on a 60 day duration

(Continued on Page 11)

Dr. Albert Sabin works on a culture for his live, oral vaccine. It has been used widely in Russia, but the United States public health service has ruled that it is not yet ready for licensing in this country.

POLIO

Is the Killer Still with Us?

(Continued from Page 9)

of paralysis in defining paralytic polio "silly."

Dr. Cox, who has worked in the virus field since 1929 and was the first person to prove that a killed vaccine could be made, commented on some of the problems of producing a potent, killed-virus vaccine.

"We are now learning, not only in the United States, but in Israel, England, and Denmark, that the killed product does a fairly good job of producing antibodies against Type II poliovirus," said Dr. Cox. "But Type II represents only about 3 per cent of paralytic cases thruout the world. The killed vaccine does a poor job against Type I, however, which causes 85 per cent of paralytic cases, and against Type III, which causes about 12 per cent.

"In other words, the killed vaccine is doing its best job against the least important type. It took time to find this out. It was proven in Israel in 1958, when it had its big Type I epidemic. They did not see any difference in protection between the vaccinated and the unvaccinated. Last year in Massachusetts during a Type III outbreak, there were more paralytic cases in the triple vaccinates than in the unvaccinated."

There have been problems, too, in the production of the killed Salk vaccine. An extra filtration step was added in November, 1955, Dr. Cox said, "because the amount of formalin used did not inactivate the poliovirus. We found residual live virus for as long as 42 consecutive days of inactivation."

Dr. Cox went on to assert that the second filtration step was "picked out of thin air with no experimentation to back it up," and that the extra filtration cut down on the effectiveness of the vaccine.

Mass vaccination with the Salk product started in April, 1955, and by April 26, there were reports of paralytic polio among vaccinated children, with deaths occurring in Idaho and California. Then came cases of polio among family members of vaccinated children. Live virus was discovered in the supposedly killed vaccine, altho it had been produced by the Salk procedure.

Dr. Ratner cited numerous instances in which live viruses were found in vaccine which was presumably safe, even in Dr. Salk's own standard vaccines. "It should be stressed that safety testing was inadequate when Dr. Salk developed the vaccine and when the vaccine was commercially prepared for the field trials of 1954 and for licensing and use in 1955," said Dr. Ratner. He added that in current vaccine, potency has been sacrificed for safety and that "at present, epidemiologic methods employed by the United States public health service to assure safety of the vaccine are inadequate."

Should the Salk vaccine continue to be used?

"There is no known way of preventing polio with a licensed product at the present time except thru the use of the Salk vaccine," answered Dr. Kleinman. "While I am an agnostic about the effectiveness of the Salk vaccine, I still believe it does something in preventing paralysis. So we owe it to the public to recommend its use. On the other hand, if we are going to act not only as public health physicians but as scientists we must continue our investigations into the truth about the Salk vaccine. On the basis of the facts as I know them, we must look for something better."

Other panel members agreed, pointing out that because all of the facts about the Salk vaccine have not been made public, physicians and public health officials find it difficult to resist the great pressures of public opinion built up thru an unprecedented publicity campaign urging the public to be vaccinated.

"Since nothing else is available, there seems to be no alternative but to push the use of it," commented Dr. Greenberg. "I don't think we should do so in ignorance, nor too complacently, believing that as long as we have something partially effective, there is no need to have something better. By being more cautious, we may make a mistake by accepting a better polio vaccine too slowly."

Dr. Salk (left) and Dr. Sabin clashed in 1955 hearings about the use of the Salk vaccine.

"When measured against its killed counterpart, a live virus vaccine (using modified virus which stimulate the production of anti-bodies but do not cause the disease) is always a superior vaccine," asserted Dr. Cox. He said it invariably costs much less. And it gives a higher degree of longer-lasting immunity. Dr. Cox has developed a live vaccine which was tested on thousands of school children and adults last year in Dade county, Fla., and also on thousands of persons in foreign countries.

Another live, oral polio vaccine has been developed by Dr. Hilary Koprowski, of Philadelphia's Wistar institute and has been tested on approximately 9 million individuals.

Dr. Koprowski has challenged the United States public health service decision last August to grant approval only to the Sabin vaccine. In a letter in the Jan. 14 Journal of the American Medical association, he said, "Altho it is a step forward that the principle of live virus immunization in poliomyelitis has at last been officially accepted, I am taking strong exception to this exclusive indorsement of one set of strains. In my opinion, such an indorsement should evoke a protest from individuals who believe that fair scientific judgment should be the basis for decisions affecting the physical welfare of man."

Amplifying his letter, Dr. Koprowski said, "It is my belief that government decisions, which are not based on proper evaluation of scientific data, are prompted by either poor choice of scientific advisers or by cryptic reasoning and that such ill-advised decisions could lead to development of an unhealthy climate in which scientists will see their contributions trampled upon by administrative agencies."

Discussing the development of live, oral vaccines, Dr. Cox explained, "Polio is unique because many more people get the infection than the disease." The problem in producing a live vaccine is to modify, or tame, the virus so that they will produce a mild infection strong enough to stimulate the formation of antibodies, but not the disease itself. A complicating factor in taming polio virus, is that three separate, tamed strains have to be developed to produce antibodies against the three chief types of polio.

A killed vaccine, such as the Salk, does not immunize an individual against an infection of polio virus in the intestines and, altho it can induce antibodies in the blood, this does not prevent the individual from becoming a carrier and spreading poliovirus, explained Dr. Cox.

Individuals receiving the live, modified, oral vaccines also eliminate poliovirus from their bodies for several days or several weeks after vaccination, but these are the tame, modified strains. Family contacts and even other individuals in the neighborhood can also acquire an immunity from these tame virus, altho they have never received the vaccine themselves.

However, some experts still fear that one of these strains may revert to its virulent type as it is passed from one individual to another, according to a report by Dr. Roderick Murray's committee, quoted in the Oct. 15, 1960, issue of "Modern Medicine." One solution, the committee suggested, might be to give the oral vaccine to entire communities in a brief time. This is a problem which must be solved before the Sabin vaccine is licensed.

Dr. Cox stated that using a live vaccine is the only way to eliminate wild, virulent polio strains in nature. Immunization with live vaccine probably would not protect a person for life, he added, but it would be cheap enough so you could afford it once a year.

Dr. Ratner compared Dr. Cox's vaccination figures with the 1954 field trials of the Salk vaccine. "The Cox live poliovirus has now been used by many investigators in over 2.5 million people, the other two live virus vaccines under study have been used in additional millions," he said. "Safety has been paramount in the minds of these investigators."

"On the other hand, Salk vaccine was used in only 400,000 persons in a single field trial which assumed safety and was primarily designed to determine effectiveness.

"An objective and fearless evaluation of the Salk vaccine is needed, for this is the necessary ingredient of an intelligent decision as to when the live virus vaccine should be licensed," Dr. Ratner continued. "Obviously, if the Salk vaccine is safe and highly effective, the United States public health service can take its time about licensing the live virus vaccine.

"If, on the other hand, polio and polio epidemics remain with us and children become paralyzed despite three, four, five, and six inoculations of Salk vaccine and vaccinees die, we cannot take our time."

What should parents do?

Take the advice of their podiatrician or family doctor and not be stampeded by TV commercials or overly-enthusiastic claims for vaccines. It is the individual physician who must decide which vaccine is safe and effective in what circumstances. But physicians must have honest, impartial, fully scientific information available to make this decision.

Currently, most physicians are still giving Salk vaccine shots. A few doctors do not. Some give them only if patients insist.

Once a live, oral vaccine is fully approved, it will be more effective than the killed Salk vaccine. Because of the doubt about the potency and effectiveness of the Salk vaccine in the past, a full course of the new vaccine will undoubtedly be recommended for everyone, regardless of how many Salk shots each individual has had.

Informed Consent Action Network

For Immediate Release: July 13, 2018

US District Court Judge signs order granting Plaintiff, Informed Consent Action Network (ICAN) and counsel, Robert F. Kennedy, Jr., the relief sought in a lawsuit against the US Department of Health and Human Services (HHS)

On Monday, June 9th, the United States District Court for the Southern District of New York signed an order granting Plaintiff, the nonprofit Informed Consent Action Network (ICAN), the relief it sought against the Defendant, the United States Department of Health and Human Services, HHS. ICAN was represented by Robert F. Kennedy, Jr.

In May 2017, ICAN Founder, Del Bigtree, Robert F. Kennedy, Jr.. and a handful of other individuals concerned about vaccine safety were selected by the White House to participate in a seminal meeting with the Counselor to the Secretary of HHS, the heads of the National Institute of Health, NIH, the Center for Disease Control, CDC, and Food and the Drug Administration, FDA. Del Bigtree and Robert F. Kennedy, Jr. suspected that HHS was not fulfilling its critical vaccine safety obligations as required by Congress in The National Childhood Vaccine Injury Act of 1986.

The 1986 Act granted unprecedented, economic immunity to pharmaceutical companies for injuries caused by their products and eviscerated economic incentive for them to manufacture safe vaccine products or improve the safety of existing vaccine products. Congress therefore charged the Secretary of HHS with the explicit responsibility to assure vaccine safety.

Hence, since 1986, HHS has had the primary and virtually sole responsibility to make and assure improvements in the licensing, manufacturing, adverse reaction reporting, research, safety and efficacy testing of vaccines in order to reduce the risk of adverse vaccine reactions. In order to assure HHS meets its vaccine safety obligations, Congress required as part of the 1986 Act that the Secretary of HHS submit a biennial reports to Congress detailing the improvements in vaccine safety made by HHS in the preceding two years.

ICAN therefore filed a Freedom of Information Act, FOIA, request on August 25th, 2017 to HHS seeking copies of the biennial reports that HHS was supposed to submit to Congress, starting in 1988, detailing the improvements it made every two years to vaccine safety. HHS stonewalled ICAN for eight months refusing to provide any substantive response to this request.

ICAN
Informed Consent Action Network

ICAN was therefore forced to file a lawsuit to force HHS to either provide copies of its biennial vaccine safety reports to Congress or admit it never filed these reports. The result of the lawsuit is that HHS had to finally and shockingly admit that it never, not even once, submitted a single biennial report to Congress detailing the improvements in vaccine safety. This speaks volumes to the seriousness by which vaccine safety is treated at HHS and heightens the concern that HHS doesn't have a clue as to the actual safety profile of the now 29 doses, and growing, of vaccines given by one year of age.

In contrast, HHS takes the other portions of the 1986 Act, which require promoting vaccine uptake, very seriously, spending billions annually and generating a steady stream of reports on how to improve vaccine uptake. Regrettably, HHS has chosen to focus on its obligation to increase vaccine uptake and defend against any claim vaccines cause harm in the National Injury Vaccine Compensation Program (aka, the Vaccine Court) to such a degree that it has abandoned its vaccine safety responsibilities. If HHS is not, as confirmed in Court this week, even fulfilling the simple task of filing a biennial report on vaccine safety improvements, there is little hope that HHS is actually tackling the much harder job of actually improving vaccine safety.

For additional information or interviews please contact:
Catharine Layton, COO, ICAN
cat@icandecide.org (512) 522-8739

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

INFORMED CONSENT ACTION NETWORK,

Plaintiff,

-against-

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES

Defendant.

STIPULATION

18-cv-03215 (JMF)

WHEREAS, 42 U.S.C. § 300aa-27, entitled "Mandate for safer childhood vaccines," provides as follows:

> (a) General rule
>
> In the administration of this part and other pertinent laws under the jurisdiction of the Secretary [of the Department of Health and Human Services], the Secretary shall—
>
> > (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and
> >
> > (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.
>
> . . .
>
> (c) Report
>
> Within 2 years after December 22, 1987, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the

> actions taken pursuant to subsection (a) of this section during the preceding 2-year period.

WHEREAS, on August 25, 2017, Informed Consent Action Network ("ICAN") submitted a Freedom of Information Act request (the "FOIA Request") to the Department of Health and Human Services ("HHS" or the "Department"), which was assigned control number 2017-01119-FOIA-OS, that sought the following records:

> **Any and all reports transmitted to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate by the Secretary of HHS pursuant to 42 U.S.C. §300aa-27(c).**

WHEREAS, on April 12, 2018, ICAN filed a Complaint for Declaratory and Injunctive Relief in the United States District Court, Southern District of New York against HHS seeking records, if any, responsive to the FOIA Request;

WHEREAS, the HHS Immediate Office of the Secretary ("IOS") maintains the official correspondence file of the Secretary of HHS, including reports to Congress by the Secretary of HHS, and therefore those files were most likely to contain records responsive to the FOIA Request;

WHEREAS, on June 27, 2018, HHS sent ICAN the following response to the FOIA Request:

> The [Department]'s searches for records did not locate any records responsive to your request. The Department of Health and Human Services (HHS) Immediate Office of the Secretary (IOS) conducted a thorough search of its document tracking systems. The Department also conducted a comprehensive review of all relevant indexes of HHS Secretarial Correspondence records maintained at Federal Records Centers that remain in the custody of HHS. These searches did not locate records responsive to your request, or indications that records responsive to your request and in the custody of HHS are located at Federal Records Centers.

WHEREAS, ICAN believes the foregoing response from HHS now resolves all claims asserted in this action;

IT IS HEREBY STIPULATED AND AGREED, by and between the parties by and through their respective counsel:

1. That the above-captioned action is voluntarily dismissed, with prejudice, pursuant to Federal Rule of Civil Procedure 41(a)(1)(A)(ii), each side to bear its own costs, attorney fees, and expenses; and

2. That this stipulation may be signed in counterparts, and that electronic (PDF) signatures may be deemed originals for all purposes.

Dated: July 6, 2018
New York, New York

KENNEDY & MODONNA LLP
Attorney for Plaintiff

By: _____
Robert F. Kennedy, Jr.
48 Dewitt Mills Road
Hurley, NY 12443
(845) 481-2622

Dated: July 6, 2018
New York, New York

GEOFFREY S. BERMAN
United States Attorney
Attorney for Defendant

By: _____
ANTHONY J. SUN
Assistant United States Attorney
86 Chambers Street, Third Floor
New York, New York 10007
(212) 637-2810
anthony.sun@usdoj.gov

SO ORDERED:

_____
HON. JESSE M. FURMAN, U.S.D.J.

Dated: New York, New York
July 6, 2018

Any pending motions are moot. All conferences are vacated. The Clerk of Court is directed to close the case.

CHCS

Center for
Health Care Strategies, Inc.

Provider Incentive Programs: *An Opportunity for Medicaid to Improve Quality at the Point of Care*

Resource Paper

By:
Dianne Hasselman
Center for Health Care Strategies, Inc.

Made possible through support from The Commonwealth Fund.

March 2009

Contents

Introduction

Can there be such a thing as *too much* focus on quality? Imagine a primary care physician whose performance in diabetes care is assessed through incentive programs from multiple health plans. Each health plan uses slightly different performance indicators, requires different chronic care interventions, and provides different feedback reports for a subsection of the physician's patient panel — an overwhelming scenario, but unfortunately all too real.

Although the purpose of pay-for-performance (P4P) programs is to use financial incentives to "move the quality needle" in a deliberate manner and to increase value-based purchasing, the proliferation of incentive programs — particularly at the individual physician or practice level — is creating a patchwork of quality efforts with negative and unintended consequences. Many providers, frustrated with the numerous and fragmented performance reports they receive, discount or simply discard the data as confusing, inefficient, inaccurate, and unhelpful.

In recent years, there has been a groundswell among health policy experts, public and private purchasers, and payers toward greater standardization of quality improvement activities. Purchasers increasingly recognize the need for standardization around evidence-based guidelines. Significant movement has occurred in adopting nationally-recognized performance indicators to assess health outcomes. The National Quality Forum and its many partners are establishing national priorities and goals around performance measurement and reporting. National initiatives like *Aligning Forces for Quality*,[1] the *Regional Quality Improvement* initiative,[2] and *Bridges to Excellence*[3] are also helping to align public and private purchasers and payers around uniform quality improvement goals, common performance measures, and, in some instances, common payment.

By jointly developing incentive programs to improve quality at the point of care, purchasers and health plans can replace well-meaning but redundant and often conflicting pay-for-performance (P4P) programs. The resulting standardization of provider incentive programs could dramatically improve physician response to P4P efforts.

[1] For more information about Aligning Forces for Quality, visit **www.forces4quality.com**.
[2] For more information about the Regional Quality Improvement initiative, visit **www.chcs.org**.
[3] For more information about Bridges to Excellence, visit **www.bridgestoexcellence.org**.

Medicaid and Provider Incentive Programs

With 63 million beneficiaries — 66 percent of whom are in managed care — and more than $361 billion in annual expenditures, state Medicaid programs are in an excellent position to impact quality at the point of care and to foster greater alignment across health plans and delivery systems.[4] Indeed, P4P programs are not new to states. Currently more than 25 states have P4P programs with their health plans or primary care case management (PCCM) programs.[5] Yet, while many states use P4P programs to motivate improvements at the health plan level, few have designed effective programs at the provider level.

Historically, states delegate responsibility for provider incentive programs to their managed care partners, particularly in risk-based managed care delivery systems. States have been reluctant to micromanage managed care operations and have encouraged plans to innovate. States have also been challenged to work within the regulatory parameters established by the Centers for Medicare and Medicaid Services (CMS) including a cap on total incentive payments in risk-based systems.

In addition to acknowledging the benefits of standardization, states are increasingly aware that quality ultimately must occur at the point of care. Many states understand that in the highly competitive managed care environment, collaboration and alignment across Medicaid plans — even around quality — occurs most readily when the regulatory and purchasing authority of the state is used. As such, there is growing involvement of state Medicaid agencies in provider incentive programs.

In 2006, with funding from The Commonwealth Fund and additional support from the Robert Wood Johnson Foundation, the Center for Health Care Strategies (CHCS) launched the *Pay-for-Performance Purchasing Institute* to help state Medicaid agencies design provider incentive programs. Seven states — Arizona, Connecticut, Idaho, Ohio, Massachusetts, Missouri, and West Virginia — worked with CHCS to develop and test physician-level financial and non-financial incentives, choose performance measures, engage providers effectively, and increase alignment across incentive programs. This resource paper presents examples, including several from that initiative, of how states are becoming increasingly involved in P4P at the practice level, particularly around efforts to improve alignment and standardization.[6]

[4] HMA projections for total spending and enrollment for federal FY 2008, based on: CBO, *Budget and Economic Outlook*, January 2008; CBO, *Medicaid Baseline*, 2008; CMS, Office of the Actuary, National Health Statistics Group, 2008; and NASBO, *State Expenditure Report*, December 2007.

[5] K. Kuhmerker. *Pay-for-Performance in State Medicaid Programs: A Survey of State Medicaid Directors and Programs*, The Commonwealth Fund, April 2007. Available at: **http://www.commonwealthfund.org/usr_doc/Kuhmerker_P4PstateMedicaidprogs_1018.pdf?section=4039**

[6] For more about the *Pay-for-Performance Purchasing Institute* as well as information about structuring P4P programs, selecting measures, choosing financial and non-financial incentives, and engaging physicians, visit **www.chcs.org**.

Innovative State Models

The provider incentive program models described in this resource paper are based on the efforts of five state Medicaid programs:

- **Rhode Island** designed and implemented a provider incentive program that required Medicaid health plans to adopt standardized program goals, but allowed plans and providers to test different approaches to achieving those goals.

- **Arizona** is exploring the development of a provider incentive program that would require all Medicaid health plans to adopt common program goals, common performance measures, and to aggregate provider financial incentives across plans using a third-party broker.

- Since 2006, **Minnesota** has been participating in a provider incentive program where Medicaid and commercial purchasers and plans adopt uniform program goals and performance measures, and combine incentive dollars into "bucket" for provider payment.

- **Massachusetts** and **Missouri** are both focusing efforts around creating P4P program strategies and tools for use across different Medicaid delivery systems.

In considering the models above, a Medicaid program needs to recognize factors in its unique marketplace and circumstances, which may include:

- **Delivery system:** Will the incentive program operate in a risk-based managed care, primary care case management delivery system, or both?

- **Focus of P4P program:** Is the program targeting a chronic condition with a nationally-recognized measure set and a strong evidence base around impacting care (e.g., diabetes), or encouraging testing a new area with a less robust evidence base (e.g., reducing inappropriate emergency room utilization)?

- **Infrastructure:** Does the state have the infrastructure and staff to operate aspects of the program in house? The program design steps are consistent across models; however, "who does what" varies by state. In Rhode Island's model, the state is responsible for establishing and funding the provider incentive program, but the plans are responsible for the remaining steps. In Arizona's model, the state is more involved in all program design steps.

- **Political support:** Does the state have the political will and support to maximize alignment across plans? To join a multi-payer P4P program?

One size does not fit all in state-designed provider incentive programs, as illustrated by each of the following models, so states should consider their own unique circumstances when designing provider incentive programs.

Model 1: Alignment of Program Goals across Health Plans (Rhode Island)

Model 1 is based on Rhode Island's RIte Care P4P program. In 2005, the state required its health plans to implement a physician-level P4P component to compliment a health plan P4P program to reduce inappropriate emergency room (ER) use. The state had an incentive program at the plan level; however, with the prudent layperson laws and the Emergency Medicaid Treatment and Active Labor Act (EMTALA), the state and plans noted a gradual increase in ER utilization. The state decided to expand the incentive program to the point of care.

The state included a $0.95 per member per month (PMPM) increase to RIte Care's health plan capitation rate to be used for a primary care provider (PCP) incentive program. The state required that the additional PMPM payment be used to reward PCPs based on performance. Each plan was charged with designing a provider incentive program that promoted timely access to quality care, including preventive care, urgent care, and care during evening hours. Plans were not required to adopt the same provider-level measures or aggregate data into one rate per practice.

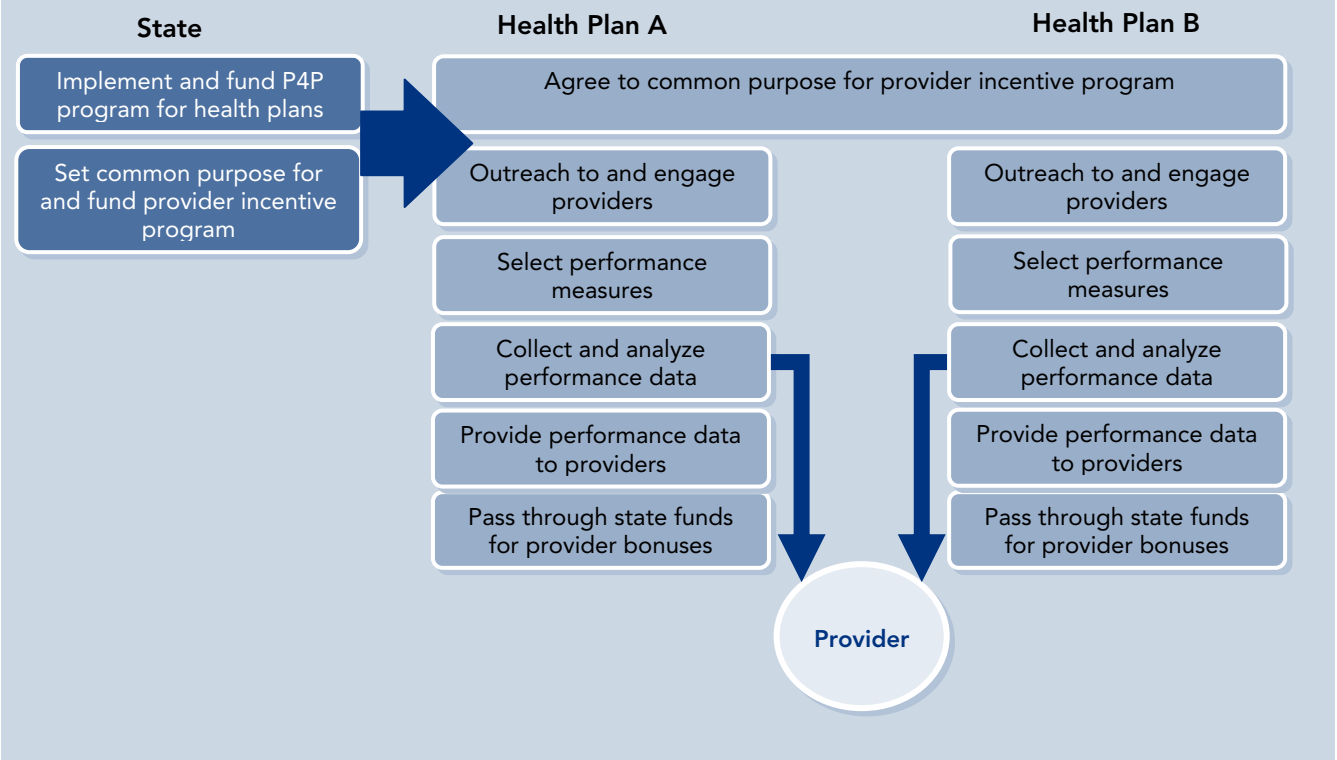
One of the plans, Neighborhood Health Plan of Rhode Island (NHPRI), targeted primary care practices with at least 200 NHPRI RIte Care members, creating a critical mass of potential new incentive dollars to "get the practice's attention." NHPRI divided the incentive payment into components. All eligible practices automatically received a payment of $0.30 PMPM during the first year. Practices that extended business hours or were open during the weekend received an additional PMPM amount. Practices that had multilingual practitioners on call after hours received an additional PMPM amount. Finally, practices that reduced ER utilization received an increase amount. Using this strategy, all eligible practices received some funding initially to work toward expanding access. Additional funding was not guaranteed or unlimited — progress had to be demonstrated over time. A subset of high-performing practices received the maximum amount for achieving specific outcomes.

Rhode Island's approach reflects its unique marketplace and delivery system. The state has a risk-based managed care program, so it operated the provider incentive program through its health plans. The program focus — reducing inappropriate ER utilization — did not have a strong evidence base of "what works." As such, the state wanted to leave ample room for the plans and providers to experiment. Adopting such an approach allowed the state and plans to test different provider incentive program designs and to compare and contrast what worked and what did not. The state is currently assessing outcomes data and convening its health plans to review, retool, and identify best practices.

States that are interested in testing provider incentive program options but are not yet ready to require greater alignment across plans or delivery systems might consider this strategy. Comparing and contrasting outcomes from different approaches would allow states to make more informed decisions in the future about how, where, and why to create greater standardization.

The figure below, based on Rhode Island's model, illustrates how a Medicaid program might design a provider incentive program across plans.

Model 1: Alignment of Purpose across Plans (Rhode Island)



Model 2: Alignment of Purpose, Measures, and Payment across Medicaid Plans Using a Third-Party Broker (Arizona)

Model 2 presents a provider incentive program that creates significant alignment across its Medicaid plans. It is based on a provider incentive approach that the Arizona Health Care Cost Containment System (AHCCCS) is exploring.

AHCCCS is considering a P4P program to improve care for 88,000 adult Medicaid beneficiaries with diabetes. In the proposed model, AHCCCS would aggregate claims data across Medicaid plans to calculate a provider's performance rate for all of his or her diabetic patients. In other words, the physician or practice would receive one consolidated diabetes performance report from the AHCCCS program, as opposed to a provider profile form each plan with whom the practice contracts. The proposed strategy aims to improve the validity and reliability of measurement and reduce the administrative burden on plans and providers alike.

Like the Rhode Island model, funds for provider bonuses would be included prospectively in the health plans' capitation rates. The health plans would be required to pass all state funds on to the providers. Incentive payments will be aggregated across plans into one payment per physician or practice. Thus a practice would receive one larger check, as opposed to multiple smaller checks. Because plans receive capitation rates prospectively, and provider performance would be measured and rewarded retrospectively, it

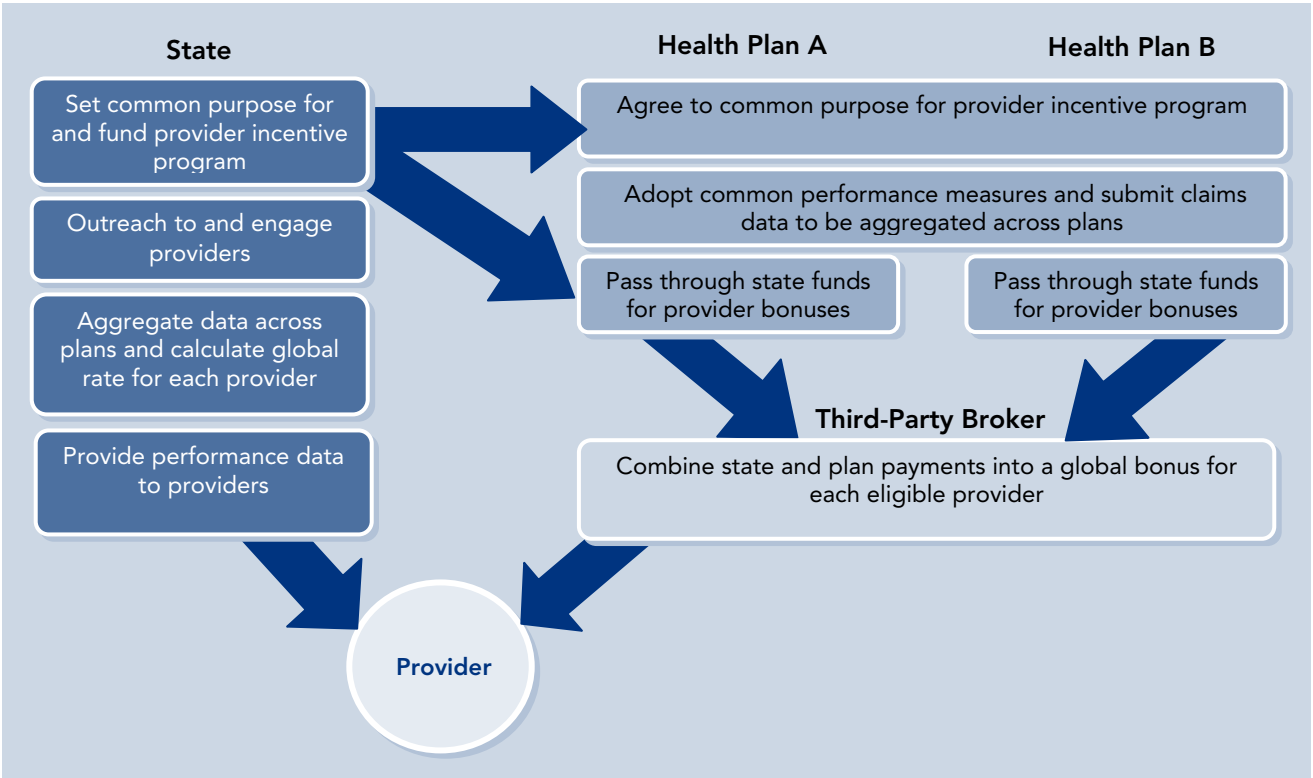
is possible that funds available for provider incentive payments might not be used in totality. Therefore, any remaining funds would accumulate and be used for provider incentive payments in the future.

The model that Arizona is exploring would use a third-party broker to receive and aggregate dollars from the plans, and to calculate and distribute bonus payments to practices. The state and CMS are currently exploring this broker model and whether and how it might be implemented.

Arizona's approach reflects its unique circumstances and delivery system. Like Rhode Island, Arizona operates a risk-based managed care delivery system, so any provider incentive program would need to operate through its plans. The potential program's focus — diabetes — has a nationally recognized set of measures and a strong evidence base around effective interventions. As such, the state could require plans to agree to a common set of measures. The state also has a rich source of high quality encounter data and a team of highly skilled data analysts who could calculate per practice or physician performance rates. Lastly, the large size of Arizona's program and the competitiveness of the managed care marketplace means that the state has significant purchasing leverage to direct quality improvement initiatives, if it so chooses.

The figure below, based on the model Arizona is exploring, illustrates how a Medicaid program might design a provider incentive program that is fully aligned across plans.

Model 2: Alignment of Purpose, Measures and Payment Across Plans Using a Third-Party Broker (Arizona)



Model 3: Alignment of Purpose, Measures, and Payment across Purchasers and Plans (Minnesota)

Model 3 is a cross-market collaboration that adopts a provider incentive program that is uniform across public *and* private purchasers (e.g., employers, Medicaid agencies, state employees, etc.) and plans (e.g., commercial and publicly funded). It is based on Minnesota's existing cross-payer provider incentive program. In this model, purchasers and plans use the same measures to assess provider performance and combine financial resources to reward high-performing physicians.

Such an approach has many benefits:

- Purchasers increase their buying power by banding together, focusing on value-based care, and demanding more efficient and effective health care.
- Plans must deliver value as purchasers make contracting decisions based on performance data. Plans benefit from creating economies of scale and reducing fragmentation of quality improvement activities.
- Practices are assessed by a common set of measures and a single report, which reduces administrative burden and confusion.
- When performance data is shared publicly, consumers have the opportunity to become more informed and active participants in their health care.

While public-private payer P4P programs are still in their infancy, the alignment and standardization created by this model holds great promise for Medicaid and commercial purchasers, providers, and consumers.

Minnesota's marketplace has unique characteristics that have helped accelerate innovations in quality. Its health care system is highly integrated. Hospitals and health systems own most primary care groups. As such, there is not only a strong business case to create alignment throughout a health care system, but the ability to do so.

Health care providers in Minnesota are required to serve the Medicaid population. This integration reinforces the importance of including Medicaid in cross-payer initiatives.

Lastly, Minnesota has created an infrastructure to support quality and innovation throughout its health care system. Three key building blocks have been particularly integral to Minnesota's achievements in value-based purchasing:

- **The Buyers Health Care Action Group** (BHCAG) is a coalition of private and public purchasers that seeks to promote purchasing strategies and develop tools that help purchasers buy and evaluate health care based on performance and value, not just price. BHCAG initiated Minnesota's diabetes provider incentive program in 2004.[7]
- **The Institute for Clinical Systems Improvement** (ICSI) develops evidence-based guidelines and measures for physician performance evaluation, and provides implementation support.[8]

[7] For more information about Minnesota's Buyers Health Care Action Group, visit **www.bhcag.com**.
[8] For more information about the Institute for Clinical Systems Improvement, visit **www.icsi.org**.

- **Minnesota Community Measurement** (MNCM) is a collaborative that receives and aggregates claims data from plans, collects clinical data from practices, and reports provider-level performance rates for conditions such as diabetes and cardiac disease. [9]

It is within this unique environment that BHCAG implemented a Bridges to Excellence (BTE) program to achieve optimal diabetes care in 2005. BTE is a national employer-led P4P program with a standard data exchange platform and performance measurements to foster cross-market collaborations in regions or states. Using evidence-based guidelines and measures developed by ICSI, MNCM collects, aggregates, and reports performance data for practices and clinics. BHCAG receives and aggregates financial incentives from purchasers, including Medicaid, and pays providers based on their performance.

In 2007, Minnesota's Department of Human Services (DHS), the state's Medicaid agency, joined BHCAG's effort and began to enroll Medicaid managed care recipients ages 18 to 75 with diabetes or cardiac disease into the initiative. DHS rewards practices based on their share of Medicaid patients, as opposed to clinical results. DHS includes dollars for provider incentives in health plan capitation rates. The plans, in turn, give those dollars to BHCAG.

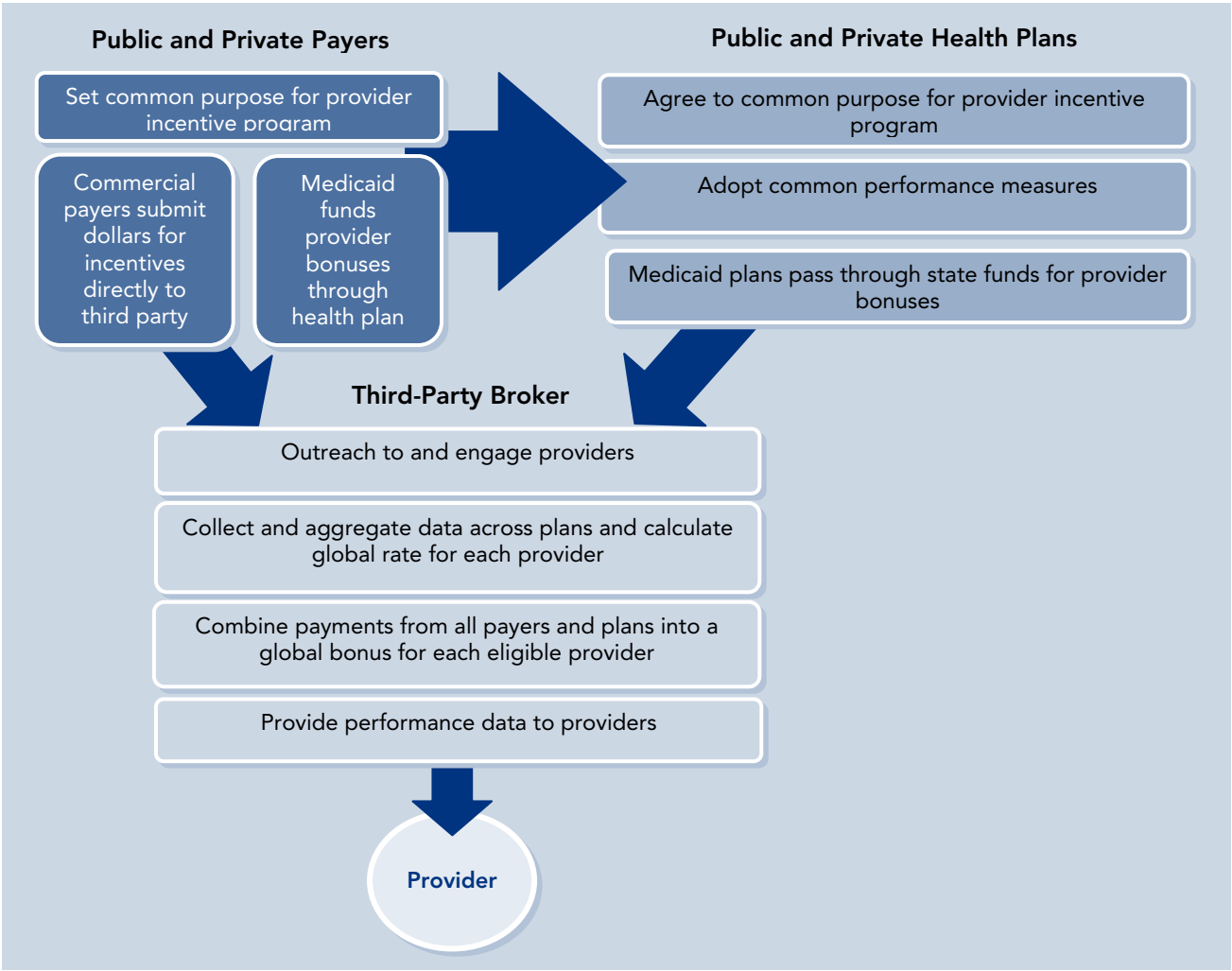
Through the BTE program, physicians providing optimal diabetes care to at least 10 percent of their patients with diabetes receive $100 per patient. In 2006, BHCAG paid physicians $97,000 in rewards, and rewarded $260,000 in 2007.[10] The percentage of Minnesotans receiving optimal diabetes care from providers participating in the BTE program has increased from 6 percent in 2004 to 22 percent in 2007.

DHS recently received approval from CMS for a new provider incentive program. This program will focus on Medicaid recipients remaining in fee-for-service. This population comprises 30% of Medicaid recipients, many of whom are disabled. Diabetes prevalence in this population is 10%, compared to 6% in the Medicaid managed care population. DHS will directly reward individual practices providing optimal care to Medicaid fee-for-service recipients with diabetes or cardiac disease. DHS will pay $125 per diabetic for the first year, and up to $500 for optimal performance in subsequent years. Practices will submit their data to DHS electronically.

The figure below, based on the model that Minnesota implemented, illustrates how to create full alignment across payers and plans.

[9] For more information about Minnesota Community Measurement, visit **www.mnhealthcare.org**.
[10] BHCAG March 2008 presentation at the CHCS Medicaid Purchasing Leadership Summit.

Model 3. Alignment of Purpose, Measures and Payment across Payers and Plans (Minnesota)



While several state Medicaid agencies have expressed interest in provider incentive programs that are aligned across purchasers and plans, Medicaid's engagement to date has been limited. States may face multiple challenges participating in a multi-payer P4P program. States have concerns about how data will be collected and used publicly. Public-private programs work best when there is a significant overlap of providers who serve both the commercial sector and Medicaid patients. States with comparatively low Medicaid reimbursement rates often have provider networks with a less integrated patient mix. Lastly, some Medicaid programs may struggle to obtain the funding necessary to adequately support and sustain provider incentive programs.

Model 4: Alignment of Purpose, Measures, and Interventions across Delivery Systems (Massachusetts and Missouri)

Model 4 depicts provider incentive programs being designed in Massachusetts and being implemented in Missouri. Both states developed P4P approaches within a non-risk-based context (PCCM or fee-for-service), with the intent to extend select program elements to the risk-based managed care delivery system in the future.

MassHealth, the Commonwealth's Medicaid program, is designing a provider incentive program for its Primary Care Clinician (PCC) Plan based on the following principles:

- Transparency and collaboration;
- Alignment with the existing data collection and reporting system;
- Minimization of provider reporting burden; and
- Consistency with established state and national P4P programs.

The program will measure performance of individual physician practices, group practices, community health centers, hospital-licensed health centers, and hospital outpatient departments. To participate in the clinical measures portion of the incentive program, providers must have a minimum number of Medicaid patients in the denominator of each clinical measure in the P4P program and must complete a practice survey.

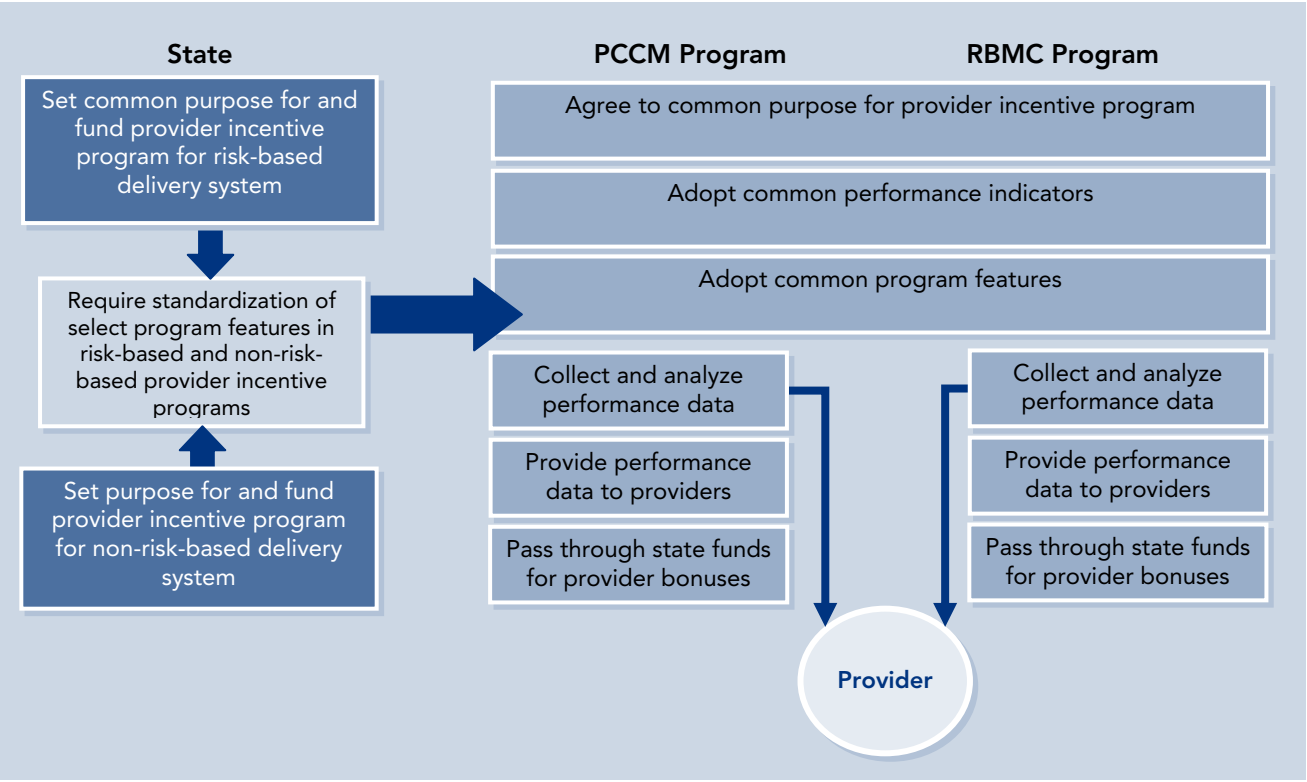
The practice infrastructure survey will be used to assess critical medical home components including: HIT capacity, follow-up from tests, referrals and acute events, guideline-based reminder systems, registries, access, and the process for gathering and tracking race and ethnicity information. During the first year of the program, practices will receive a "pay for reporting" amount if they fully complete and return the practice survey. Practices completing the survey will be assessed for eligibility for P4P funds based on their clinical indicator performance.

Provider performance around prevention and diabetes care will be assessed using HEDIS-based measures that are already collected and reported through the PCC Plan's profiling activities. MassHealth's new P4P program will allow providers to review their individual rates and submit additional information if they believe the rates are inaccurate. Payments will be based on achieving the performance benchmark for the clinical measures, or achieving improvement for clinical measures even though they do not meet the established benchmark rate. Incentives will be paid on a PMPM basis, based on the provider's total PCC Plan member enrollment. The state is still developing the specific PMPM amount.

The state is creating alignment across MassHealth's P4P programs. Specifically, all individual health plan provider incentive programs, including the new PCC Plan, will be required to use the same measures. They will also be required to use the same practice infrastructure survey tool.

The state of Missouri is also creating alignment with its fee-for-service (FFS) and risk-based managed care delivery system through a provider incentive program. Currently, physicians or mid-level practitioners in high-volume federally qualified health centers (FQHCs) in targeted geographic areas receive incentives for developing electronic care plans for patients with diabetes, asthma, gastroesophageal reflux disease, cardiovascular disease, or chronic obstructive pulmonary disease. The state pays providers $25 for developing the initial patient assessment online, and an additional $10 for updating web-based care plans. To assist providers with developing care plans, the state is placing care coordinators in the high-volume FQHCs to act as a liaison between the PCP and the patient. Missouri is currently revising its health plan contract to include the same provider incentive program.

Model 4. Alignment of Purpose, Measures, and Interventions Across Delivery Systems (Massachusetts and Missouri)



State Provider Incentive Program Profiles

Following are brief descriptions of additional state provider incentive programs:

Connecticut
Connecticut is working closely with its health plans to design and phase in a provider incentive program aimed at improving EPSDT rates. The first phase is to reward PCPs for completeness of EPSDT encounters. To do this, the state added payment incentives directly to the EPSDT reimbursement process so that medical practices can devote the time and resources necessary for care coordination. The state is now focusing on options for measuring and rewarding care coordination at the practice level. Specifically, the state will provide bonus payments through the health plan capitation rate to PCPs who coordinate care with specialists as appropriate based on EPSDT screening results.

Idaho
Idaho is piloting a provider incentive program within its PCCM delivery system and disease management program. Although the program will ultimately target five chronic diseases (diabetes, asthma, depression, hyperlipidemia and hypertension), the state made a strategic decision to "start small" by focusing first on diabetes. The state is targeting the pilot program to three high-volume FQHCs equipped with electronic medical records to facilitate data capture.

The diabetes program aligns with the state's existing disease management program and targets approximately 500 diabetics within the state. While Idaho is using nationally-recognized performance measures to assess changes in outcomes, it is initially rewarding practices based on process measures. Specifically, practices receive $50 per patient enrolled in the state's diabetes disease management program. They also receive $10 for each of the six diabetes measures reported. To date, the state has paid $20,000 to the three FQHCs. The state has $500,000 available for incentive payments as it continues to expand the P4P program. Next steps include establishing a secure web-based data submission and collection system.

Ohio
Ohio began exploring options for provider incentive programs by soliciting feedback from its health plans, provider community and other key stakeholders. A series of focus groups revealed physician frustration regarding the variety of measurement sets across different payers and plans. One medical director of a large primary care network described nine different measurement sets for which his organization is accountable. Physicians also voiced concerns with the accuracy of administrative data and were more likely to support P4P if their own data was used for measurement.

The state also surveyed health plans regarding the range of P4P methodologies, potential performance indicators, and estimated distribution of physician rewards over the various performance measurement domains. One key finding was that physician-level measurement, reporting and incentives could be complicated by the small numbers of encounters and measurable events at the physician-level. The state identified that only 12 percent of practices had a volume of 30 or more Medicaid patients — the number they estimate to sufficiently evaluate performance.

One option being considered is joining Cincinnati's Bridges to Excellence Diabetes Care Link program. Cincinnati, one of the original BTE pilot markets, has been active since 2003. Physicians in the program who demonstrate they are top performers in diabetes care can earn up to $100 for each patient covered by a participating employer. Employers (currently private only) fund incentives from documented savings achieved through lower health care costs and increased employee productivity that results from improved diabetes care.

Due to budgetary constraints, Ohio Medicaid has "tabled" short-term plans around developing a provider incentive program, but continues to consider its opportunities moving forward.

West Virginia
West Virginia is considering a provider incentive program that would support the state's Mountain Health Choices program. Mountain Health Choices offers a two-tiered benefit system — beneficiaries must sign a "personal responsibility" agreement to receive enhanced benefits. Through the agreement, the beneficiary acknowledges the role he/she plays in his/her health care delivery. The state is considering implementing a provider incentive program that rewards physicians and mid-level practitioners as they encourage and work with Medicaid recipients in completing the agreements. Due to budgetary constraints and limited resources, the state plans to revisit its P4P programs — both at the plan and provider level — in the near future.

Conclusion

While the number of provider-level incentive programs is low compared to plan-level programs, provider P4P initiatives are increasing with the greater awareness that health care is local and quality ultimately occurs at the point of care when the patient meets face-to-face with the provider.

The provider P4P models highlighted herein can help states identify options for creating greater standardization in their quality improvement activities, particularly in a risk-based managed care delivery system. Alignment of P4P programs can improve the validity and reliability of performance measurement, reduce administrative burdens on plans and providers, and create economies of scale for plans and breakthroughs in quality for patients — all of which lead to reductions in future cost growth. This resource paper deliberately highlights states that have chosen different levels of alignment, recognizing that states will vary in terms of their interest in and ability to create standardization.

This resource paper reflects the growing recognition of the need to standardize quality improvement initiatives to send a stronger message to providers. Fragmentation in quality improvement efforts creates duplication and confusion for providers. Provider incentive programs offer purchasers an opportunity to become more involved in improving quality at the point of care and in achieving a greater level of standardization across P4P programs. Although P4P is just one tool in the quality improvement "arsenal," Medicaid programs can play an important role in creating much needed alignment in P4P.

Appendix

Background on P4P

Pay-for-performance (P4P) programs are voluminous and growing throughout the public and private sectors as payers increasingly look for ways to link payment and quality. While many events have contributed to the proliferation of P4P programs, a few seminal events and initiatives are highlighted in this section.

The earliest P4P efforts were initiated by plans seeking to measure provider performance around cost and utilization, more so than quality. As employers saw their health care costs rising, they sought to link payment with health outcomes through health plans, which were responsible for a growing proportion of their employees. Plans were a logical starting place because they already collect standardized performance measures through the Healthcare Effectiveness and Data Information Set (HEDIS®) measures and customer satisfaction information through the Consumer Assessment of Healthcare Providers and Systems (CAHPS®) tool. Plans also have the capacity to collect and report data and are responsible for performance in many settings.

In 2001, the Institute of Medicine (IOM) released its groundbreaking report, *Crossing the Quality Chasm*, which revealed that up to 98,000 Americans die each year as a result of medical errors.[11] The IOM report stated that payers need to align payment policies to support quality improvement, as they often were paying more for poorer outcomes. This report was followed by one from RAND in 2003 that documented that patients receive the recommended care approximately half the time.[12] Both of these reports resonated deeply with health care purchasers, payers, providers, and consumers, and reinforced the need to link payment with performance.

As P4P grew in the private sector, public payers also began to link payment to performance. Medicare, for example, launched several P4P demonstration programs, targeting hospitals and physician practices. State Medicaid programs also began implementing P4P programs — some as early as the 1990s. Initial efforts focused on accountability, rather than quality or value, and targeted health plans. Because states began managed care enrollment with the Temporary Assistance for Needy Families (TANF) population, early P4P programs tended to focus on measures specific to services that mothers and children typically received, such as prenatal care visits, well-child checkups, and immunizations. Over time, as states have enrolled high-cost, high-need Medicaid beneficiaries into care management programs, P4P programs have expanded to focus on outcomes related to complex conditions and special needs.

As states have become more sophisticated purchasers of care and more proficient at collecting and using performance data and measures, P4P programs have become more advanced and targeted. As of July 2006, 28 state Medicaid agencies operated P4P programs, and half of those programs were operating for five or more years. Again, the majority of these programs were at the health plan level, followed by those targeting primary care case management (PCCM) programs, nursing homes, hospitals, behavioral health care providers, and lastly, individual physicians. In 2006, 19 states were planning to expand existing P4P programs in the next five years, and 15 Medicaid agencies were planning to start their first P4P programs.[13]

[11] Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. National Academy Press, 2001.
[12] RAND. *The Quality of Health Care Delivered to Adults in the United States*. McGlynn, June 2003.
[13] The Commonwealth Fund. *Pay-for-Performance in State Medicaid Programs: A Survey of State Medicaid Directors and Programs*. Kuhmerker and Hartman. April 2007.

The growing availability of performance data, the increasing demand for value-based purchasing, and a greater national focus on creating more alignment and standardization around quality have contributed to the proliferation of P4P initiatives, particularly to measure performance at the point of care. A few of the most notable ones are described below.

Rewarding Results: Aligning Incentives with High-Quality Health Care

Rewarding Results was a three-year effort funded by the Robert Wood Johnson Foundation, the California HealthCare Foundation, and The Commonwealth Fund. The three foundations selected seven demonstration projects that made providers eligible for financial and non-financial rewards based on the achievement of specific quality goals linked to clinical quality. The demonstration projects offered varied approaches, typically targeting primary care physicians or physician organizations, and represented several types of insurance arrangements, (e.g., health maintenance organizations (HMOs), preferred provider organizations (PPOs), and Medicaid.)

Through use of incentives, the *Rewarding Results* projects significantly increased patient visits to the doctor; pushed physicians to embrace health information technology (HIT) and electronic medical records (EMRs) at a faster pace; increased the number of patients receiving annual mammograms and other screenings; and motivated physicians to monitor patient care more aggressively, particularly for chronically ill patients. The initiative included seven experimental projects — three of which are described below — designed to test a variety of P4P models.

Integrated Healthcare Association (IHA)
Created in 1996, the Integrated Healthcare Association is a California-based, statewide coalition of health plans, physicians, health care systems, purchasers, and consumers working to create the business case for quality at the physician group level. In 2003, IHA initiated its P4P program with the goal of rewarding physician groups for performance in clinical care, patient experience, and HIT investment based on common metrics and public reporting. Key to the program's success has been the use of uniform measures to evaluate performance across multiple health plans, physician groups, and patient populations. To date, it is the largest P4P initiative in the country.

Bridges to Excellence
Bridges to Excellence (BTE) is the largest employer-sponsored effort rewarding and recognizing physicians for meeting specific quality benchmarks. For the *Rewarding Results* initiative, the BTE employer coalition focused on four locations across the country and financially rewarded physicians per patient per year for excellence in diabetes and/or cardiac care. The BTE model is now in several markets across the country and has found that physicians who are recognized for providing high-quality and more efficient care deliver it at 15 to 20 percent lower cost than physicians not participating in the program.

Local Initiative Rewarding Results
Local Initiative Rewarding Results was the largest collaborative P4P effort to improve the health of babies and teens in Medicaid. The California-based project involved seven health plans that collaborated to test the impact of financial and non-financial incentives on provider quality. The program, which ran from 2002 through 2004, ultimately paid $5 million in provider incentives and involved 3,300 physicians touching the lives of 350,000 babies, adolescents, and parents. Five of the seven plans improved the rate of well-baby visits, with increases from 4 to 35 percent. Visits to the doctor by teens increased from 7 to 14 percent at six of the seven plans. Of the seven *Rewarding Results* projects nationwide, the *Local Initiative Rewarding Results* project was the only activity focusing on the Medicaid population and the first known collaborative effort to establish financial incentives within Medicaid among multiple plans with the same objective.

The Leapfrog Group

The Leapfrog Group was established in 2002 to mobilize employers' purchaser power in relation to health care services and to influence the quality and affordability of care. The *Crossing the Quality Chasm* report focused Leapfrog initially on reducing preventable medical mistakes, recommending that large employers provide more market reinforcement for the quality and safety of health care. The Leapfrog Group launched its Hospital Rewards Program in 2005 and continues to measure hospital cost and quality performance. Hospitals that demonstrate excellence or show improvement along both dimensions receive rewards.

Medicare P4P Demonstration Programs

The Centers for Medicare and Medicaid Services (CMS) has been instrumental in establishing demonstration projects for P4P at the point of care. Two of its key P4P demonstration projects focused on physician practices are described below.

Physician Group Practice (PGP) Demonstration
In 2005, CMS launched its two-year Physician Group Practice (PGP) Demonstration focusing on improving the quality of care delivered to patients with congestive heart failure, coronary artery disease, and diabetes mellitus. Ten large, multi-specialty group practices participated in the demonstration project and received $16.7 million in incentive payments for improving health outcomes and coordinating the overall health care needs of Medicare patients assigned to their groups.

Physician Quality Reporting Initiative (PQRI)
A related CMS value-based purchasing initiative is the Physician Quality Reporting Initiative (PQRI), which uses a pay-for-reporting approach. Under PQRI, physicians and other health care professionals earn incentive payments for reporting measurement data about the quality of care they provide to Medicare patients. CMS is now developing a program that moves from the PQRI pay-for-reporting approach to a performance-based payment plan.

CMS Payment Polices and Federal Regulations

The Centers for Medicare and Medicaid Services provides policy guidance on provider incentive programs that states must consider as they develop P4P programs in risk-based managed care and PCCM programs.

Payments to Providers
Under risk-based managed care, because a contractual relationship exists between the state and its plans, states are prohibited from paying providers outside of the health plan contract. In other words, states are restricted from making direct incentives payments to providers. As an alternative, a state can include funds for a provider incentive program in the health plan's capitation rate, then contractually require the health plan to pass the full incentive payment on to eligible providers.

In a PCCM environment, a state can make incentive payments directly to eligible providers or have the PCCM administrator pass through the bonuses to eligible providers. The state must specify the incentives in its State Plan, and the incentives must be tied to payments for services, as specified in the State Plan.

Incentive Payment Amounts
Incentive payments from the state cannot exceed 105 percent of the payments attributable to services covered by the incentive arrangement.[14] In risk-based managed care, total payments (capitation payments

[14] 42 CFR 438.

plus any incentive amounts) cannot exceed 105 percent of the approved capitation rate attributable to services covered by the incentive arrangement. A state could not, for example, offer a 3 percent incentive payment to its health plans, and an additional 3 percent as a "pass through" to physicians.

In a PCCM delivery system, the 105 percent ceiling is based on services that impact the P4P program target, and may include inpatient hospital, emergency room services, and other services as well as those provided or authorized by the physician, practice, or other PCCM provider. A state should work with CMS to develop an incentive methodology that fits its PCCM program design. Research shows that incentive payments must be large enough to be meaningful in order to motivate a change in behavior. As such, limits on incentive payments may present an even greater reason to collaborate with other purchasers, particularly when Medicaid can benefit from pre-existing quality improvement programs.

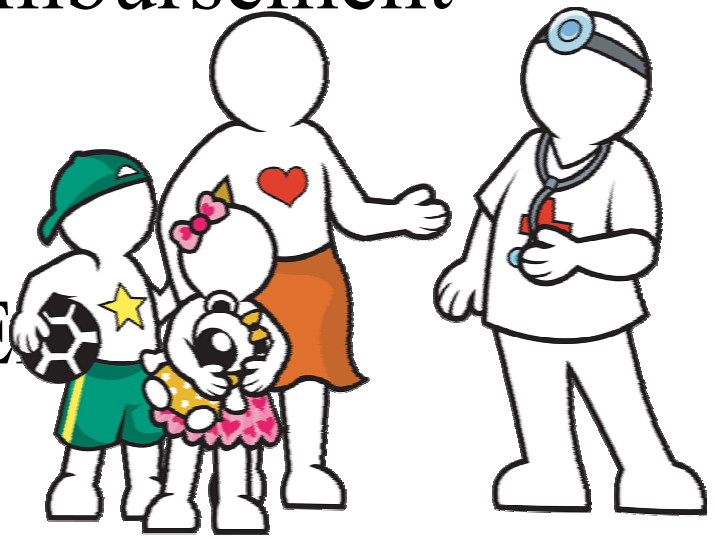
The IEHP Pay For Performance Program

IEHP Pay for Performance Program (P4P)

- ⇨**Goals**
- ⇨**Methodology**
- ⇨**Evolution**
- ⇨**Outcomes**

Goals

- Motivate Physicians to Provide Services
  - Outreach to assigned Members
  - 'Capture' when Member in office
  - Report the event
- Increase Physician Reimbursement
  - Beyond Capitation payments
  - Pediatricians
  - OB/Gyns
- 'Bind' Physicians to IE
  - Direct Payments from IEHP
  - Significant Percent of Income



Methodology

- Direct to Physician Payments
- Fee For Service Model
- ‘Easy’ Billing
- Timely Submission
- Timely Payments

➢ NOT CHDP or CPSP

The Beginning

The Evolution of P4P at IEHP

- The IEHP Immunization Program was the first attempt at a physician incentive program
- Launched September 1997
- Goal was to increase the immunization rate of IEHP Members 0-2 years of age.

The Beginning cont….

- Program provided direct reimbursement to physicians for immunizations
- Immunizations were submitted to IEHP via the PM160 form - only change was adding series #

PIP: The Physician Incentive Program

- In April 2000, the Physician Incentive Program was launched
- The new PIP program consisted of 5 components
  1. Immunizations
  2. Well Child Visits
  3. IHA/Adult Physical
  4. Perinatal Services
  5. Health Education Behavioral Assessment (HEBA)

PIP: The Physician Incentive Program cont…

- Well Child Visit Component
  - Physicians were reimbursed $50 for each well child visit done in accordance with the IEHP Well Child Visit schedule for Members 0 to 18 years old
  - Exams done during the first 120 days of enrollment were paid an additional $50 bonus

PIP: The Physician Incentive Program cont…

- Perinatal Services Component
  - Designed to ensure that all IEHP Members receive timely prenatal and postpartum care
  - Reimbursement Schedule

    $200 if date of service for initial visit in the 1st trime

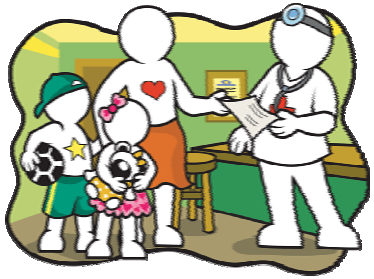
    $100 if the 2nd trimester

    $50 if in the 3rd trimester

    $50 for a postpartum exam within 8 weeks of delive

PIP: The Physician Incentive Program cont…

- In January 2001 the PIP program was redesigned
  - The IHA and HEBA components were removed
  - Reimbursement for Pap Tests was added - $25 reimbursement on CMS 1500
- In August 2001, Chlamydia Screening was added to the P4P program - $25 on CMS 1500



PIP: The Physician Incentive Program cont…

- In January 2003, the Diabetes component was added to PIP
- Providers were reimbursed $25 for each of the following:
  - HbA1c Tests
  - LDL Screening
  - Retinal Exams
  - Foot Exams

Pay For Performance

- With an increasing importance being placed on HEDIS results by DHS, MRMIB, and NCQA, IEHP decided to overhaul the PIP program
- In July 2004, the new Pay For Performance Program (P4P) was launched
- The P4P program is HEDIS-centered

Pay For Performance cont…

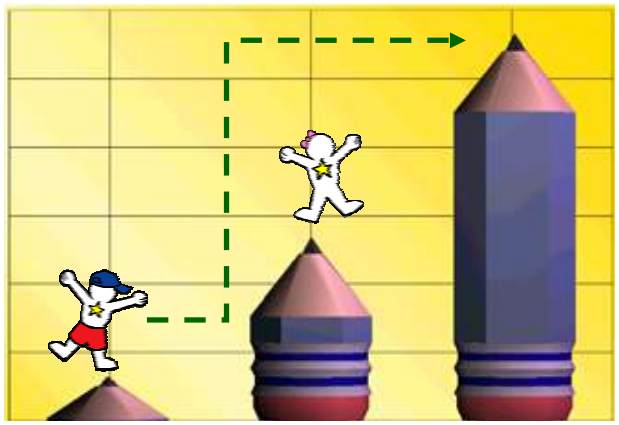
- Implemented a $100 bonus for
  - Completion of 6 well child visits by 15 months
  - Submission of a complete immunization record prior to age 2
- Significantly increased perinatal payments
- Implemented outcomes bonuses for Diabetes:
  - $50 For HgbA1c of 7.0 or less
  - $50 For LDL of 100 or less
- Added Asthma Component (9/1/05)
  - $25 for asthma progress note on-line
  - $20 for paper

Pay For Performance

Questions

The Payoff

- The Program is designed to increase the provision of preventive health services to our Members as well as to improve HEDIS results and we have achieved success in both areas
- Our P4P program has made a tremendous impact on our HEDIS results



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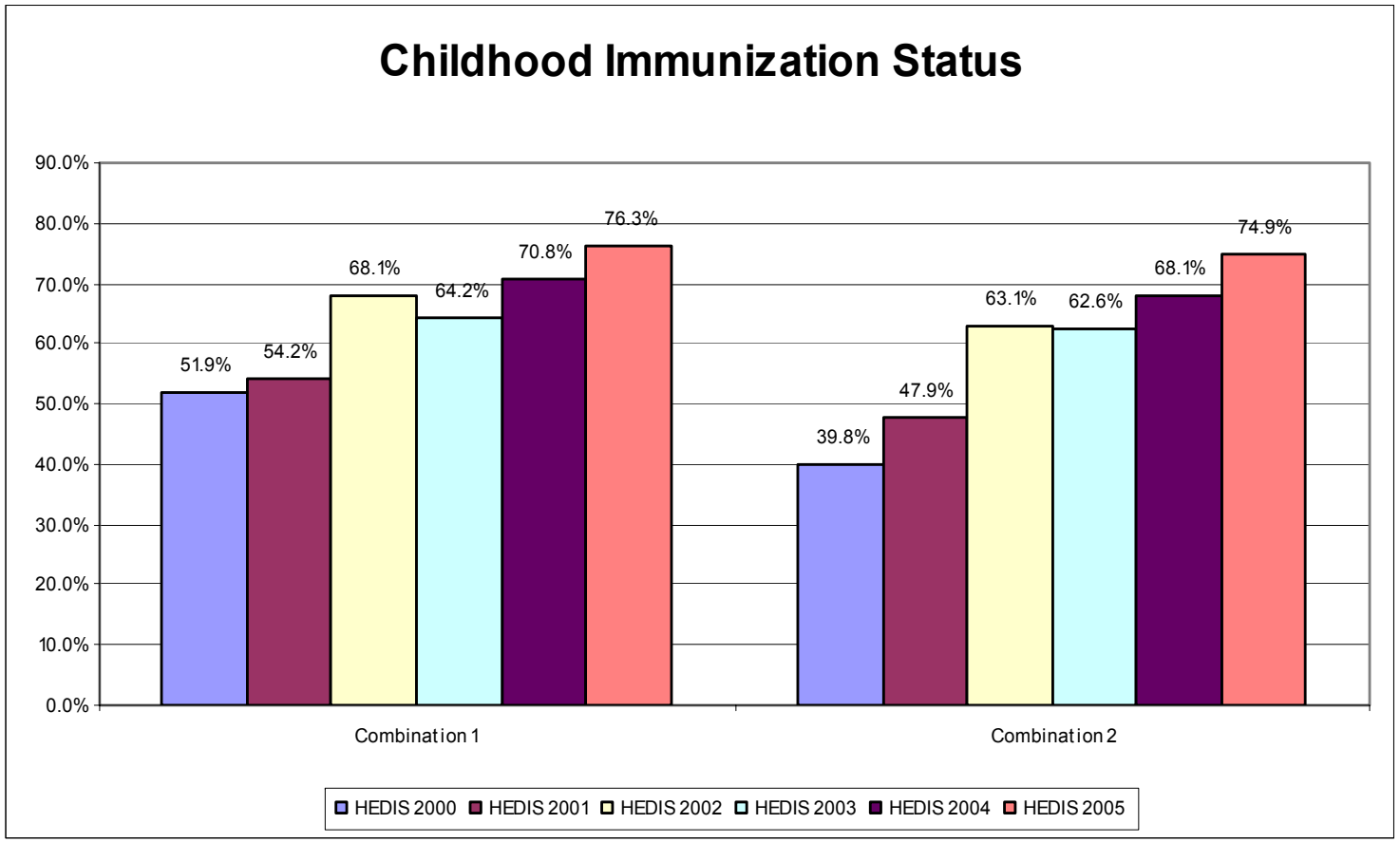
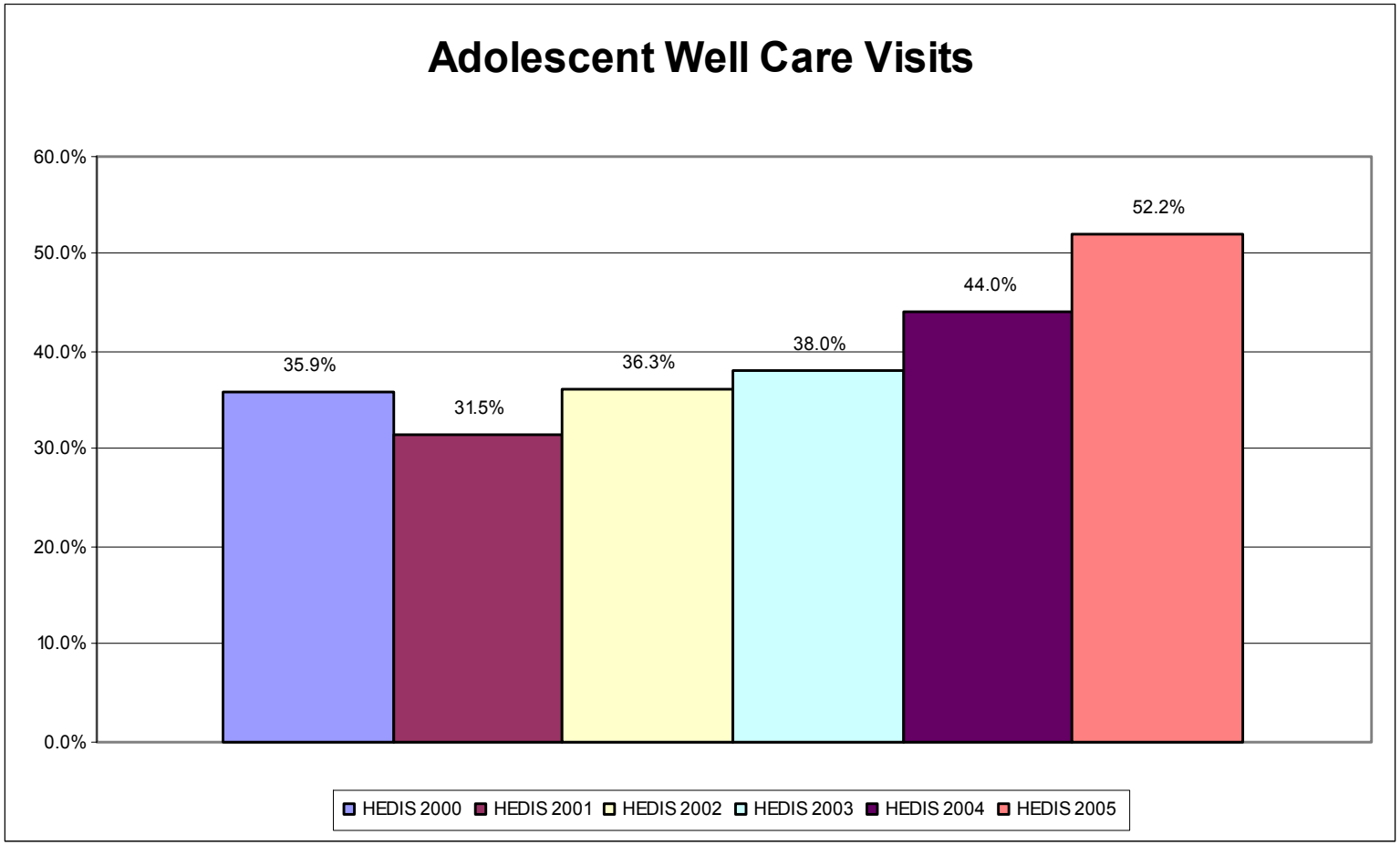
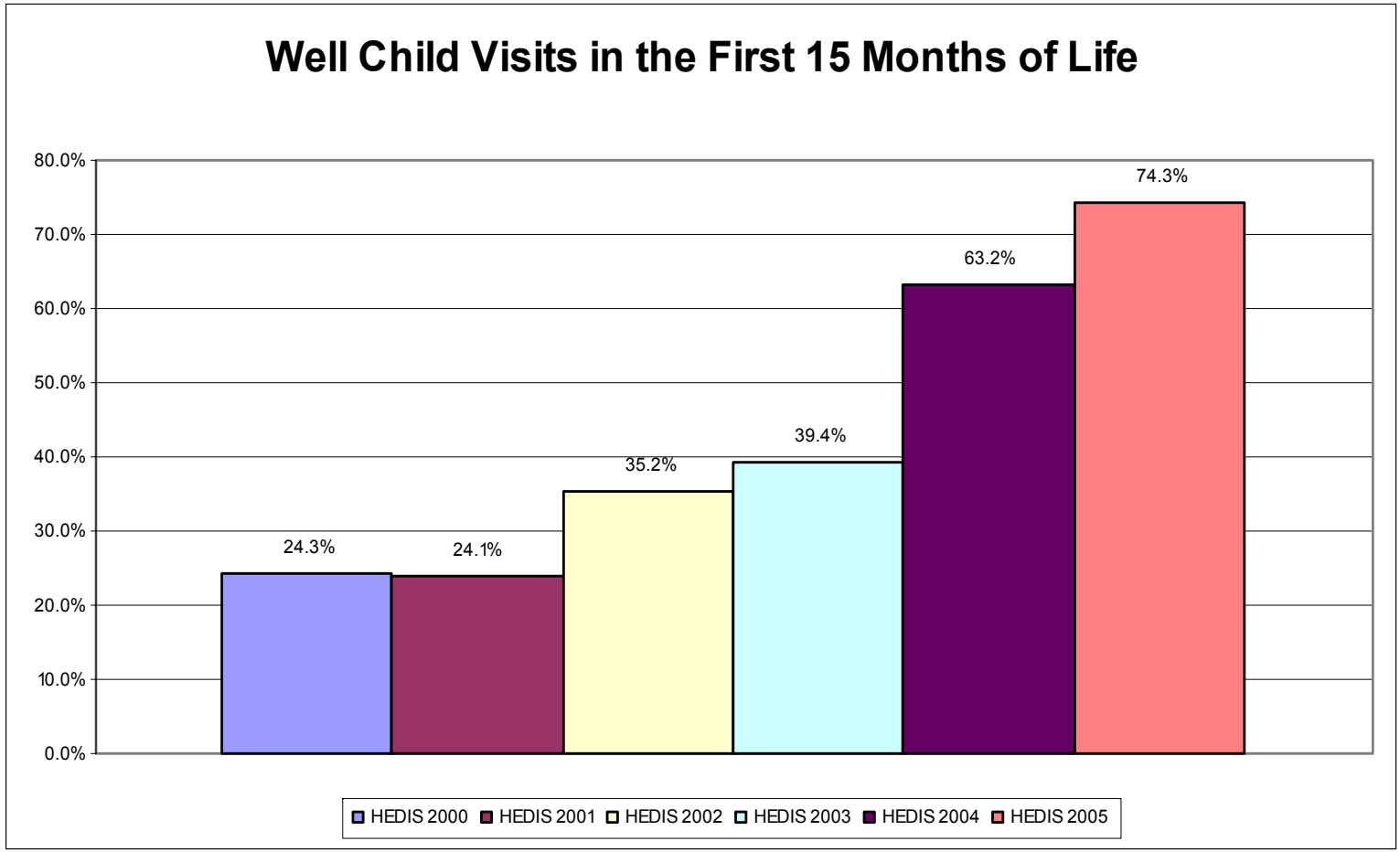

Childhood Immunization Status
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
51.9%
54.2%
68.1%
64.2%
70.8%
76.3%
39.8%
47.9%
63.1%
62.6%
68.1%
74.9%
Combination 1
Combination 2
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

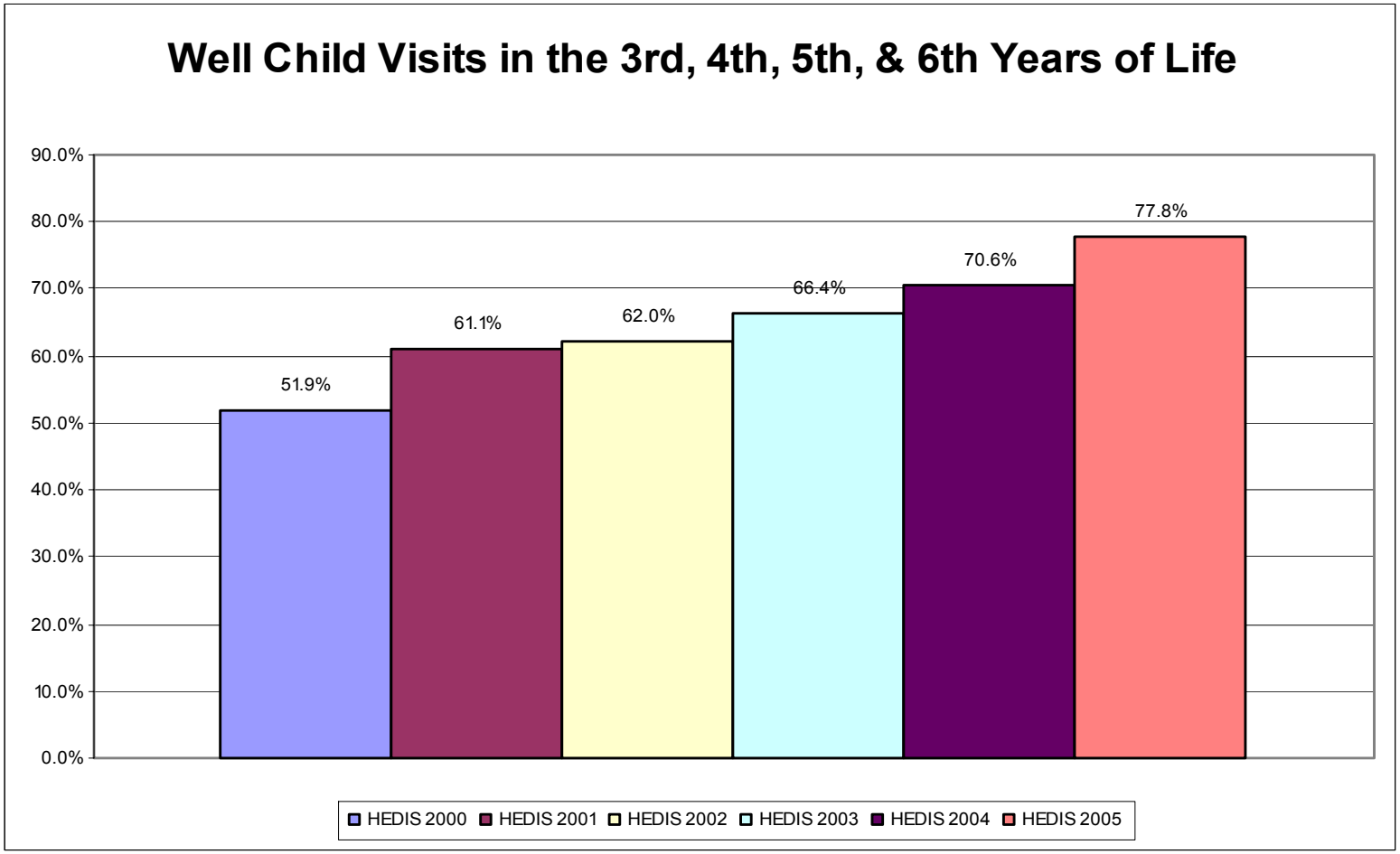
The Payoff


Adolescent Well Care Visits
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
35.9%
31.5%
36.3%
38.0%
44.0%
52.2%
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

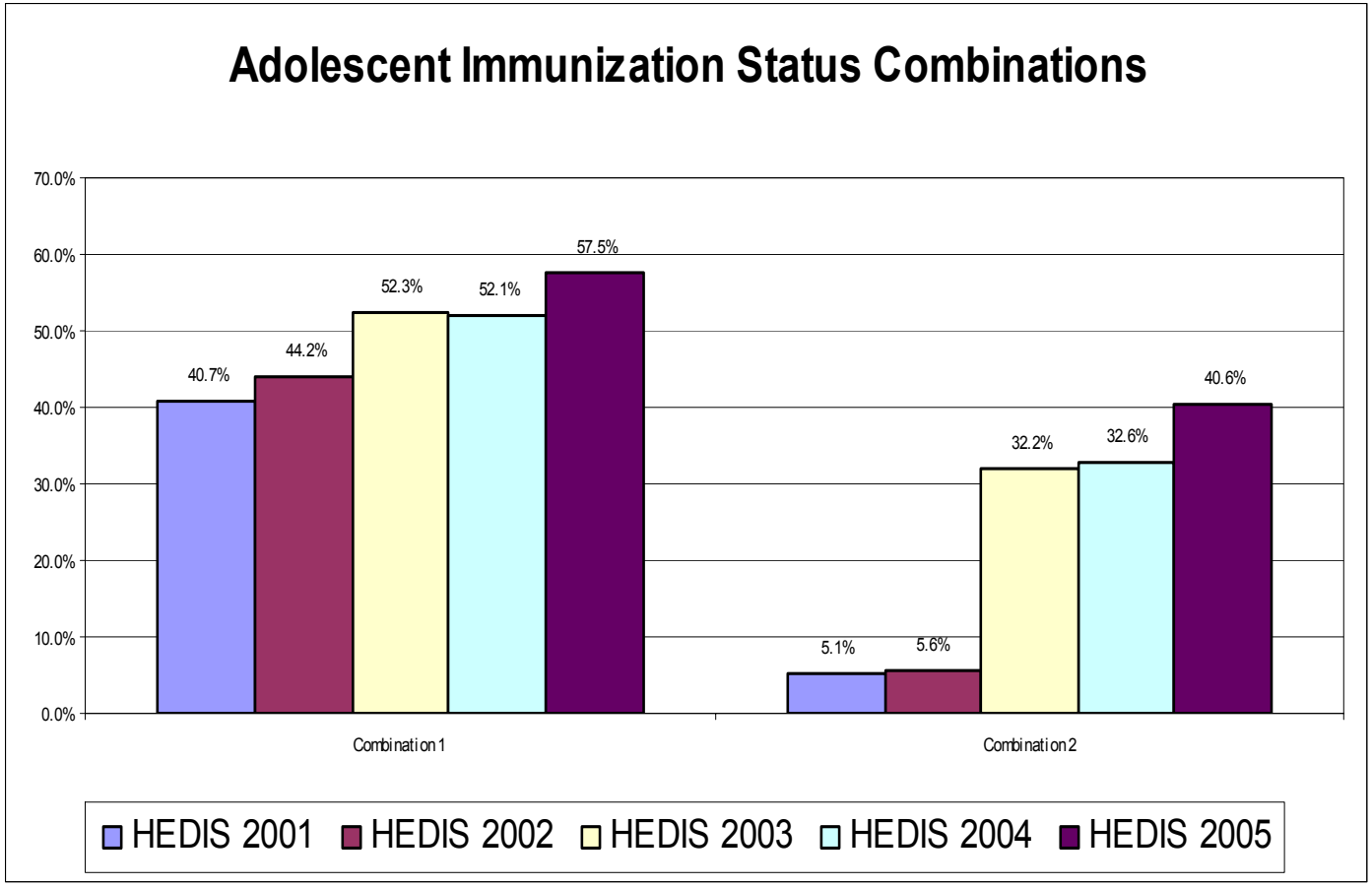
The Payoff


Well Child Visits in the First 15 Months of Life
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
24.3%
24.1%
35.2%
39.4%
63.2%
74.3%
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

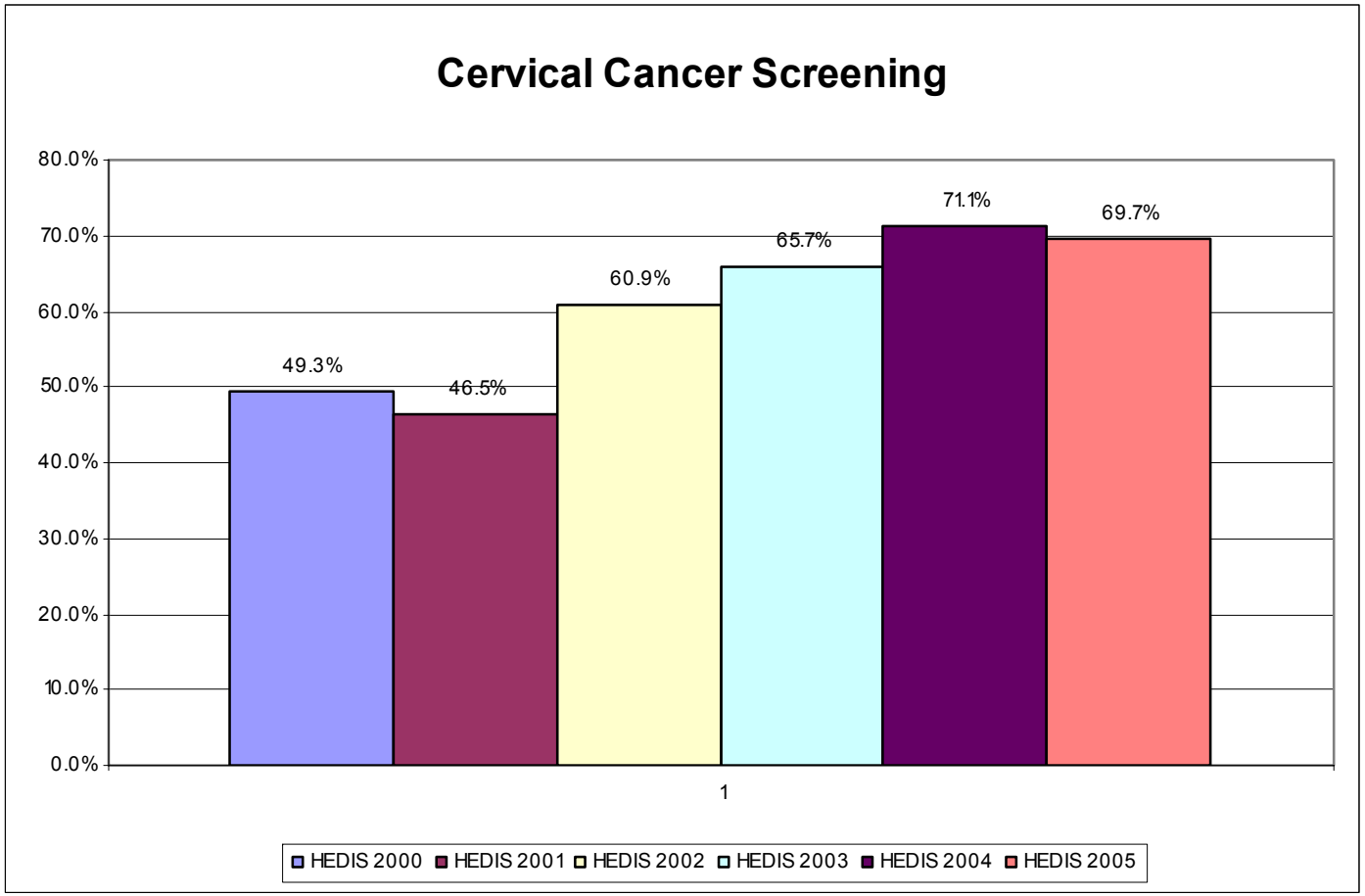
The Payoff


Well Child Visits in the 3rd, 4th, 5th, & 6th Years of Life
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
51.9%
61.1%
62.0%
66.4%
70.6%
77.8%
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

The Payoff


Adolescent Immunization Status Combinations
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
40.7%
44.2%
52.3%
52.1%
57.5%
5.1%
5.6%
32.2%
32.6%
40.6%
Combination 1
Combination 2
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

The Payoff


Cervical Cancer Screening
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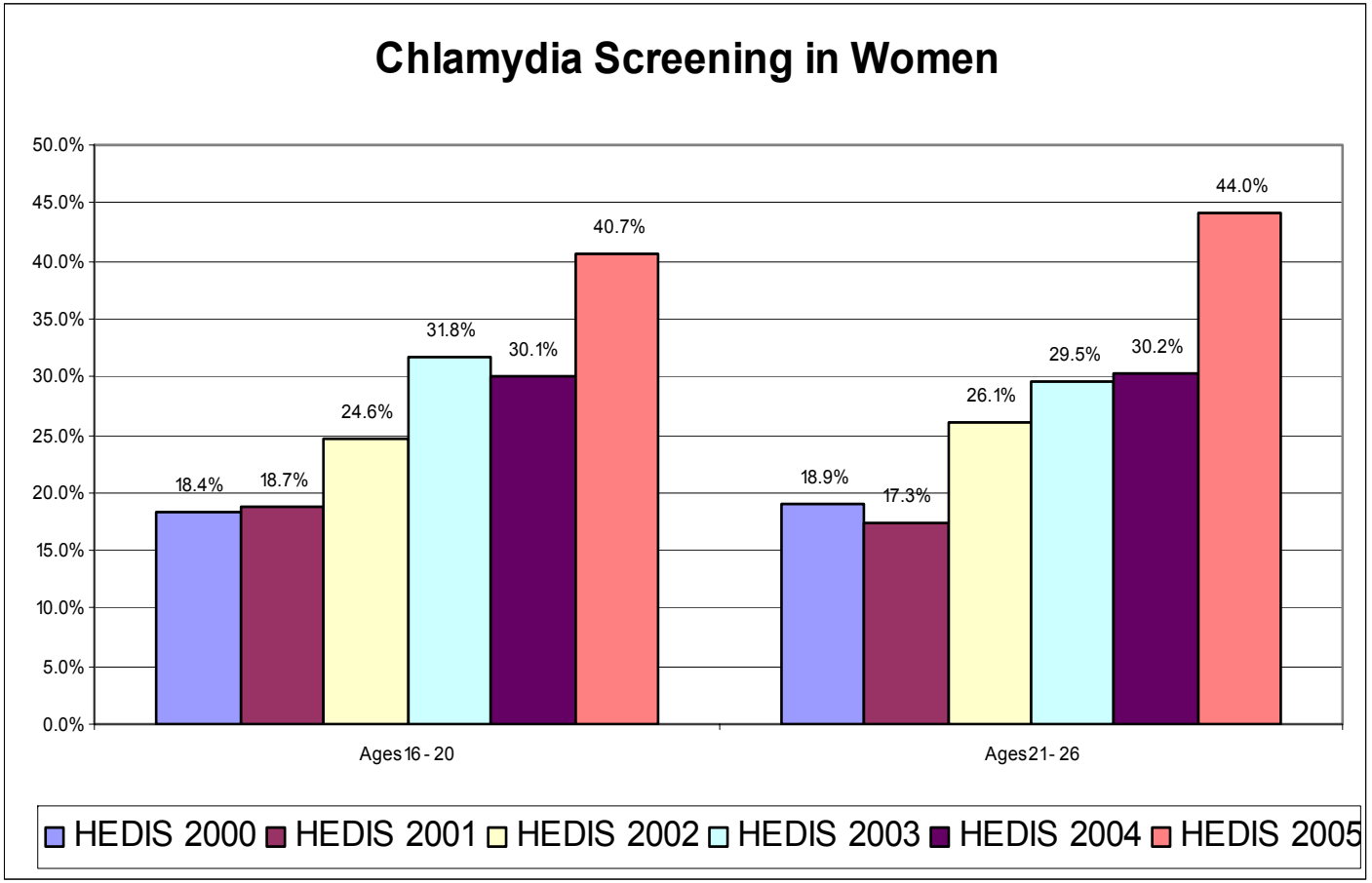
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
49.3%
46.5%
60.9%
65.7%
71.1%
69.7%
1
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

The Payoff


Chlamydia Screening in Women
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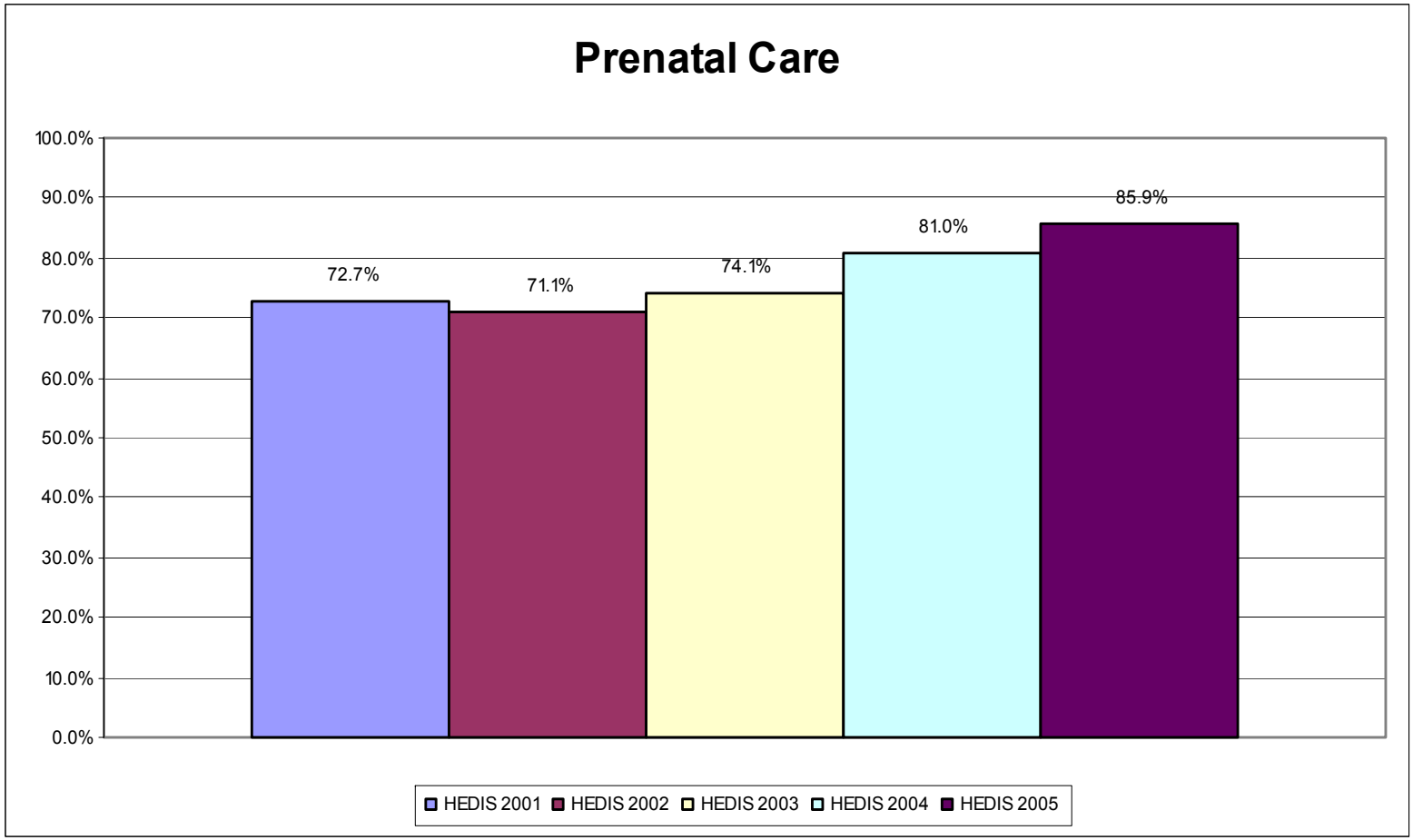
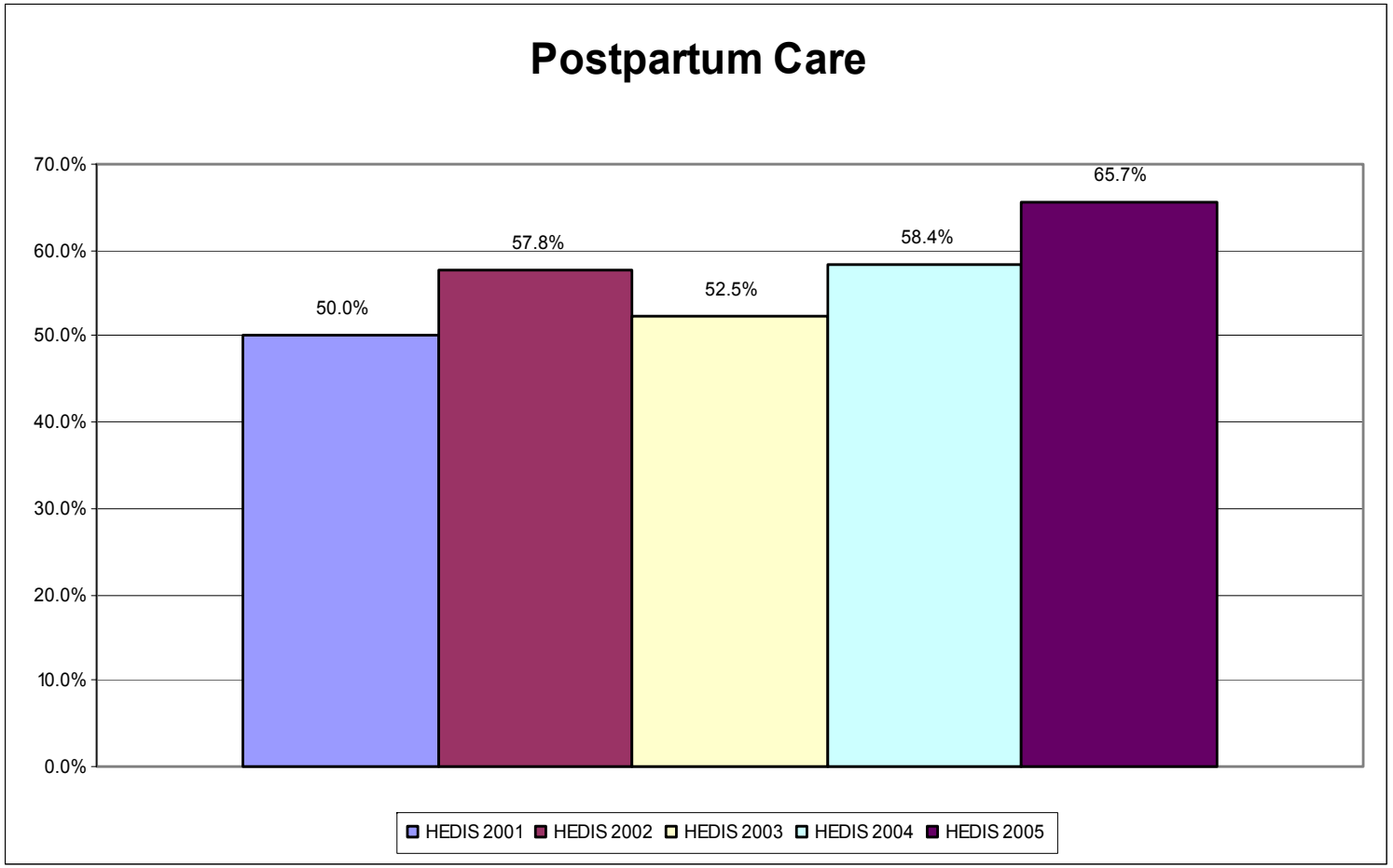
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
18.4%
18.7%
24.6%
31.8%
30.1%
40.7%
18.9%
17.3%
26.1%
29.5%
30.2%
44.0%
Ages 16 - 20
Ages 21 - 26
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

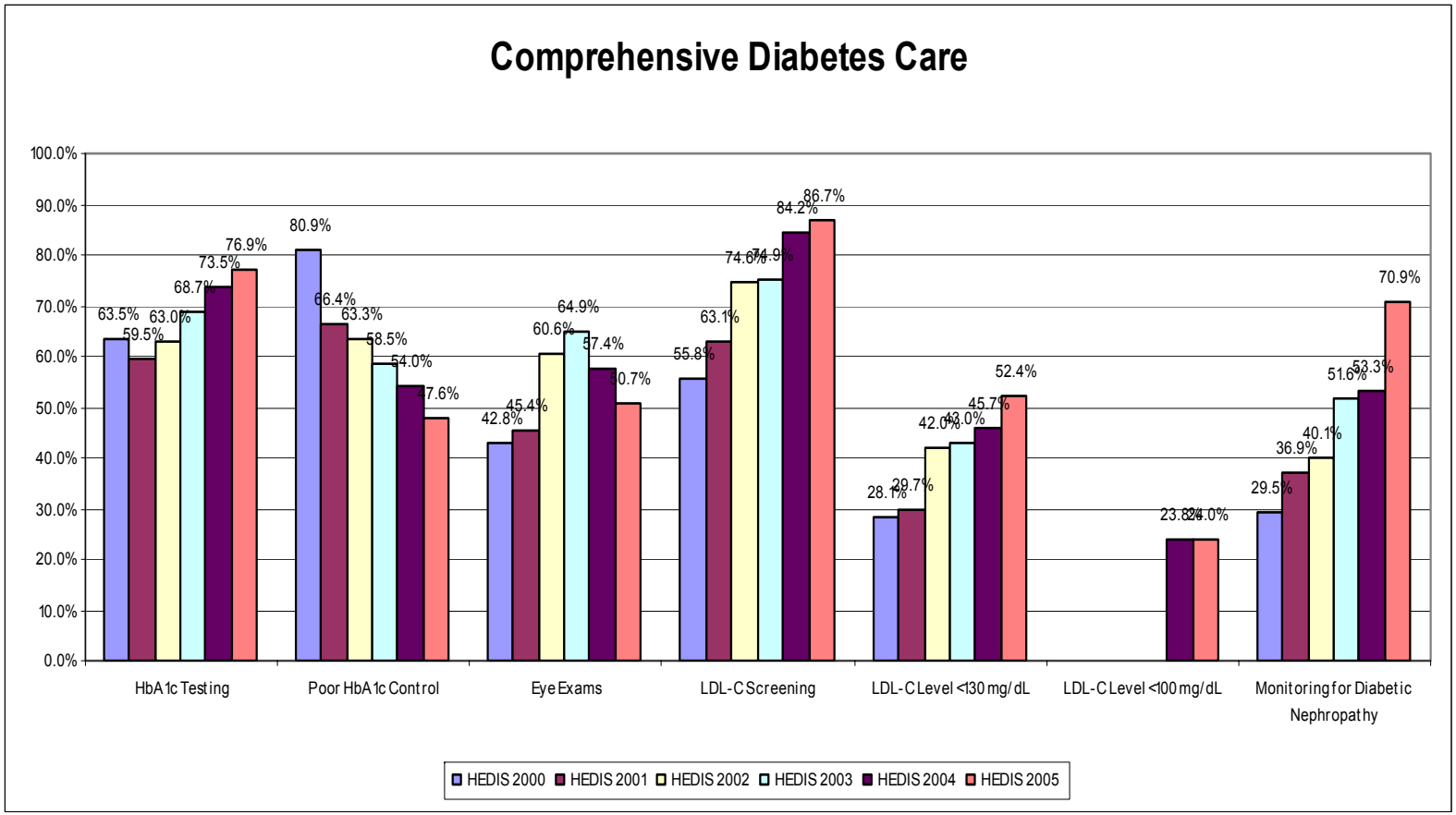
The Payoff


Prenatal Care
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
72.7%
71.1%
74.1%
81.0%
85.9%
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

The Payoff


Postpartum Care
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
50.0%
57.8%
52.5%
58.4%
65.7%
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

The Payoff


Comprehensive Diabetes Care
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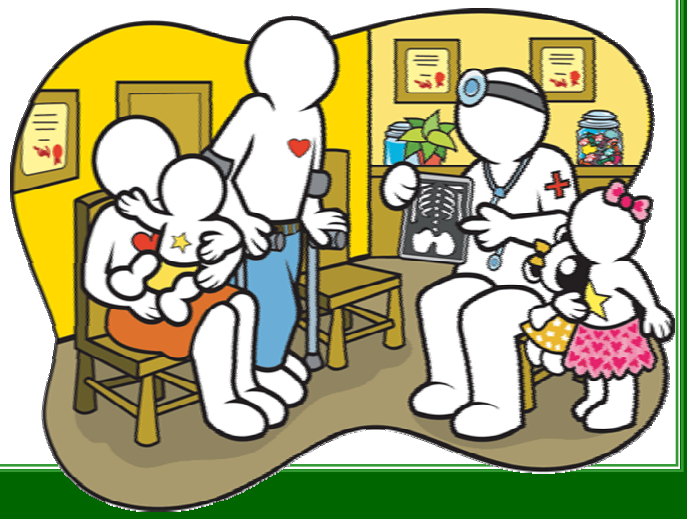
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
63.5%
59.5%
63.0%
68.7%
73.5%
76.9%
80.9%
66.4%
63.3%
58.5%
54.0%
47.6%
42.8%
45.4%
60.6%
64.9%
57.4%
50.7%
55.8%
63.1%
74.6%
74.9%
84.2%
86.7%
28.1%
29.7%
42.0%
43.0%
45.7%
52.4%
23.8%
24.0%
29.5%
36.9%
40.1%
51.6%
53.3%
70.9%
HbA1c Testing
Poor HbA1c Control
Eye Exams
LDL-C Screening
LDL-C Level <130 mg/dL
LDL-C Level <100 mg/dL
Monitoring for Diabetic Nephropathy
HEDIS 2000
HEDIS 2001
HEDIS 2002
HEDIS 2003
HEDIS 2004
HEDIS 2005

Update

- Program is now $12 million annually
- IPA P4P
  - HEDIS Measures
  - Physician Specific Web Data
  - Further Motivation



Pay For Performance

Questions

IPA

2018

Pay for Performance (P4P) Program Guide

Contact: QualityPrograms@iehp.org
Published: March 28, 2018

PROGRAM OVERVIEW

This program guide provides an overview of the 2018 Global Quality Pay for Performance (GQ P4P) Program for Independent Physician Associations (IPAs). In this third year of the program, IEHP has made program enhancements based on feedback from Providers in an effort to continually improve effectiveness. The IEHP GQ P4P program for IPAs is designed to reward IPAs for high performance and year-over-year improvement in key quality performance measures. This program overview is designed for IPAs and their staff as an easy guide to help maximize GQ P4P.

This year's GQ P4P Program continues to provide financial rewards to IPAs for improving healthcare quality across multiple domains and measures. The 2018 GQ P4P program focuses on performance-based incentives to IPAs for services rendered in 2018.

If you would like to get more information about IEHP's GQ P4P Program or best practices to help improve quality scores and outcomes, visit our Secure Provider Portal at ***www.iehp.org***, email the Quality Team at ***QualityPrograms@iehp.org*** or call the IEHP Provider Relations Team at 909-890-2054.

What's New?

Two measures were retired

- Annual Monitoring for Patients on Persistent Medications - Total
- Childhood Immunizations - Combo 3

Three measures were added to the Clinical Quality Domain

- Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis
- Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents
- Concurrent Use of Opioids and Benzodiazepines (monitoring only)

New Tier 1 and Tier 2 goal methodology includes a 'practical significance' standard

The budget was reduced from $30 million to $20 million, with removal of the condition to pass through 33-50 percent of the funding to Primary Care Providers (PCPs), which was in place for previous program years.

Eligibility and Participation

To be eligible for incentive payments in the 2018 GQ P4P Program, IPAs must meet the following criteria:

- Have at least 5,000 IEHP Medi-Cal Members assigned as of January 2018
- Have at least 30 Members in the denominator as of December 2018 for each quality measure to qualify
- Submit a GQ P4P Quality Work Plan to IEHP by March 1, 2018 in order to enroll in the program (see Work Plan details in Appendix 5)
- Meet minimum Encounter Data Gates in order to qualify for incentive payments

Minimum Data Requirements

Encounter Data

Encounter data is foundational to performance scoring and is essential to success in the GQ P4P Program. Complete, timely and accurate encounter data should be submitted through normal reporting channels for all services rendered to IEHP Members. Please use the codes listed in Appendix 2 to help with proper coding to meet measure requirements.

Lab Results

Data from lab results is also foundational to Program performance scoring. Providers should ensure they submit complete lab results data for services rendered to IEHP Members. IPAs should work with their network Providers to ensure they are using the appropriate lab vendors for IEHP Members, and submitting complete lab results data to IEHP.

Lab results that are performed in the office (e.g., point of care HbA1c testing, urine tests, etc.) should be coded and submitted through Providers' encounter data.

Immunizations

To maximize performance in immunization-based measures, **IEHP strongly encourages all Providers to report all immunizations via the California Immunization Registry (CAIR2)**. For more information on how to register for CAIR2, please visit *http://cairweb.org/*. IEHP is working closely with CAIR to establish a data sharing arrangement to be used in Global Quality P4P reporting.

Supplemental Data

What is Supplemental Data?

When services are not captured in traditional encounter data systems, other Supplemental Data sources may be used to collect information about services rendered to Members to support Quality Reporting.

When Supplemental Data may be needed

- For services that were provided prior to eligibility
- When a Provider has "proof-of-service" for a noted gap in care (e.g. cervical cancer screening, immunizations rendered by another provider)
- When Provider has "proof-of-service" for an eligible-population exclusion (e.g. total hysterectomy, bilateral mastectomy)

How to use Supplemental Data to support Global Quality P4P

Create an electronic log that includes minimum required data elements. See Appendix 6 for file layout requirements. Below is a listing of minimum data elements needed in a supplemental data log.

- Member ID
- Date of Service
- Provider Identification
- Provider Specialty
- Diagnosis Code(s) – if applicable
- Procedure Code(s)
- Lab Results – if applicable

Requirements for using Supplemental Data in Global Quality P4P Reporting

- The IPA must have clearly defined policies and procedures (in writing) that describe how Supplemental Data is collected, validated and used for P4P reporting
- Policies/procedures must be shared with IEHP and must be in place to validate quality / accuracy of Supplemental Data
- The IPA must collect "proof-of-service" documentation to confirm all services that are reported in the Supplemental Data log
- The IPA must receive approval from IEHP's Quality Team to use Supplemental Data in Global Quality Reporting (deadline for approval is October 31, 2018)
- The IPA must complete a P4P Roadmap no later than December 1, 2018
- The IPA must complete IPA data validation activities prior to submitting Supplemental Data to IEHP
- The IPA must submit a final Supplemental Data log to IEHP via SFTP no later than February 1, 2019

Data Validation Requirements for Supplemental Data in Global Quality P4P Reporting

- To be counted in final IPA Global Quality P4P rates, Supplemental Data file must pass IEHP's independent HEDIS® audit process
- The IPA must present "proof-of-service" documents within required timeframes when requested by IEHP's auditors
- An auditor review will compare "proof-of-service" documents to submitted data
- Supplemental Data records must pass 100 percent validation to be included in the final P4P reporting

Financial Overview

Providers are eligible to receive financial rewards for performance excellence and for performance improvement. Financial rewards are based on a tiered system, providing increasing financial rewards for reaching higher tiered level performance. The 2018 GQ P4P Program incentive pool is $20 million for the IPA Program. Incentive dollars for the 2018 performance period will be distributed monthly via a new monthly per Member per month (PMPM) Quality Payment beginning in July 2019 and continuing through June 2020.

IPA Encounter Data Gates

IPA encounter data submissions must meet minimum adequacy requirements in order to receive GQ P4P Program incentive dollars. IPA encounter data performance is based on all professional encounters submitted by the IPA for services rendered during the measurement year (e.g., 2018 dates of service). IPA encounter data volume will be compared to established encounter data benchmarks for Seniors and Persons with Disabilities (SPD) and Non-SPD Members. IPA performance will be calculated against each IPA's proportion of SPD and Non-SPD Members.

Encounter data benchmarks have been established and correspond to an Encounter Data Gate, reflecting higher encounter data volumes. As IPAs reach higher levels of encounter data performance, they become eligible for a larger percentage of the total possible GQ P4P incentive. Encounter rates are expressed as the number of encounters per Member per year (PMPY). An encounter is defined as a unique visit per Member per Provider per day. The table below describes the Encounter Data Gates, performance levels, and their impact to IPA GQ P4P Program incentive payments.

PERCENT OF POSSIBLE INCENTIVE PAYMENT	ENCOUNTER DATA GATE	NON-SPD PMPY	SPD PMPY
50%	Gate 1	3.0	9.0
75%	Gate 2	4.0	11.0
100%	Gate 3	5.0	13.0

The Encounter Data Gating methodology only applies to the IPA methodology. Encounter data must be submitted to IEHP in a timely way and must adhere to the reporting timeframes delineated in IEHP's Provider Policy and Procedure Manual - Policy 21A.

Performance Measures

Appendix 1 provides a list of the 23 measures included in the 2018 GQ P4P Program and includes the thresholds and benchmarks associated with respective tier goals. These measures have been categorized into four domains: *Clinical Quality; Behavioral Health Integration; Patient Experience; Encounter Data*.

Most measures included in the *Clinical Quality Domain* primarily use standard Healthcare Effectiveness Data and Information Set (HEDIS®) process and outcomes measures that are based on the specifications published by the National Committee for Quality Assurance (NCQA). Non-HEDIS® measures that are included in the Clinical Quality Domain come from the California Department of Health Care Services (DHCS) Medi-Cal Managed Care Quality Program and the Pharmacy Quality Alliance (PQA).

Clinical Quality Domain Measures:

- Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis (New)
- Breast Cancer Screening
- Cervical Cancer Screening
- Childhood Immunizations – Combo 10
- Comprehensive Diabetes Care – Eye Exam
- Comprehensive Diabetes Care – HbA1c Control < 8
- Concurrent Use of Opioids and Benzodiazepines (New)
- Immunizations for Adolescents – Combo 2
- Initial Health Assessment
- Medication Management for People with Asthma – 75% rate
- Timely Postpartum Care
- Timely Prenatal Care
- Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents (New)
    - Counseling for Physical Activity
    - Counseling for Nutrition
    - BMI Percentile
- Well-Child 3-6 Years of Life

IEHP's HEDIS® 2019 data set (measurement year 2018) will be used to evaluate Providers' year-end performance. This measure set undergoes an independent audit review prior to rate finalization.

The Initial Health Assessment (IHA) measure follows IEHP's IHA internal compliance monitoring methodology and is not a HEDIS® measure.

The Concurrent Use of Opioids and Benzodiazepines measure specification is developed and maintained by the PQA. This measure will not be used for incentive calculations but will be collected to establish a baseline rate for 2018. See Appendix 2 for measure details.

Behavioral Health Integration Domain Measures:

The Behavioral Health Integration Domain includes two measures derived from the Centers for Medicare and Medicaid Services (CMS) Physician Quality Reporting System (PQRS) measure set.[1]

- Screening for Clinical Depression in Primary Care
- Positive Depression Screening with Follow-Up Plan

Patient Experience Domain Measures:

Patient Experience Domain measures include Member Satisfaction Survey questions from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey that is published by the Agency for Healthcare Research and Quality (AHRQ). IEHP conducts a Member Satisfaction Survey that is a modified CAHPS survey and is the sole data source supporting the performance scoring methodology for this measure domain. The IEHP Member Satisfaction Survey is conducted between June and December of each year. Surveys received from the 2018 Member Satisfaction Survey will be used to calculate the Patient Experience Domain measures. A copy of the current Member Satisfaction Survey is included in Appendix 4.

- Access to Care Needed Right Away
- Access to Routine Care
- Coordination of Care

Encounter Data Domain Measures:

The fourth measure domain is *Encounter Data*. IPAs eligible for the GQ P4P Program become eligible to receive payment dollars once they have met the minimum encounter data gate. Higher encounter gate performance qualifies an IPA to receive a higher percentage of incentive dollars. See the 'IPA Encounter Data Gates' section of this program guide for additional details on this methodology.

[1] For information on the PQRS measure set: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html.

2018 IPA Global Quality P4P Scoring and Payment Flowchart

PROGRAM ELIGIBILITY REQUIREMENTS

Membership will be determined as of 01/2018

IPAs with 5,000 or more assigned Members

SCORING METHOD

Incentive eligible IPAs will receive a Quality Score for each Measure

IPAs must have 30 or more Members in each measure to be eligible for a Quality Score

The Quality Score is averaged to determine the Global Quality Performance Score

At least three measures are required to determine the Global Quality Performance Score

IPA PAYMENT CALCULATION

[Global Quality Performance Score] x [# Medi-Cal average Member months] = Member Points

[Member Points] x [payment amount per Member pint] = Max Payment Amount

[Max Payment Amount] x [Encounter Gate %] = Final Payment Amount

Scoring Methodology

Payment will be awarded to IPAs based on individual performance in reaching established Quality Goals (e.g., Tier Goals for each measure).

In the *Clinical Quality Domain,* HEDIS® measure results are based on each measure's total eligible population assigned to the IPA. The eligible population is defined as the set of Members that meet the denominator criteria specified in the current year's HEDIS® Technical Specifications (Volume 2) published by NCQA. Members in the eligible population are attributed to the assigned PCP on the anchor date of each measure, as defined within the HEDIS® measure. Members contribute to a IPA's HEDIS® measure denominator if continuous enrollment criteria are met at the health plan level. For each measure, the HEDIS® score reflects the proportion of the eligible population that is in compliance with the numerator criteria, as defined in the current HEDIS® technical specifications (Volume 2).

In the *Clinical Quality Domain*, Non-HEDIS® measure results (i.e., Initial Health Assessment) are based on new health plan Members who are assigned to the IPA during the measurement year and who remain enrolled with IEHP and the IPA through the 120 day post enrollment period.
See Appendix 2 for measure details.

In the *Patient Experience Domain*, monthly Member Satisfaction Survey measures are based on Members who meet eligibility criteria to receive a mailed survey between June and December of the measurement year. Members eligible to receive a Member Satisfaction Survey must have been continuously enrolled with IEHP for at least six months in the measurement year (2018) and must have had an office visit in the prior six months, based on encounter data submitted to IEHP. Members who meet the survey eligibility criteria are randomly sampled to receive a survey. Survey measure results are attributed to the Member's assigned IPA based on the most recent encounter that qualified the Member for the survey. A Member is eligible to receive only one survey per calendar year.

For IPAs, the *Encounter Data Domain* measures assess the volume of IPA encounters received for all assigned IPA Members. The denominator is all assigned Medi-Cal Members each month of the measurement year (2018). All monthly assigned Members are summed to create the denominator (i.e., Member months). The numerator is the sum of all unique encounters (e.g., unique Member, Provider, date of service) in the measurement year for all assigned Members in the denominator. A Per Member Per Year (PMPY) rate is calculated following this formula:

(Total Unique Encounters / Total Member Months) x 12 = PMPY

Payment Methodology

IPA performance for each quality measure will be given a point value (i.e., a Quality Score). Points are assigned based on the Tier Goal achieved (e.g., Tier 1 = one point, Tier 2 = two points, Tier 3 = three points) for each measure.

IPAs that have at least three quality measures which meet the minimum denominator size (n = 30) will be considered for payment calculations. An average of all eligible Quality Scores will determine the overall GQ Performance Score. GQ P4P Program payments will be awarded according to the following formula:

[Global Quality Performance Score] x [# Medi-Cal Average Member Months] = ***Member Points***

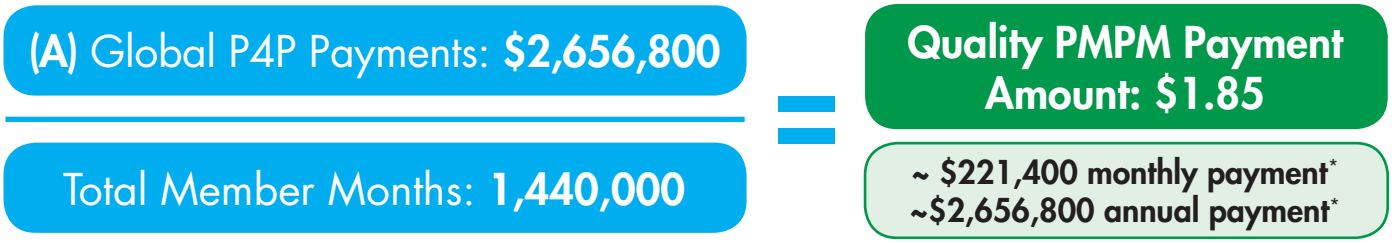
[Member Points] x [Payment Amount per Member Point] = ***Incentive Payout Total***

The payment amount per Member point is dependent on the total incentive money available for IPAs.

IPA PMPM Quality Payment Methodology

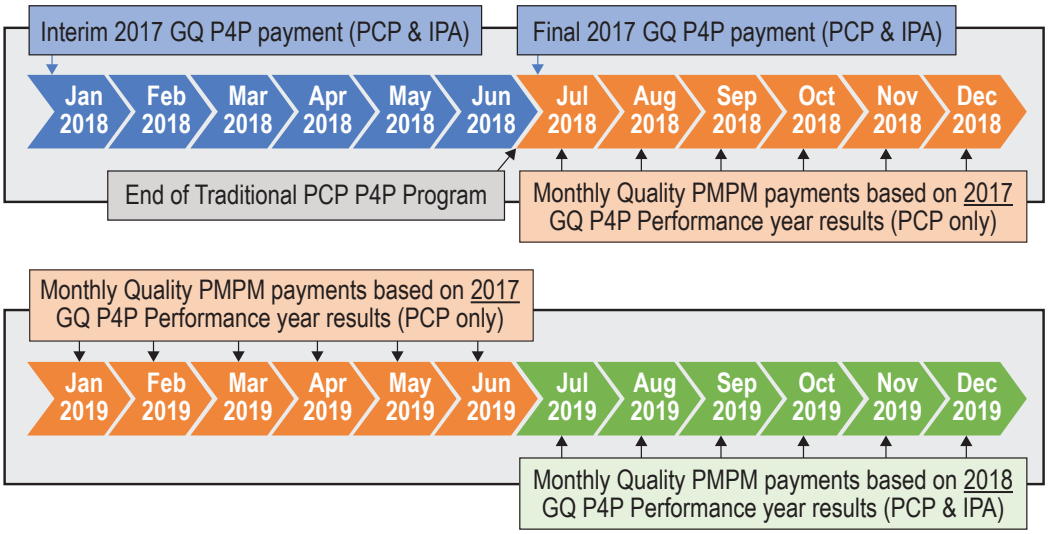
From July 2019 – June 2020, IPAs will receive a monthly PMPM (per member per month) quality payment based on 2018 GQ P4P performance using the following formula:

IPA payment example: *IPA with monthly average of 120,000 Members (1,440,000 Member Months), 2.0 GQ Quality Score and Encounter Data Gate 2 met*



**assuming stable membership volume*

Quality Incentive Payout Timeline: Provider Communication Timeline



Getting Help

Please direct questions and/or comments related to this program to IEHP's Provider Call Center at 909-890-2054 or to IEHP's Quality Department at ***QualityPrograms@iehp.org***.

Program Terms and Conditions

- Participation in IEHP's GQ P4P Program, as well as acceptance of incentive payments, does not in any way modify or supersede any terms or conditions of any agreement between IEHP and Providers or IPAs, whether that agreement is entered into, prior to or subsequent to, the date of this communication.
- There is no guarantee of future funding for, or payment under, any IEHP Provider incentive program. The IEHP GQ P4P Program and/or its terms and conditions may be modified or terminated at any time, with or without notice, at IEHP's sole discretion.
- Criteria for calculating incentive payments are subject to change at any time, with or without notice, at IEHP's sole discretion.
- In consideration of IEHP's offering of the IEHP GQ P4P Program, participants agree to fully and forever release and discharge IEHP from any and all claims, demands, causes of action, and suits, of any nature, pertaining to or arising from the offering by IEHP of the IEHP GQ P4P Program.
- The determination of IEHP regarding performance scoring and payments under the IEHP GQ P4P Program is final.
- As a condition of receiving payment under the IEHP GQ P4P Program, Providers and IPAs must be active and contracted with IEHP and have active assigned Members at the time of payment.

APPENDIX 1: *2018 IPA Global Quality P4P Program Measures*

2018 GQ P4P PROGRAM MEASURE LIST					
Domain	**Measure Name**	**Population**	**Tier 1**	**Tier 2**	**Tier 3[2]**
Clinical Quality	Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis [1]	Adult	Improvement demonstrated by meeting the following 2 conditions: 10% reduction in non-compliance AND Improvement of at least 2.0 percentage points	Improvement demonstrated by meeting the following 2 conditions: 20% reduction in non-compliance AND Improvement of at least 3.0 percentage points	39.0%
Clinical Quality	Comprehensive Diabetes Care - HbA1c Control <8	Adult			58.0%
Clinical Quality	Comprehensive Diabetes Care - Eye Exam	Adult			68.0%
Clinical Quality	Medication Management for People with Asthma - 75%	Adult			48.0%
Behavioral Health Integration	Screening for Clinical Depression in Primary Care	Adult and Adolescent			50.0%
Behavioral Health Integration	Positive Depression Screening with Follow-Up Plan	Adult and Adolescent			90.0%
Clinical Quality	Breast Cancer Screening	Women			71.0%
Clinical Quality	Cervical Cancer Screening	Women			70.0%
Clinical Quality	Timeliness of Prenatal Care	Women			91.0%
Clinical Quality	Postpartum Care	Women			74.0%
Clinical Quality	Childhood Immunizations - Combo 10	Child	Improvement demonstrated by meeting the following 2 conditions: 10% reduction in non-compliance AND Improvement of at least 2.0 percentage points	Improvement demonstrated by meeting the following 2 conditions: 20% reduction in non-compliance AND Improvement of at least 3.0 percentage points	46.0%
Clinical Quality	Immunizations for Adolescents - Combo 2	Child			32.3%
Clinical Quality	Well-Child Visits 3-6 Years of Life	Child			83.0%
Clinical Quality	Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents - Counseling for Physical Activity [1]	Child			72.0%
Clinical Quality	Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents - Counseling for Nutrition [1]	Child			80.0%
Clinical Quality	Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents - BMI Percentile [1]	Child			86.0%
Clinical Quality	Initial Health Assessment	All			50.0%
Clinical Quality	Concurrent Use of Opioids and Benzodiazepines [1] **	All	Baseline Reporting Year		
Patient Experience	Member Satisfaction Survey - Access to Care Needed Right Away	All	84.00%	86.00%	88.0%
Patient Experience	Member Satisfaction Survey - Coordination of Care	All	82.00%	84.00%	86.0%
Patient Experience	Member Satisfaction Survey – Access to Routine Care	All	82.00%	85.00%	86.0%
Encounter Data	Encounter Data for PCPs PMPY – SPD***	All	9.0	11.0	13.0
Encounter Data	Encounter Data for PCPs PMPY - Non-SPD***	All	3.0	4.0	5.0

*[1] New Measure for 2018 [2] Tier 3 goals set at the 90th percentile as published in the NCQA 2017 Mid-year Benchmarks and Thresholds and 2016 HEDIS® and Exclusion Audit Means, Percentiles source files ** Reporting Only Measure. Not eligible for incentive dollars*
*** Encounter Data measure benchmarks are "gates" not "tiers"*

APPENDIX 2: *Measures Overview*

Population: Adult

Avoidance of Antibiotic Treatment in Adults With Acute Bronchitis (AAB)

Methodology: HEDIS®

Measure Description: The percentage of adults 18-64 years of age with a diagnosis of acute bronchitis who were not dispensed an antibiotic prescription on or three days after the Index Episode Start Date (IESD).

- Episode Date is the date of service for any outpatient or emergency department (ED) visit during the Intake Period (January 1, 2018-December 24, 2018) with a diagnosis of acute bronchitis
- IESD: the earliest Episode Date during the Intake Period with a diagnosis of acute bronchitis that meets all of the following criteria:
    1. Episode Date is the date of service for any outpatient or ED visit during the Intake Period with a diagnosis of acute bronchitis.
    2. A 30-day Negative Medication History prior to the Episode Date.
    3. A 12-month Negative Comorbid Condition History prior to and including the Episode Date.
    4. A Negative Competing Diagnosis during the 38-day period from 30 days prior to the Episode Date through seven days after the Episode Date.
    5. The member was continuously enrolled one year prior to the Episode Date through seven days after the Episode Date.
- The measure is reported as an inverted rate [1 – (numerator/eligible population)]. A higher rate indicates appropriate treatment of adults with acute bronchitis (i.e., the proportion for whom antibiotics were not prescribed).
- Members in hospice are excluded from the eligible population.
- Exclude denied claims when assessing numerator criteria.
- Do not include ED visits or observation visits that result in an inpatient stay. When an ED or observation visit and an inpatient stay are billed on separate claims, the visit results in an inpatient stay when the admission date for the inpatient stay occurs on the ED/observation date of service or one calendar day after. An ED or observation visit billed on the same claim as an inpatient stay is considered a visit that resulted in an inpatient stay.

Denominator: Members 18-64 years of age, who had an outpatient visit, an observation visit or an ED visit between January 1 – December 24 of the measurement year (2018) with a diagnosis of acute bronchitis.

Numerator: Dispensed prescription for an antibiotic medication on or three days after IESD for the Members in denominator.

AAB ANTIBIOTIC MEDICATIONS			
Description	**Prescription**		
Aminoglycosides	• Amikacin • Gentamicin	• Tobramycin • Streptomycin	
Aminopenicillins	• Amoxicillin	• Ampicillin	
Beta-lactamase inhibitors	• Amoxicillin-clavulanate • Ticarcillin-clavulanate	• Piperacillin-tazobactam • Ampicillin-sulbactam	
First-generation cephalosporins	• Cefadroxil	• Cefazolin	• Cephalexin
Fourth-generation cephalosporins	• Cefepime		
Ketolides	• Telithromycin		
Lincomycin derivatives	• Clindamycin	• Lincomycin	
Macrolides	• Azithromycin • Clarithromycin	• Erythromycin • Erythromycin ethylsuccinate	• Erythromycin lactobionate • Erythromycin stearate
Miscellaneous antibiotics	• Aztreonam • Chloramphenicol • Dalfopristin-quinupristin	• Daptomycin • Erythromycin-sulfisoxazole	• Metronidazole • Vancomycin • Linezolid
Natural penicillins	• Penicillin G benzathine-procaine • Penicillin G potassium	• Penicillin G procaine • Penicillin G sodium	• Penicillin V potassium • Penicillin G benzathine
Penicillinase resistant penicillins	• Dicloxacillin	• Nafcillin	• Oxacillin
Quinolones	• Ciprofloxacin • Gemifloxacin	• Levofloxacin • Moxifloxacin	• Norfloxacin • Ofloxacin
Rifamycin derivatives	• Rifampin		
Second-generation cephalosporin	• Cefaclor • Cefotetan	• Cefoxitin • Cefprozil	• Cefuroxime
Sulfonamides	• Sulfadiazine	• Sulfamethoxazole-trimethoprim	
Tetracyclines	• Doxycycline	• Minocycline	• Tetracycline
Third-generation cephalosporins	• Cefdinir • Cefditoren • Cefixime	• Cefotaxime • Cefpodoxime • Ceftazidime	• Ceftibuten • Ceftriaxone
Urinary anti-infectives	• Fosfomycin • Nitrofurantoin • Trimethoprim	• Nitrofurantoin macrocrystals-monohydrate • Nitrofurantoin macrocrystals	

Comprehensive Diabetes Care (CDC) – HbA1c Control (<8.0)

Methodology: HEDIS®

Measure Description: The percentage of Members 18-75 years of age with diabetes (type 1 and type 2) who had the following:

- HbA1c Control (<8.0%) – This includes diabetics whose most recent HbA1c test during the measurement year (2018) has a value <8.0%.
  - The Member is not numerator compliant if the result for the most recent HbA1c test is ≥8.0% or is missing a result, or if an HbA1c test was not done during the measurement year (2018).
- The eligible population in this measure meets all of the following criteria:
  1. Members who are 18-75 years old as of December 31 of the measurement year (2018).
  2. Continuous enrollment in the measurement year (2018) with no more than one gap of up to 45 days during the measurement year.
  3. Members who meet any of the following criteria during the measurement year (2018) or the year prior to the measurement year (2017). Count services that occur over both years:
     - At least two outpatient visits, observation visits, ED visits or nonacute inpatient encounters on different dates of service, with a diagnosis of diabetes. Visit type need not be the same for the two visits.
     - At least one acute inpatient encounter with a diagnosis of diabetes.
     - Members who were dispensed insulin or hypoglycemics/ antihyperglycemics on an ambulatory basis during the measurement year (2018) or the year prior to the measurement year (2017).

CODES TO IDENTIFY HbA1c TESTS			
Service	**Code Type**	**Code**	**Code Description**
HbA1c Test (<7.0%)	CPT-CAT-II	3044F	Hg A1c Level Lt 7.0%
HbA1c Test	CPT	83036	Hemoglobin Glycated
HbA1c Test	CPT	83037	Hemoglobin; glycosylated (A1C) by device cleared by FDA for home use
HbA1c Test	CPT-CAT-II	3044F	Most recent hemoglobin A1c (HbA1c) level < 7.0%
HbA1c Test	CPT-CAT-II	3045F	Most recent hemoglobin A1c (HbA1c) level 7.0-9.0%
HbA1c Test	CPT-CAT-II	3046F	Most recent hemoglobin A1c (HbA1c) level > 9.0%
HbA1c Test	LOINC	17856-6	Hemoglobin A1c/hemoglobin.total In Blood By Hplc
HbA1c Test	LOINC	4548-4	Hemoglobin A1c/hemoglobin.total In Blood
HbA1c Test	LOINC	4549-2	Hemoglobin A1c/hemoglobin.total In Blood By Electrophoresis

- Members who meet any of the following criteria are excluded:
    1. Members in hospice
    2. Members who did not have a diagnosis of diabetes, in any setting, during the measurement year (2018) or the year prior to the measurement year (2017) and who had a diagnosis of gestational diabetes or steroid-induced diabetes, in any setting, during the measurement year (2018) or the year prior to the measurement year (2017)

Denominator: Members 18-75 years of age who meet all the criteria for eligible population.

Numerator: Members in the denominator who had the most recent HbA1c level <8 during the measurement year (2018).

Comprehensive Diabetes Care (CDC) – Eye Exam

Methodology: HEDIS®

Measure Description: The percentage of Members 18-75 years of age with diabetes (type 1 and type 2) who had the following:

- Eye Exam (retinal) performed – This includes diabetics who had one of the following:
  - A retinal or dilated eye exam by an eye care professional (optometrist or ophthalmologist) in the measurement year (2018)
  - A negative retinal or dilated eye exam (negative for retinopathy) by an eye care professional in the year prior to the measurement year (2018)
- The eligible population in this measure meets all of the following criteria:
  1. Members who were 18-75 years old as of December 31 of the measurement year (2018).
  2. Continuous enrollment in the measurement year (2018) with no more than one gap of up to 45 days during the measurement year.
  3. Members who meet any of the following criteria during the measurement year (2018) or the year prior to the measurement year (2017). Count services that occur over both years:
     - At least two outpatient visits, observation visits, ED visits or nonacute inpatient encounters on different dates of service, with a diagnosis of diabetes. Visit type need not be the same for the two visits.
     - At least one acute inpatient encounter with a diagnosis of diabetes.
     - Members who were dispensed insulin or hypoglycemics/ antihyperglycemics on an ambulatory basis during the measurement year (2018) or the year prior to the measurement year (2017).

CODES TO IDENTIFY EYE EXAMS			
Service	**Code Type**	**Code**	**Code Description**
Diabetic Retinal Screening	CPT	67028	Intravitreal Injection Of A Pharmacologic Agent (separate Procedure)
Diabetic Retinal Screening	CPT	67030	Discission Of Vitreous Strands (without Removal) Pars Plana Approach
Diabetic Retinal Screening	CPT	67031	Severing Of Vitreous Strands Vitreous Face Adhesions Sheets Membranes Or Opacities Laser Surgery (one Or More Stages)
Diabetic Retinal Screening	CPT	67036	Vitrectomy Mechanical Pars Plana Approach
Diabetic Retinal Screening	CPT	67039	Vitrectomy Mechanical Pars Plana Approach With Focal Endolaser Photocoagulation
Diabetic Retinal Screening	CPT	67040	Vitrectomy Mechanical Pars Plana Approach With Endolaser Panre Tinal Photocoagulation
Diabetic Retinal Screening	CPT	67041	Vitrectomy Mechanical Pars Plana Approach With Removal Of Preretinal Cellular Membrane (eg Macular Pucker)
Diabetic Retinal Screening	CPT	67042	Vitrectomy Mechanical Pars Plana Approach With Removal Of Internal Limiting Membrane Of Retina (eg For Repair Of Macular Hole
Diabetic Retinal Screening	CPT	67043	Vitrectomy mechanical pars plana approach, with removal of subretinal membrane (eg, Choroidal Neovascularization), includes, if performed, intraocular tamponade (ie, air, gas or silicone oil)
Diabetic Retinal Screening	CPT	67101	Repair Retinal Detachment, Incld Drainage Of Subretinal Fluid When Performed; Cryotherapy
Diabetic Retinal Screening	CPT	67105	Repair Retinal Detachment, Incld Drainage Of Subretinal Fluid When Performed; Photocoagulation
Diabetic Retinal Screening	CPT	67107	Repair Of retinal detachment scleral buckling (such as lamellar scleral dissection, Imbrication or encircling procedure), including, when performed, implant, cryotherapy, photocoagulation, and drainage of subretinal fluid
Diabetic Retinal Screening	CPT	67108	Repair Of Retinal Detachment With Vitrectomy Any Method With OR Without Air Or Gas Tamponade Focal Endolaser Photocoagulation
Diabetic Retinal Screening	CPT	67110	Repair Of Retinal Detachment By Injection Of Air Or Other Gas (e G Pneumatic Retinopexy)
Diabetic Retinal Screening	CPT	67112	Repair Of Retinal Detachment By Scleral Buckling Or Vitrectomy On Patient Having Previous Ipsilateral Retinal Detachment Repair
Diabetic Retinal Screening	CPT	67113	Repair Of Complex Retinal Detachment (eg, Proliferative Vitreoretinopathy Stage C-1 or greater, diabetic Traction Retinal Detachment, retinopathy of prematurity, retinal tear of greater than 90 degrees), with vitrectomy and membrane peeling, including, when performed, air, gas, or silicone oil tamponade, cryotherapy, endolaser photocoagulation, drainage of subretinal fluid, scleral buckling, and/or removal of lens
Diabetic Retinal Screening	CPT	67121	Removal Of Implanted Material Posterior Segment Intraocular

CODES TO IDENTIFY EYE EXAMS			
Service	**Code Type**	**Code**	**Code Description**
Diabetic Retinal Screening	CPT	67141	Prophylaxis Of Retinal Detachment (eg, retinal break lattice degeneration) without drainage, 1 or more sessions; cryotherapy, diathermy
Diabetic Retinal Screening	CPT	67145	Prophylaxis Of Retinal Detachment (eg, retinal break lattice degeneration) without drainage, 1 or more sessions; photocoagulation (laser or xenon arc)
Diabetic Retinal Screening	CPT	67208	Destruction Of Localized Lesion Of Retina (eg Macular Edema Tumors) One Or More Sessions Cryotherapy Diathermy
Diabetic Retinal Screening	CPT	67210	Destruction Of Localized Lesion Of Retina (eg Macular Edema Tumors) One Or More Sessions Photocoagulation
Diabetic Retinal Screening	CPT	67218	Destruction Of Localized Lesion Of Retina (eg Macular Edema Tumors) One Or More Sessions Radiation By Implantation Of Source
Diabetic Retinal Screening	CPT	67220	Destruction Of Localized Lesion Of Choroid (eg Choroidal Neovasc Ularization) Photocoagulation (eg Laser) One Or More Sessions
Diabetic Retinal Screening	CPT	67221	Destruction Of Localized Lesion Of Choroid (eg Choroidal Neovasc Ularization) Photodynamic Therapy (includes Intravenous Infusion
Diabetic Retinal Screening	CPT	67227	Destruction Of Extensive Or Progressive Retinopathy (eg Diabetic Retinopathy) One Or More Sessions Cryotherapy Diathermy
Diabetic Retinal Screening	CPT	67228	Destruction of extensive or progressive retinopathy (eg, Diabetic Retinopathy), 1 or more sessions; Photocoagulation
Diabetic Retinal Screening	CPT	92002	Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program; Intermediate, new patient
Diabetic Retinal Screening	CPT	92004	Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program; comprehensive, new patient, 1 or more visits
Diabetic Retinal Screening	CPT	92012	Ophthalmological services: medical examination and evaluation with initiation or continuation of diagnostic and treatment program; intermediate, established patient
Diabetic Retinal Screening	CPT	92014	Ophthalmological services: medical examination and evaluation with initiation or continuation of diagnostic and treatment program; comprehensive, established patient, 1 or more visits
Diabetic Retinal Screening	CPT	92018	Ophthalmological examination and evaluation under general anesthesia with or without manipulation of globe for passive range of motion or other manipulation to facilitate diagnostic examination; complete
Diabetic Retinal Screening	CPT	92019	Ophthalmological examination and evaluation under general anesthesia with or without manipulation of globe for passive range of motion or other manipulation to facilitate diagnostic examination; limited
Diabetic Retinal Screening	CPT	92134	Scanning computerized ophthalmic diagnostic imaging posterior segment, with interpretation and report, unilateral or bilateral: optic nerve
Diabetic Retinal Screening	CPT	92225	Ophthalmoscopy extended with retinal drawing (eg, for retinal detachment melanoma), with Interpretation and report; initial

CODES TO IDENTIFY EYE EXAMS			
Service	**Code Type**	**Code**	**Code Description**
Diabetic Retinal Screening	CPT	92226	Ophthalmoscopy Extended With Retinal Drawing (eg For Retinal Detachment Melanoma) With Interpretation And Report Subsequent
Diabetic Retinal Screening	CPT	92227	Remote imaging for detection of retinal disease (eg, Retinopathy in a patient with diabetes) with analysis and report under Physician supervision, unilateral or bilateral
Diabetic Retinal Screening	CPT	92228	Remote imaging for monitoring and management of active retinal disease (eg, Diabetic Retinopathy) with Physician review, interpretation and report, unilateral or bilateral
Diabetic Retinal Screening	CPT	92230	Fluorescein Angioscopy With Interpretation And Report
Diabetic Retinal Screening	CPT	92235	Fluorescein Angiography (includes Multiframe Imaging) With Interpretation And Report (unilateral Or Bilateral)
Diabetic Retinal Screening	CPT	92240	Indocyanine-green Angiography (includes Multiframe Imaging) With Interpretation And Report (unilateral Or Bilateral)
Diabetic Retinal Screening	CPT	92250	Fundus Photography With Interpretation And Report
Diabetic Retinal Screening	CPT	92260	Ophthalmodynamometry
Diabetic Retinal Screening	CPT	99203	Office or other patient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history: A detailed exam: Medical decision making of low complexity.
Diabetic Retinal Screening	CPT	99204	Office or other patient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history: A comprehensive exam: Medical decision making of moderate complexity.
Diabetic Retinal Screening	CPT	99205	Office or other patient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history: A comprehensive exam: Medical decision making of high complexity.
Diabetic Retinal Screening	CPT	99213	Office or other patient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 components: An expanded problem focused history: An expanded problem focused examination: Medical decision making of low complexity.
Diabetic Retinal Screening	CPT	99214	Office or other patient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 components: A detailed history: A detailed exam: Medical decision making of moderate complexity.
Diabetic Retinal Screening	CPT	99215	Office or other patient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 components: A comprehensive history: A comprehensive exam: Medical decision making of high complexity.

CODES TO IDENTIFY EYE EXAMS			
Service	**Code Type**	**Code**	**Code Description**
Diabetic Retinal Screening	CPT	99242	Office consultation for a new or established patient which requires these 3 key components: An expanded problem focused history: An expanded problem focused examination: and, Straightforward medical decision making.
Diabetic Retinal Screening	CPT	99243	Office consultation for a new or established patient which requires these 3 key components: A detailed history: A detailed exam: and, Medical decision making of low complexity.
Diabetic Retinal Screening	CPT	99244	Office consultation for a new or established patient which requires these 3 key components: A comprehensive history: A comprehensive examination: and, Medical decision making of moderate complexity.
Diabetic Retinal Screening	CPT	99245	Office consultation for a new or established patient which requires these 3 key components: A comprehensive history: A comprehensive examination: and, Medical decision making of high complexity.
Diabetic Retinal Screening	HCPCS	S0620	Routine Ophthalmological Examination Including Refraction; New Patient (s0620)
Diabetic Retinal Screening	HCPCS	S0621	Routine Ophthalmological Examination Including Refraction; Established Patient (s0621)
Diabetic Retinal Screening	HCPCS	S3000	Diabetic Indicator; Retinal Eye Exam, Dilated, Bilateral (s3000)

- Members who meet any of the following criteria are excluded:
    1. Members in hospice
    2. Members who did not have a diagnosis of diabetes, in any setting, during the measurement year (2018) or the year prior to the measurement year (2017) and who had a diagnosis of gestational diabetes or steroid-induced diabetes, in any setting, during the measurement year or the year prior to the measurement year

Denominator: Members 18-75 years of age who meet all the criteria for eligible population.

Numerator: Members in the denominator who had an eye exam during the measurement year (2018).

Medication Management for People with Asthma – 75% rate (MMA)

Methodology: HEDIS®

Measure Description: The percentage of Members 5–64 years of age during the measurement year (2018) who were identified as having persistent asthma and were dispensed appropriate medications which they remained on for at least 75 percent of their treatment period. (Treatment Period: The period of time beginning on the Index Prescription Start Date through December 31, 2018.)

- Eligible population in this measure meets all of the following criteria:
  1. Age 5- 64 as of December 31 of the measurement year (2018).
  2. Continuous enrollment during the measurement year (2018) and the year prior to the measurement year (2017) with no more than one gap in enrollment of up to 45 days during each year of continuous enrollment.
  3. Members had a) At least one ED visit with a principal diagnosis of asthma, OR b) At least one acute inpatient encounter with a principal diagnosis of asthma, OR c) At least four outpatient visits or observation visits on different dates of service, with any diagnosis of asthma and at least two asthma medication dispensing events for any controller medication or reliever medication. Visit type need not be the same for the four visits, OR d) At least four asthma medication dispensing events for any controller medication or reliever medication.

ASTHMA CONTROLLER MEDICATIONS:			
Description	**Prescription**		
Antiasthmatic combinations	• Dyphylline-guaifenesin	• Guaifenesin-theophylline	
Antibody inhibitors	• Omalizumab		
Anti-interleukin-5	• Mepolizumab	• Reslizumab	
Inhaled steroid combinations	• Budesonide-formoterol • Fluticasone-salmeterol	• Fluticasone-vilanterol • Mometasone-formoterol	
Inhaled corticosteroids	• Beclomethasone • Budesonide • Ciclesonide	• Flunisolide • Fluticasone CFC free • Mometasone	
Leukotriene modifiers	• Montelukast	• Zafirlukast	• Zileuton
Mast cell stabilizers	• Cromolyn		
Methylxanthines	• Dyphylline	• Theophylline	

ASTHMA RELIEVER MEDICATIONS			
Description	**Prescriptions**		
Short-acting, inhaled beta-2 agonists	• Albuterol	• Levalbuterol	• Pirbuterol

- Members who meet any of the following criteria are excluded:
    1. Members who had no asthma controller medications dispensed during the measurement year (2018).
    2. Members in hospice are excluded.
    3. Members with the following diagnosis any time during the Member's history through December 31 of the measurement year (2018) are excluded: COPD, Acute Respiratory Failure, Cystic Fibrosis, Chronic respiratory conditions and Emphysema.

Denominator: Members 5–64 years of age during the measurement year (2018) who were identified as having persistent asthma and were dispensed appropriate medications which they remained on during the treatment period.

Numerator: Members in denominator who remained on an asthma controller medication for at least 75 percent of their treatment period.

Population: Adult and Adolescent

Screening for Clinical Depression in Primary Care

Methodology: IEHP-defined Quality Metric – Modified from PQRS measure (NQF 0418)

Measure Description: The percentage of Members aged 12 years and older screened for clinical depression on the date of the encounter using an age appropriate standardized depression screening tool during the measurement year (2018).

Denominator: All Members aged 12 years and older with a PCP visit in the measurement year (2018). Member counted only once in the denominator.

PRIMARY CARE PROVIDER VISIT CODES:			
Service	**Code Type**	**Code**	**Code Description**
Screening for Clinical Depression in Primary Care	CPT	99201	Office or other outpatient visit for the evaluation and management of a new patient which requires these three key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Typically, 10 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99202	Office or other outpatient visit for the evaluation and management of a new patient which requires these three key components: An expanded problem focused history; An expanded problem focused examination; Straightforward medical decision making. Typically, 20 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99203	Office or other outpatient visit for the evaluation and management of a new patient which requires these three key components: A detailed history; A detailed examination; Medical decision making of low complexity. Typically, 30 minutes are spent face-to- face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99204	Office or other outpatient visit for the evaluation and management of a new patient which requires these three key components: A comprehensive history; A comprehensive examination; Medical decision making of moderate complexity. Typically, 45 minutes are spent face-to-face with the patient and/or family.

PRIMARY CARE PROVIDER VISIT CODES:			
Service	**Code Type**	**Code**	**Code Description**
Screening for Clinical Depression in Primary Care	CPT	99205	Office or other outpatient visit for the evaluation and management of a new patient which requires these three key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Typically, 60 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99212	Office or other outpatient visit for the evaluation and management of an established patient which requires at least two of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Typically, 10 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99213	Office or other outpatient visit for the evaluation and management of an established patient which requires at least two of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity. Typically, 15 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99214	Office or other outpatient visit for the evaluation and management of an established patient which requires at least two of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Typically, 25 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	CPT	99215	Office or other outpatient visit for the evaluation and management of an established patient which requires at least two of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Typically, 40 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	HCPCS	G0101	Office or other outpatient visit for the evaluation and management of an established patient which requires at least two of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Typically, 40 minutes are spent face-to-face with the patient and/or family.
Screening for Clinical Depression in Primary Care	HCPCS	G0402	Initial preventive physical examination face-to-face visits services limited to new beneficiary during the first 12 months
Screening for Clinical Depression in Primary Care	HCPCS	G0438	Annual wellness visit includes a personalized prevention plan of service (pps) initial visit
Screening for Clinical Depression in Primary Care	HCPCS	G0439	Annual wellness visit includes a personalized prevention plan of service (pps) subsequent visit

PRIMARY CARE PROVIDER VISIT CODES:			
Service	**Code Type**	**Code**	**Code Description**
Screening for Clinical Depression in Primary Care	HCPCS	G0444	Annual depression screening 15 minutes
Screening for Clinical Depression in Primary Care	CPT	97003	Occupational therapy evaluation

Numerator: Members screened for clinical depression on the date of the encounter using an age appropriate standardized tool during the measurement year (2018).

CODES TO IDENTIFY SCREENING FOR CLINICAL DEPRESSION			
Service	**Code Type**	**Code**	**Code Description**
Screening for Clinical Depression in Primary Care	CPT	1220F	Patient screened for depression (sud)
Screening for Clinical Depression in Primary Care	CPT	3351F	Negative screen for depressive symptoms as categorized by using a standardized depression screening/ assessment tool (mdd)
Screening for Clinical Depression in Primary Care	CPT	3352F	No significant depressive symptoms as categorized by using a stan dardized depression assessment tool (mdd)
Screening for Clinical Depression in Primary Care	CPT	3353F	Mild to moderate depressive symptoms as categorized by using a standardized depression screening/ assessment tool (mdd)
Screening for Clinical Depression in Primary Care	CPT	3354F	Clinically significant depressive symptoms as categorized by usin g a standardized depression screening/assessment tool (mdd)
Screening for Clinical Depression in Primary Care	CPT	3725F	Screening for depression performed (dem)
Screening for Clinical Depression in Primary Care	HCPCS	G0444	Annual depression screening 15 minutes
Screening for Clinical Depression in Primary Care	HCPCS	G8431	Positive screen for clinical depression using a standardized tool and a follow-up plan documented
Screening for Clinical Depression in Primary Care	HCPCS	G8433	Screening for clinical depression using a standardized tool not documented patient not eligible/appropriate
Screening for Clinical Depression in Primary Care	HCPCS	G8510	Negative screen for clinical depression using a standardized tool patient not eligible/appropriate for follow-up plan documented
Screening for Clinical Depression in Primary Care	HCPCS	G8511	Screen for clinical depression using a standardize tool documented follow up plan not documented reason not specified
Screening for Clinical Depression in Primary Care	HCPCS	G8940	Screening for clinical depression documented follow-up plan not documented patient not eligible/ appropriate

Definitions:

Screening – Completion of a clinical or diagnostic tool used to identify people at risk of developing or having a certain disease or condition, even in the absence of symptoms.

Standardized Depression Screening Tool – A normalized and validated depression screening tool developed for the Member population in which it is being utilized. The name of the age appropriate standardized depression screening tool utilized must be documented in the medical record.

Examples of depression screening tools include but are not limited to:

- **Adolescent Screening Tools (12-17 years):** Patient Health Questionnaire for Adolescents (PHQ-A), Beck Depression Inventory-Primary Care Version (BDI-PC), Mood Feeling Questionnaire (MFQ), Center for Epidemiologic Studies Depression Scale (CES-D), and PRIME MD-PHQ2
- **Adult Screening Tools (18 years and older):** Patient Health Questionnaire (PHQ-9 or PHQ-2), Beck Depression Inventory (BDI or BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Depression Scale (DEPS), Duke Anxiety-Depression Scale (DADS), Geriatric Depression Scale (GDS), Cornell Scale Screening, and PRIME MD-PHQ2

Positive Depression Screening with Follow Up Plan

Methodology: IEHP-defined Quality Metric – Modified from PQRS measure (NQF 0418)

Measure Description: The percentage of Members aged 12 years and older who screened positive for clinical depression using an age appropriate standardized depression screening tool who also have a follow-up plan documented during the measurement year (2018).

Denominator: All Members aged 12 years and older with a PCP visit with a positive depression screening in the measurement year (2018). Member counted only once in the denominator.

CODES TO IDENTIFY POSITIVE DEPRESSION SCREENING DURING A PRIMARY CARE PROVIDER VISIT:			
Service	**Code Type**	**Code**	**Code Description**
Positive Depression Screening with Follow Up Plan	CPT	3353F	Mild to moderate depressive symptoms as categorized by using a standardized depression screening/assessment tool (mdd)
Positive Depression Screening with Follow Up Plan	CPT	3354F	Clinically significant depressive symptoms as categorized by using a standardized depression screening/assessment tool (mdd)
Positive Depression Screening with Follow Up Plan	HCPCS	G8431	Positive screen for clinical depression using a standardized tool and a follow-up plan documented
Positive Depression Screening with Follow Up Plan	HCPCS	G8511	Screen for clinical depression using a standardize tool documented follow up plan not documented reason not specified
Positive Depression Screening with Follow Up Plan	HCPCS	G8940	Screening for clinical depression documented follow-up plan not documented patient not eligible/ appropriate

Numerator: Members screened positive for clinical depression with a follow-up plan documented during the measurement year (2018).

CODES TO IDENTIFY POSITIVE DEPRESSION SCREENING WITH FOLLOW-UP PLAN			
Service	**Code Type**	**Code**	**Code Description**
Positive Depression Screening with Follow Up Plan	CPT	0545F	Plan for follow-up care for major depressive disorder documented (mdd adol)
Positive Depression Screening with Follow Up Plan	HCPCS	G8431	Positive screen for clinical depression using a standardized tool and a follow-up plan documented
Positive Depression Screening with Follow Up Plan	HCPCS	G8940	Screening for clinical depression documented follow-up plan not documented patient not eligible/ appropriate

Definitions:

Follow-Up Plan – Documented follow-up for a positive depression screening ***must*** include one or more of the following:

- Additional evaluation for depression
- Suicide Risk Assessment
- Referral to a practitioner who is qualified to diagnose and treat depression
- Pharmacological interventions
- Other interventions or follow-up for the diagnosis or treatment of depression

Population: Women

Breast Cancer Screening (BCS)

Methodology: HEDIS®

Measure Description: The percentage of women 50–74 years of age who had a mammogram to screen for breast cancer any time on or between October 1 two years prior to the measurement year (2016) and December 31 of the measurement year (2018).

- The eligible population in the measure meets all of the following criteria:
  1. Women 52-74 years as of December 31 of the measurement year (2018).
  2. Continuous enrollment from October 1 two years prior to the measurement year (2016) through December 31 of the measurement year (2018) with no more than one gap in enrollment of up to 45 days for each calendar year of continuous enrolment. No gaps in enrollment are allowed from October 1 two years prior to the measurement year (2016) through December 31 two years prior to the measurement year (2016).

CODES USED TO IDENTIFY MAMMOGRAPHY:			
Service	**Code Type**	**Code**	**Code Description**
Breast Cancer Screening	CPT	77055	Mammography Unilateral
Breast Cancer Screening	CPT	77056	Mammography Bilateral
Breast Cancer Screening	CPT	77057	Screening Mammography Bilateral (2-view Film Study Of Each Breast)
Breast Cancer Screening	CPT	77061	Digital Breast Tomosynthesis Unilateral
Breast Cancer Screening	CPT	77062	Digital Breast Tomosynthesis Bilateral
Breast Cancer Screening	CPT	77063	Screening Digital Breast Tomosynthesis Bilateral (list Separately In Addition To Code For Primary Procedure)
Breast Cancer Screening	CPT	77065	Diagnostic Mammography W/computer-aided Detection; Unilateral
Breast Cancer Screening	CPT	77066	Diagnostic Mammography W/computer-aided Detection; Bilateral
Breast Cancer Screening	CPT	77067	Screening Mammography Bilateral (2-view Film Study Of Each Breast Including Computer-aided Detection (cad)
Breast Cancer Screening	HCPCS	G0202	Screening Mammography, Bilateral (2-view Study Of Each Breast), Including Computer-aided Detection (cad) When Performed (g0202)
Breast Cancer Screening	HCPCS	G0204	Diagnostic Mammography, Including Computer-aided Detection (cad) When Performed; Bilateral (g0204)
Breast Cancer Screening	HCPCS	G0206	Diagnostic Mammography, Including Computer-aided Detection (cad) When Performed; Unilateral (g0206)

- Members who meet any of the following criteria are excluded:
    1. Members who have had a bilateral mastectomy anytime during their history through December 31, 2018 may be excluded.

       To exclude Members who meet the exclusion criteria, please complete Member Historical Data Form and fax to IEHP's Quality Informatics Team at: 909-477-8568.

       A copy of the Historical Data Form is available in Appendix 3.

    2. Members in hospice are excluded.

Denominator: Women 52-74 years of age who met the criteria for eligible population.

Numerator: Members in denominator who had one or more mammograms any time on or between October 1 two years prior to the measurement year (2016) and December 31 of the measurement year (2018).

Cervical Cancer Screening (CCS)

Methodology: HEDIS®

Measure Description: The percentage of Women 21–64 years of age who were screened for cervical cancer using either of the following criteria:

- Women age 21–64 who had cervical cytology performed every 3 years.
- Women age 30–64 who had cervical cytology/human papillomavirus (HPV) co-testing performed every 5 years.
- The eligible population in the measure meets all of the following criteria:
    1. Women 24-64 years as of December 31 of the measurement year (2018).
    2. Continuous enrollment during the measurement year (2018) with no more than one gap in enrollment of up to 45 days.

CODES TO IDENTIFY CERVICAL CYTOLOGY:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	CPT	88141	Cytopathology Cervical Or Vaginal (any Reporting System) Requiring Interpretation By Physician (List separately In addition to code for technical service.)
Cervical Cancer Screening	CPT	88142	Cytopathology Cervical Or Vaginal (any Reporting System) Collected In Preservative Fluid Automated Thin Layer Preparation Manual screening Under Physician Supervision

CODES TO IDENTIFY CERVICAL CYTOLOGY:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	CPT	88143	Cytopathology Cervical Or Vaginal (any Reporting System) Collec Ted In Preservative Fluid Automated Thin Layer Preparation; manual screening Under Physician Supervision: With manual screening and rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88147	Cytopathology Smears Cervical Or Vaginal Screening By Automated System Under Physician Supervision
Cervical Cancer Screening	CPT	88148	Cytopathology Smears Cervical Or Vaginal Screening By Automated System With Manual Rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88150	Cytopathology Slides Cervical Or Vaginal Manual Screening Under Physician Supervision
Cervical Cancer Screening	CPT	88152	Cytopathology Slides Cervical Or Vaginal With Manual Screening And Computer-assisted Rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88153	Cytopathology Slides Cervical Or Vaginal With Manual Screening And Rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88154	Cytopathology Slides Cervical Or Vaginal With Manual Screening And Computer-assisted Rescreening Using Cell Selection And Review Under Physician Supervision
Cervical Cancer Screening	CPT	88164	Cytopathology Slides Cervical Or Vaginal (the Bethesda System) Manual Screening Under Physician Supervision
Cervical Cancer Screening	CPT	88165	Cytopathology Slides Cervical Or Vaginal (the Bethesda System) With Manual Screening And Rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88166	Cytopathology Slides Cervical Or Vaginal (the Bethesda System) With Manual Screening And Computer-assisted Rescreening Under Physician Supervision
Cervical Cancer Screening	CPT	88167	Cytopathology Slides Cervical Or Vaginal (the Bethesda System) With Manual Screening And Computer-assisted Rescreening Using cell selection and review Under Physician Supervision
Cervical Cancer Screening	CPT	88174	Cytopathology Cervical Or Vaginal (any Reporting System) Collected In Preservative Fluid Automated Thin Layer Preparation
Cervical Cancer Screening	CPT	88175	Cytopathology Cervical Or Vaginal (any Reporting System) Collected In Preservative Fluid Screening Automated By System
Cervical Cancer Screening	HCPCS	G0123	Screening Cytopathology, Cervical Or Vaginal (any Reporting System), Collected In Preservative Fluid, Automated Thin Layer Preparation, Screening By Cytotechnologist Under Physician Supervision (g0123)
Cervical Cancer Screening	HCPCS	G0124	Screening Cytopathology, Cervical Or Vaginal (any Reporting System), Collected In Preservative Fluid, Automated Thin Layer Preparation, Requiring Interpretation By Physician (g0124)

CODES TO IDENTIFY CERVICAL CYTOLOGY:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	HCPCS	G0141	Screening Cytopathology Smears, Cervical Or Vaginal, Performed By Automated System, With Manual Rescreening, Requiring Interpretation By Physician (g0141)
Cervical Cancer Screening	HCPCS	G0143	Screening Cytopathology, Cervical Or Vaginal (any Reporting System), Collected In Preservative Fluid, Automated Thin Layer Preparation, With Manual Screening And Rescreening By Cytotechnologist Under Physician Supervision (g0143)
Cervical Cancer Screening	HCPCS	G0144	Screening Cytopathology, Cervical Or Vaginal (any Reporting System), Collected In Preservative Fluid, Automated Thin Layer Preparation, With Screening By Automated System, Under Physician Supervision (g0144)
Cervical Cancer Screening	HCPCS	G0145	Screening Cytopathology, Cervical Or Vaginal (any Reporting System), Collected In Preservative Fluid, Automated Thin Layer Preparation, With Screening By Automated System And Manual Rescreening Under Physician Supervision (g0145)
Cervical Cancer Screening	HCPCS	G0147	Screening Cytopathology Smears, Cervical Or Vaginal, Performed By Automated System Under Physician Supervision (g0147)
Cervical Cancer Screening	HCPCS	G0148	Screening Cytopathology Smears, Cervical Or Vaginal, Performed By Automated System With Manual Rescreening (g0148)
Cervical Cancer Screening	HCPCS	P3000	Screening Papanicolaou Smear, Cervical Or Vaginal, Up To Three Smears, By Technician Under Physician Supervision (p3000)
Cervical Cancer Screening	HCPCS	P3001	Screening Papanicolaou Smear, Cervical Or Vaginal, Up To Three Smears, Requiring Interpretation By Physician (p3001)
Cervical Cancer Screening	HCPCS	Q0091	Screening Papanicolaou Smear; Obtaining, Preparing And Conveyance Of Cervical Or Vaginal Smear To Laboratory (q0091)
Cervical Cancer Screening	LOINC	10524-7	Microscopic Observation [identifier] In Cervix By Cyto Stain
Cervical Cancer Screening	LOINC	18500-9	Microscopic Observation [identifier] In Cervix By Cyto Stain Thinprep
Cervical Cancer Screening	LOINC	19762-4	General Categories [interpretation] Of Cervical Or Vaginal Smear Or Scraping By Cyto Stain
Cervical Cancer Screening	LOINC	19764-0	Statement Of Adequacy [interpretation] Of Cervical Or Vaginal Smear Or Scraping By Cyto Stain
Cervical Cancer Screening	LOINC	19765-7	Microscopic Observation [identifier] In Cervical Or Vaginal Smear Or Scraping By Cyto Stain
Cervical Cancer Screening	LOINC	19766-5	Microscopic Observation [identifier] In Cervical Or Vaginal Smear Or Scraping By Cyto Stain Narrative
Cervical Cancer Screening	LOINC	19774-9	Cytology Study Comment Cervical Or Vaginal Smear Or Scraping Cyto Stain

CODES TO IDENTIFY CERVICAL CYTOLOGY:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	LOINC	33717-0	Cytology Cervical Or Vaginal Smear Or Scraping Study
Cervical Cancer Screening	LOINC	47527-7	Cytology Report Of Cervical Or Vaginal Smear Or Scraping Cyto Stain.thin Prep
Cervical Cancer Screening	LOINC	47528-5	Cytology Report Of Cervical Or Vaginal Smear Or Scraping Cyto Stain

CODES TO IDENTIFY HPV TESTS:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	CPT	87620	Infectious Agent Detection By Nucleic Acid (dna Or Rna) Papillom Avirus Human Direct Probe Technique
Cervical Cancer Screening	CPT	87621	Infectious Agent Detection By Nucleic Acid (dna Or Rna) Papillom Avirus Human Amplified Probe Technique
Cervical Cancer Screening	CPT	87622	Infectious Agent Detection By Nucleic Acid (dna Or Rna) Papillom Avirus Human Quantification
Cervical Cancer Screening	CPT	87624	Infectious Agent Detection By Nucleic Acid (dna Or Rna) Human Pap Illomavirus (hpv) High-risk Types (eg 16 18 31 33 35 39 45 51 52 56 58 59 68)
Cervical Cancer Screening	CPT	87625	Infectious Agent Detection By Nucleic Acid (dna Or Rna) Human Pap Illomavirus (hpv) Types 16 And 18 Only Includes Type 45, If Performed
Cervical Cancer Screening	HCPCS	G0476	Infectious Agent Detection By Nucleic Acid (dna Or Rna); Human Papillomavirus (hpv), High-risk Types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) For Cervical Cancer Screening, Must Be Performed In Addition To Pap Test (g0476)
Cervical Cancer Screening	LOINC	21440-3	Human Papilloma Virus 16+18+31+33+35+45+51+52+56 Dna [presence] In Cervix By Dna Probe
Cervical Cancer Screening	LOINC	30167-1	Human Papilloma Virus 16+18+31+33+35+39+45+51+52+56+58+59+68 Dna [presence] In Cervix By Probe And Signal Amplification Method
Cervical Cancer Screening	LOINC	38372-9	Human Papilloma Virus 6+11+16+18+31+33+35+39+42+43+44+45+51+52+56+58+59+68 Dna [presence] In Cervix By Probe And Signal Amplification Method
Cervical Cancer Screening	LOINC	59263-4	Human Papilloma Virus 16 Dna [presence] In Cervix By Probe And Signal Amplification Method
Cervical Cancer Screening	LOINC	59264-2	Human Papilloma Virus 18 Dna [presence] In Cervix By Probe And Signal Amplification Method
Cervical Cancer Screening	LOINC	59420-0	Human Papilloma Virus 16+18+31+33+35+39+45+51+52+56+58+59+66+68 Dna [presence] In Cervix By Probe And Signal Amplification Method
Cervical Cancer Screening	LOINC	69002-4	Human Papilloma Virus E6+e7 Mrna [presence] In Cervix By Probe And Target Amplification Method

CODES TO IDENTIFY HPV TESTS:			
Service	**Code Type**	**Code**	**Code Description**
Cervical Cancer Screening	LOINC	71431-1	Human Papilloma Virus 31+33+35+39+45+51+52+56+58 +59+66+68 Dna [presence] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	75694-0	Human Papilloma Virus 18+45 E6+e7 Mrna [presence] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	77379-6	Human Papiloma Virus 16 And 18 And 31+33+35+39+45+51+52+56+58+59+66+68 Dna [interpretation] In Cervix
Cervical Cancer Screening	LOINC	77399-4	Human Papilloma Virus 16 Dna [presence] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	77400-0	Human Papilloma Virus 18 Dna [presence] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	82354-2	Human Papilloma Virus 16 And 18+45 E6+e7 Mrna [identifier] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	82456-5	Human Papilloma Virus 16 E6+e7 Mrna [presence] In Cervix By Probe And Target Amplification Method
Cervical Cancer Screening	LOINC	82675-0	Human Papilloma Virus 16+18+31+33+35+39+45+51+52+56 +58+59+66+68 Dna [presence] In Cervix By Probe And Target Amplification Method

- Members who meet any of the following criteria are excluded:
    1. Members who have had a hysterectomy with no residual cervix, cervical agenesis or acquired absence of cervix any time during their history through December 31, 2018 may be excluded.

       To exclude Members who meet the exclusion criteria, please complete the Member Historical Data Form and fax to IEHP's Quality Informatics Team at: 909-477-8568.

       A copy of the Historical Data Form is available in Appendix 3.
    2. Members in hospice are excluded.

Denominator: Women 24-64 years of age who met the criteria for eligible population.

Numerator: Women in the denominator who received a timely screen for cervical cancer.

Timeliness of Prenatal Care (PPC)

Methodology: HEDIS®

Measure Description: The percentage of deliveries of live births on or between November 6, 2017 and November 5, 2018 that received a prenatal care visit as a Member of the organization in the first trimester, on the enrollment start date or within 42 days of enrollment in the organization.

- The eligible population in this measure meets all of the following criteria:
    1. Continuous enrollment 43 days prior to delivery through 56 days after delivery with no allowable gap.
    2. Members who delivered a live birth on or between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018). This includes women who delivered in any setting. Women who had two separate deliveries (different dates of service) between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018) count twice. Women who had multiple live births during one pregnancy count once.

CODES TO IDENTIFY STAND ALONE PRENATAL VISITS:			
Service	**Code Type**	**Code**	**Code Description**
Prenatal Visit	CPT	0500F	Initial Prenatal Care Visit
Prenatal Visit	CPT	0501F	Prenatal Flow Sheet
Prenatal Visit	CPT	0502F	Subsequent Prenatal Care Visit
Prenatal Visit	CPT	99500	Home Visit Prenatal
Prenatal Visit	HCPCS	H1000	Prenatal Care, At-risk Assessment
Prenatal Visit	HCPCS	H1001	Prenatal Care, At-risk Enhanced Service; Antepartum Management
Prenatal Visit	HCPCS	H1002	Prenatal Care, At Risk Enhanced Service; Care Coordination
Prenatal Visit	HCPCS	H1003	Prenatal Care, At-risk Enhanced Service; Education
Prenatal Visit	HCPCS	H1004	Prenatal Care, At-risk Enhanced Service; Follow-up Home Visit
Prenatal Visit	HCPCS	Z1032	Initial Antepartum Office Visit
Prenatal Visit	HCPCS	Z1034	Antepartum Follow-Up Visit

Prenatal care visit to an OB/GYN or other prenatal care practitioner or PCP. For visits to a PCP, a diagnosis of pregnancy must be present. Documentation in the medical record must include a note indicating the date when the prenatal care visit occurred, and evidence of one of the following.

- A basic physical obstetrical examination that includes auscultation for fetal heart tone, or pelvic exam with obstetric observations, or measurement of fundus height (a standardized prenatal flow sheet may be used).

- Evidence that a prenatal care procedure was performed, such as:
  - Screening test in the form of an obstetric panel (must include all of the following: hematocrit, differential WBC count, platelet count, hepatitis B surface antigen, rubella antibody, syphilis test, RBC antibody screen, Rh and ABO blood typing), OR
  - TORCH antibody panel alone, OR
  - A rubella antibody test/titer with an Rh incompatibility (ABO/Rh) blood typing, OR
  - Echography of a pregnant uterus.
- Documentation of LMP or EDD in conjunction with either of the following.
  - Prenatal risk assessment and counseling/education.
  - Complete obstetrical history.
- Members in hospice are excluded.

Denominator: Members who delivered a live birth on or between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018).

Numerator: Members in the denominator who had a prenatal care visit as a member of the organization in the first trimester, on the enrollment start date or within 42 days of enrollment in the organization.

Postpartum Care (PPC)

Methodology: HEDIS®

Measure Description: The percentage of deliveries of live births on or between November 6, 2017 and November 5, 2018 that had a postpartum visit on or between 21 and 56 days after delivery.

- The eligible population in this measure meets all of the following criteria:
  1. Continuous enrollment 43 days prior to delivery through 56 days after delivery with no allowable gap.
  2. Members who delivered a live birth on or between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018). This includes women who delivered in any setting. Women who had two separate deliveries (different dates of service) between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018) count twice. Women who had multiple live births during one pregnancy count once.

CODES TO IDENTIFY POSTPARTUM CARE:			
Service	**Code Type**	**Code**	**Code Description**
Postpartum Care	CPT	57170	Diaphragm Or Cervical Cap Fitting With Instructions
Postpartum Care	CPT	58300	Insertion Of Intrauterine Device (iud)
Postpartum Care	CPT	59430	Postpartum Care Only (separate Procedure)
Postpartum Care	CPT	99501	Home Visit Postnatal
Postpartum Care	CPT-CAT-II	0503F	Postpartum Care Visit
Postpartum Care	HCPCS	G0101	Cervical Or Vaginal Cancer Screening; Pelvic And Clinical Breast Examination (g0101)
Postpartum Care	ICD10CM	Z01.411	[z01.411] Encounter For Gynecological Examination (general) (routine) With Abnormal Findings
Postpartum Care	ICD10CM	Z01.419	[z01.419] Encounter For Gynecological Examination (general) (routine) Without Abnormal Findings
Postpartum Care	ICD10CM	Z01.42	[z01.42] Encounter For Cervical Smear To Confirm Findings Of Recent Normal Smear Following Initial Abnormal Smear
Postpartum Care	ICD10CM	Z30.430	[z30.430] Encounter For Insertion Of Intrauterine Contraceptive Device
Postpartum Care	ICD10CM	Z39.1	[z39.1] Encounter For Care And Examination Of Lactating Mother
Postpartum Care	ICD10CM	Z39.2	[z39.2] Encounter For Routine Postpartum Follow-up
Postpartum Care	HCPCS	Z1038	Postpartum Follow-Up Office Visit

- Members in hospice are excluded.

Denominator: Members who delivered a live birth on or between November 6 of the year prior to the measurement year (2017) and November 5 of the measurement year (2018).

Numerator: Members in the denominator who had a postpartum visit on or between 21 and 56 days after delivery.

Population: Child

Childhood Immunizations (CIS) – Combo 10

Methodology: HEDIS®

Measure Description: The percentage of children 2 years of age who had four diphtheria, tetanus and acellular pertussis (DTaP); three polio (IPV); one measles, mumps and rubella (MMR); three haemophilus influenza type B (HiB); three hepatitis B (HepB), one chicken pox (VZV); four pneumococcal conjugate (PCV); one hepatitis A (HepA); two or three rotavirus (RV); and two influenza (flu) vaccines by their second birthday. The measure calculates a rate for each vaccine and one combination rate.

- Combo 10 includes the timely completion of the following antigens:
  - DTaP; IPV; MMR; HiB; HepB; VZV; PCV; HepA; Rotavirus; Flu
- The eligible population in this measure meets all of the following criteria:
  1. Children who turn 2 years of age during the measurement year (2018).
  2. Continuous enrollment 12 months prior to the child's second birthday with no more than one gap in enrollment of up to 45 days during the 12 months prior to the child's second birthday.

CHILDHOOD IMMUNIZATION CODE SET:			
Antigen	**Code Type**	**Code**	**Code Description**
DTaP	CPT	90698	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine And Hemophilus Influenza B Vaccine And Activated Poliovirus Vaccine, (DTaP-IPV/Hib), For Intramuscular Use
DTaP	CPT	90700	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine (dta P) For Intramuscular Use
DTaP	CPT	90721	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine And Hemophilus Influenza B Vaccine (dtap-hib) For Intramuscular Use
DTaP	CPT	90723	Diphtheria Tetanus Toxoids Acellular Pertussis Vaccine Hepatitis B, and Inactivated poliovirus vaccine (dtap-hepb-ipv), For Intramuscular Use
IPV	CPT	90698	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine And Hemophilus Influenza B Vaccine and activated poliovirus vaccine, (DTaP-IPV/Hib), For Intramuscular Use
IPV	CPT	90713	Poliovirus Vaccine Inactivated (ipv) For Subcutaneous Use
IPV	CPT	90723	Diphtheria Tetanus Toxoids Acellular Pertussis Vaccine Hepatitis B, and Inactivated poliovirus vaccine (dtap-hepb-ipv), For Intramuscular Use
MMR	CPT	90707	Measles Mumps And Rubella Virus Vaccine (mmr) Live For Subcuta Neous Use

CHILDHOOD IMMUNIZATION CODE SET:			
Antigen	**Code Type**	**Code**	**Code Description**
MMR	CPT	90710	Measles Mumps Rubella And Varicella Vaccine (mmrv) Live For Subcutaneous Use
HiB	CPT	90644	Meningococcal Conjugate Vaccine, Serogroups C & Y And Hemophilus Influenzae Type B Vaccine (hib-mency), 4 dose schedule, When Administered to children 6 wks to 18 mos of age, For Intramuscular Use
HiB	CPT	90645	Hemophilus Influenza B Vaccine (hib) Hboc Conjugate (4 Dose Schedule) For Intramuscular Use
HiB	CPT	90646	Hemophilus Influenza B Vaccine (hib) Prp-d Conjugate For Booster Use Only Intramuscular Use
HiB	CPT	90647	Hemophilus Influenza B Vaccine (hib) Prp-omp Conjugate (3 Dose S Chedule) For Intramuscular Use
HiB	CPT	90648	Hemophilus Influenza B Vaccine (hib)prp-t Conjugate (4 Dose Sche Dule) For Intramuscular Use
HiB	CPT	90698	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine And Hemophilus Influenza B Vaccine and activated poliovirus vaccine, (DTaP-IPV/Hib), For Intramuscular Use
HiB	CPT	90721	Diphtheria Tetanus Toxoids And Acellular Pertussis Vaccine And Hemophilus Influenza B Vaccine (dtap-hib) For Intramuscular Use
HiB	CPT	90748	Hepatitis B And Hemophilus Influenza B Vaccine (hepb-hib) For Intramuscular Use
HepB	CPT	90723	Diphtheria Tetanus Toxoids Acellular Pertussis Vaccine Hepatitis B, and Inactivated poliovirus vaccine (dtap-hepb-ipv), For Intramuscular Use
HepB	CPT	90740	Hepatitis B Vaccine Dialysis Or Immunosuppressed Patient Dosage (3 Dose Schedule) For Intramuscular Use
HepB	CPT	90744	Hepatitis B Vaccine Pediatric/adolescent Dosage (3 Dose Schedule) For Intramuscular Use
HepB	CPT	90747	Hepatitis B Vaccine Dialysis Or Immunosuppressed Patient Dosage (4 Dose Schedule) For Intramuscular Use
HepB	CPT	90748	Hepatitis B And Hemophilus Influenza B Vaccine (hepb-hib) For Intramuscular Use
HepB	HCPCS	G0010	Administration Of Hepatitis B Vaccine (g0010)
VZV	CPT	90710	Measles Mumps Rubella And Varicella Vaccine (mmrv) Live For Subcutaneous Use
VZV	CPT	90716	Varicella Virus Vaccine Live For Subcutaneous Use
PCV	CPT	90669	Pneumococcal Conjugate Vaccine Polyvalent For Children Under Five Years For Intramuscular Use
PCV	CPT	90670	Pneumococcal Conjucate Vaccine 13 Valent For Intramuscular Use
PCV	HCPCS	G0009	Administration Of Pneumococcal Vaccine (g0009)
HepA	CPT	90633	Hepatitis A Vaccine Pediatric/adolescent Dosage-2 Dose Schedule For Intramuscular Use
Rotavirus - 2 Dose	CPT	90681	Rotavirus Vaccine Human Attenuated 2 Dose Schedule Live For Oral Use.

CHILDHOOD IMMUNIZATION CODE SET:			
Antigen	**Code Type**	**Code**	**Code Description**
Rotavirus - 3 Dose	CPT	90680	Rotavirus Vaccine Tetravalent Live For Oral Use
Flu	CPT	90655	Flu Virus Vaccine, Trivalent (iiv3), Split Virus, Preservative Free, 0.25ml Dosage, For Intramuscular Use
Flu	CPT	90657	Influenza Virus Vaccine Split Virus For Children 6-35 Months Of Age For Intramuscular Use
Flu	CPT	90661	Influenza Virus Vaccine Derived From Cell Cultures Subunit Preservative And Antibiotic Free For Intramuscular Use
Flu	CPT	90662	Influenza Virus Vaccine Split Virus Preservative Free Enhanced Immunogenicity Via Increased Antigen Content, For Intramuscular Use
Flu	CPT	90673	Influenza Virus Vaccine Trivalent Derived From Recombinant Dna (r Iv3) Hemagglutinin (ha) Protein Only Preservative And Antibiotic
Flu	CPT	90685	Influenza Virus Vaccine Quadrivalent (II4V) Split Virus preservative free, 0.25 ml dosage, For Intramuscular Use
Flu	CPT	90686	Influenza Virus Vaccine Quadrivalent (II4V) Split Virus preservative free, 0.5 ml dosage, For Intramuscular Use
Flu	CPT	90687	Influenza Virus Vaccine Quadrivalent (II4V) Split Virus, 0.25 ml dosage, For Intramuscular Use
Flu	CPT	90688	Influenza Virus Vaccine Quadrivalent (II4V) Split Virus, 0.5 ml dosage, For Intramuscular Use
Flu	HCPCS	G0008	Administration Of Influenza Virus Vaccine (g0008)

- Members who meet any of the following criteria are excluded:
    1. Members in hospice are excluded.
    2. Children who had a contraindication for a specific vaccine are excluded from the denominator for all antigen rates and the combination rates.

Denominator: Children 2 years of age in the eligible population.

Numerator: Members in denominator who show timely completion of all antigens in combo10.

Immunizations for Adolescents (IMA) – Combo 2

Methodology: HEDIS®

Measure Description: The percentage of adolescents 13 years of age who had one dose of meningococcal conjugate; vaccine, one tetanus, diphtheria toxoids and acellular pertussis (Tdap); vaccine and two or three doses of the human papillomavirus (HPV) vaccine on or before their 13th birthday. The measure calculates a rate for each vaccine and a combination rate.

- At least one dose of meningococcal conjugate vaccine on or between the Member's 11th and 13th birthdays.
- At least one tetanus, diphtheria toxoids and acellular pertussis (Tdap) vaccine on or between the Member's 10th and 13th birthdays.
- At least two HPV vaccines, with different dates of service on or between the Member's 9th and 13th birthdays.
  - There must be at least 146 days between the first and second dose of the HPV vaccine. For example, if the service date for the first vaccine was March 1, then the service date for the second vaccine must be after July 25.

    OR

    At least three HPV vaccines, with different dates of service on or between the Member's 9th and 13th birthdays.
- The eligible population in this measure meets all of the following criteria:
  1. Adolescents who turn 13 years of age during the measurement year (2018).
  2. Continuous enrollment 12 months prior to the member's 13th birthday with no more than one gap in enrollment of up to 45 days during the 12 months prior to the 13th birthday.

CODES TO IDENTIFY MENINGOCOCAL:			
Antigen	**Code Type**	**Code**	**Code Description**
Meningococcal conjugate	CPT	90734	Meningococcal Conjugate Vaccine Serogroups A, C, Y and W-135, quadrivalent (MCV4 or MenACWY), For Intramuscular Use

CODES TO IDENTIFY TDAP:			
Antigen	**Code Type**	**Code**	**Code Description**
Tdap	CPT	90715	Tetanus Diphtheria Toxoids And Acellular Pertussis Vaccine (Tdap) When Administered To Individuals 7 Years Or Older For Intramuscular Use

CODES TO IDENTIFY HPV:			
Antigen	**Code Type**	**Code**	**Code Description**
HPV	CPT	90649	Human Papilloma Virus (hpv) Vaccine Types 6 11 16 18 Quadrivalent (4vHPV), 2 or 3 Dose Schedule, For Intramuscular Use
HPV	CPT	90650	Human Papilloma Virus (hpv) Vaccine Types 16, 18 bivalent (2vHPV) 2 or 3 Dose Schedule, For Intramuscular Use
HPV	CPT	90651	Human Papilloma Virus Vaccine 6 11 16 18 31 33 45 52 58, nonavalent (9vHPV) 2 or 3 Dose Schedule, For Intramuscular Use

- Members who meet any of the following criteria are excluded:
    1. Members in hospice are excluded.
    2. Adolescents who had a contraindication for a specific vaccine are excluded from the denominator for all antigen rates and the combination rates.

Denominator: Adolescents 13 years of age who meet all the criteria for eligible population.

Numerator: Members in the denominator who had one dose of meningococcal conjugate vaccine, one tetanus, diphtheria toxoids and acellular pertussis (Tdap) vaccine, and have completed the human papillomavirus (HPV) vaccine series by their 13th birthday during the measurement year (2018).

Well-Child 3-6 Years of life (W34)

Methodology: HEDIS®

Measure Description: The percentage of Members 3–6 years of age who had one or more well-child visits with a PCP during the measurement year (2018).

- The eligible population in this measure meets all of the following criteria:
  1. Age 3-6 years as of December 31 of the measurement year (2018).
  2. Continuous enrollment in the measurement year (2018) with no more than one gap in enrollment of up to 45 days.

CODES TO IDENTIFY WELL-CHILD: (*NOTE: These codes must be provided by a Primary Care Provider in an office setting.*)			
Service	**Code Type**	**Code**	**Code Description**
Well-Child 3-6 Years of Life	CPT	99382	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient: early childhood (age 1 through 4 years)
Well-Child 3-6 Years of Life	CPT	99383	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient: late childhood (age 5 through 11 years)
Well-Child 3-6 Years of Life	CPT	99392	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; early childhood (age 1 through 4 years)
Well-Child 3-6 Years of Life	CPT	99393	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; late childhood (age 5 through 11 years)
Well-Child 3-6 Years of Life	HCPCS	G0438	Annual Wellness Visit; Includes A Personalized Prevention Plan Of Service (pps), Initial Visit (g0438)
Well-Child 3-6 Years of Life	HCPCS	G0439	Annual Wellness Visit, Includes A Personalized Prevention Plan Of Service (pps), Subsequent Visit (g0439)
Well-Child 3-6 Years of Life	ICD10CM	Z00.121	Encounter For Routine Child Health Examination With Abnormal Findings
Well-Child 3-6 Years of Life	ICD10CM	Z00.129	Encounter For Routine Child Health Examination Without Abnormal Findings
Well-Child 3-6 Years of Life	ICD10CM	Z00.5	Encounter For Examination Of Potential Donor Of Organ And Tissue

CODES TO IDENTIFY WELL-CHILD: (*NOTE: These codes must be provided by a Primary Care Provider in an office setting.*)			
Service	**Code Type**	**Code**	**Code Description**
Well-Child 3-6 Years of Life	ICD10CM	Z00.8	Encounter For Other General Examination
Well-Child 3-6 Years of Life	ICD10CM	Z02.0	Encounter For Examination For Admission To Educational Institution
Well-Child 3-6 Years of Life	ICD10CM	Z02.1	Encounter For Pre-employment Examination
Well-Child 3-6 Years of Life	ICD10CM	Z02.2	Encounter For Examination For Admission To Residential Institution
Well-Child 3-6 Years of Life	ICD10CM	Z02.5	Encounter For Examination For Participation In Sport
Well-Child 3-6 Years of Life	ICD10CM	Z02.6	Encounter For Examination For Insurance Purposes
Well-Child 3-6 Years of Life	ICD10CM	Z02.71	Encounter For Disability Determination
Well-Child 3-6 Years of Life	ICD10CM	Z02.79	Encounter For Issue Of Other Medical Certificate
Well-Child 3-6 Years of Life	ICD10CM	Z02.81	Encounter For Paternity Testing
Well-Child 3-6 Years of Life	ICD10CM	Z02.82	Encounter For Adoption Services
Well-Child 3-6 Years of Life	ICD10CM	Z02.83	Encounter For Blood-alcohol And Blood-drug Test
Well-Child 3-6 Years of Life	ICD10CM	Z02.89	Encounter For Other Administrative Examinations
Well-Child 3-6 Years of Life	ICD10CM	Z02.9	Encounter For Administrative Examinations, Unspecified

- Members in hospice are excluded.

Denominator: Members 3-6 years of age who meet all the criteria for eligible population.

Numerator: Members in the denominator who had at least one well-child visit with a PCP during the measurement year (2018).

The Well-Child visit must occur with a PCP, but the PCP does not have to be the practitioner assigned to the child.

Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents (WCC)

Methodology: HEDIS®

Measure Description: The percentage of Members 3–17 years of age who had an outpatient visit with a PCP or OB/GYN and who had evidence of the following during the measurement year (2018). Report each of the three indicators below.

- BMI percentile documentation*
- Counseling for nutrition
- Counseling for physical activity
- The eligible population in this measure meets all of the following criteria:
    1. Members who are 3-17 years of age as of December 31 of the measurement year (2018).
    2. Continuous enrollment in the measurement year (2018) with no more than one gap up to 45 days.
    3. An outpatient visit with a PCP or an OB/GYN during the measurement year (2018).

* Because BMI norms for youth vary with age and gender, this measure evaluates whether BMI percentile is assessed rather than an absolute BMI value.

CODES TO IDENTIFY BMI PERCENTILE:		
Code	**Code Type**	**Description**
Z68.51	ICD10	Body Mass Index (BMI) Pediatric, Less Than 5th Percentile For Age
Z68.52	ICD10	Body Mass Index (BMI) Pediatric, 5th Percentile To Less Than 85th Percentile For Age
Z68.53	ICD10	Body Mass Index (BMI) Pediatric, 85th Percentile To Less Than 95th Percentile For Age
Z68.54	ICD10	Body Mass Index (BMI) Pediatric, Greater Than Or Equal To 95th Percentile For Age

CODES TO IDENTIFY COUNSELING FOR PHYSICAL ACTIVITY:		
Code	**Code Type**	**Description**
G0447	HCPCS	Face-to-face Behavioral Counseling For Obesity, 15 Minutes
S9451	HCPCS	Exercise Classes, Non-Physician Provider, Per Session
Z02.5	ICD10	Encounter For Examination For Participation In Sport
Z71.82	ICD10	Exercise Counseling

CODES TO IDENTIFY COUNSELING FOR NUTRITION:		
Code	**Code Type**	**Description**
97802	CPT	Medical Nutrition Therapy Initial Assessment And Intervention Individual Face-to-face With The Patient Each 15 Minutes
97803	CPT	Medical Nutrition Therapy Re-assessment And Intervention Individual Face-to-face With The Patient Each 15 Minutes
97804	CPT	Medical Nutrition Therapy Group (2 Or More Individual(s)) Each 30 Minutes
G0270	HCPCS	Medical Nutrition Therapy; Reassessment And Subsequent Intervention(s) Following Second Referral In Same Year For Change In Diagnosis, Medical Condition Or Treatment Regimen (including Additional Hours Needed For Renal Disease), Individual, Face To Face
G0271	HCPCS	Medical Nutrition Therapy, Reassessment And Subsequent Intervention(s) Following Second Referral In Same Year For Change In Diagnosis, Medical Condition, Or Treatment Regimen (including Additional Hours Needed For Renal Disease), Group (2 Or More Individuals)
G0447	HCPCS	Face-to-face Behavioral Counseling For Obesity, 15 Minutes (G0447)
S9449	HCPCS	Weight Management Classes, Non-Physician Provider, Per Session (S9449)
S9452	HCPCS	Nutrition Classes, Non-Physician Provider, Per Session (S9452)
S9470	HCPCS	Nutritional Counseling, Dietitian Visit (S9470)
Z71.3	ICD10	Dietary Counseling And Surveillance

Members who meet any of the following criteria are excluded:

1. Members in hospice are excluded.
2. Female Members who have a diagnosis of pregnancy during the measurement year (2018) are excluded. A diagnosis of pregnancy will be determined using claims and encounter data only.

Denominator: Members 3-17 years of age who meet all the criteria for eligible population.

Numerator: Members in the denominator who had evidence of BMI, counseling of nutrition or physical activity during the measurement year (2018).

Population: All

Initial Health Assessment (IHA)

Methodology: IEHP-Defined Compliance Metric

Measure Description: The IHA is a comprehensive assessment that is completed during the Member's initial encounter with a PCP, appropriate medical specialist, or Non-Physician medical Provider and must be documented in the Member's medical record. The IHA enables the Member's PCP to assess and manage the acute, chronic and preventive health needs of the Member.

IEHP provides PCPs a monthly detailed Member roster on the IEHP Secure Provider Portal for all newly enrolled IEHP Members who are due for an IHA after 120 days of enrollment.

- The eligible population is newly assigned Members with an IEHP effective enrollment date of January 1, 2018 through December 31, 2018. The IHA must be provided within 120 days of enrollment (e.g., Member enrolled in December 2018 must be seen by April 2019 and PCP must submit encounter by May 2019)
- IHA visits completed during the 11 months prior to enrollment with IEHP count towards numerator compliance.

CODES TO IDENTIFY IHA VISITS:		
Code	**Code Type**	**Description**
99201	CPT	Office/Outpt E&M New Minor 10
99202	CPT	Office/Outpt E&M New Low-Mod
99203	CPT	Office/Outpt E&M New Mod Seve
99204	CPT	Office/Outpt E&M New Mod-Hi 4
99205	CPT	Office/Outpt E&M New Mod-Hi 6
99211	CPT	Office/Outpt E&M Estab 5 Min
99212	CPT	Office/Outpt E&M Estab Minor
99213	CPT	Office/Outpt E&M Estab Low-Mo
99214	CPT	Office/Outpt E&M Estab Mod-Hi
99215	CPT	Office/Outpt E&M Estab Mod-Hi
99241	CPT	Office Cons New/Estab Minor 1
99242	CPT	Office Cons New/Est Lo Sever
99243	CPT	Office Cons New/Estab Mod 40
99244	CPT	Office Cons New/Estab Mod-Hi
99245	CPT	Office Cons New/Estab Mod-Hi
99304	CPT	Nursing Facility Care Init
99305	CPT	Nursing Facility Care Init
99306	CPT	Nursing Facility Care Init
99307	CPT	Nursing Fac Care Subseq

CODES TO IDENTIFY IHA VISITS:		
Code	**Code Type**	**Description**
99308	CPT	Nursing Fac Care Subseq
99309	CPT	Nursing Fac Care Subseq
99310	CPT	Nursing Fac Care Subseq
99315	CPT	Nurs Facil D/C Da Mgmt; 30 M
99316	CPT	Nurs Facil D/C Da Mgmt; > 30
99318	CPT	Annual Nursing Fac Assessmnt
99324	CPT	Domicil/R-Home Visit New Pat
99325	CPT	Domicil/R-Home Visit New Pat
99326	CPT	Domicil/R-Home Visit New Pat
99327	CPT	Domicil/R-Home Visit New Pat
99328	CPT	Domicil/R-Home Visit New Pat
99334	CPT	Domicil/R-Home Visit Est Pat
99335	CPT	Domicil/R-Home Visit Est Pat
99336	CPT	Domicil/R-Home Visit Est Pat
99337	CPT	Domicil/R-Home Visit Est Pat
99341	CPT	Home Visit E&M New Pt Lo Sev
99342	CPT	Home Visit E&M New Pt Mod Se
99343	CPT	Home Visit E&M New Pt Mod-Hi
99344	CPT	Home Visit E&M New Pt Hi Sev
99345	CPT	Home Visit E&M New Pt Unstbl
99347	CPT	Home Visit E&M Estab Minor-1
99348	CPT	Home Visit E&M Estab Low-Mod
99349	CPT	Home Visit E&M Estab Mod-Hi
99350	CPT	Home Visit E&M Estab Mod-Hi
99354	CPT	Prolong Md Serv Outpt W/Pt;
99355	CPT	Prolong Md Serv Outpt W/Pt;
99381	CPT	Init Preven Meds E&M New Pt;
99382	CPT	Init Preven Meds E&M New Pt;
99383	CPT	Init Preven Meds E&M New Pt;
99384	CPT	Init Preven Meds E&M New Pt;
99385	CPT	Init Preven Meds E&M New Pt;
99386	CPT	Init Preven Meds E&M New Pt;
99387	CPT	Init Preven Meds E&M New Pt;
99391	CPT	Preven Meds E&M Estab Pt; In
99392	CPT	Preven Meds E&M Estab Pt; 1-
99393	CPT	Preven Meds E&M Estab Pt; 5-
99394	CPT	Preven Meds E&M Estab Pt; 12
99395	CPT	Preven Meds E&M Estab Pt; 18
99396	CPT	Preven Meds E&M Estab Pt; 40
99397	CPT	Preven Meds E&M Estab Pt; 65

CODES TO IDENTIFY IHA VISITS:		
Code	**Code Type**	**Description**
99401	CPT	Preven Med Counsl (Sep Pro);
99402	CPT	Preven Med Counsl (Sep Pro);
99403	CPT	Preven Med Counsl (Sep Pro);
99404	CPT	Preven Med Counsl (Sep Pro);
99411	CPT	Preven Med Counsl Grp (Sep P
99412	CPT	Preven Med Counsl Grp (Sep P
99420	CPT	Admin/Intrpt Health Risk Ass
99429	CPT	Unlisted Preven Meds Serv
99444	CPT	Online E/M By Phys
99446	CPT	Interprof Phone/Online 5-10
99447	CPT	Interprof Phone/Online 11-2
99448	CPT	Interprof Phone/Online 21-3
99449	CPT	Interprof Phone/Online 31/>
99450	CPT	Basic Life &/Or Disability E
99455	CPT	Work Relat/Disabl Exam-Treat
99456	CPT	Work Relat/Disabl Exam-Not T
G0402	HCPCS	Initial Preventive Exam
G0438	HCPCS	Ppps Initial Visit
G0439	HCPCS	Ppps Subseq Visit
G0463	HCPCS	Hospital Outpt Clinic Visit
T1015	HCPCS	Clinic Service
Z00.00	ICD10CM	Encounter for general adult medical examination without abnormal findings
Z00.01	ICD10CM	Encounter for general adult medical examination with abnormal findings
Z00.121	ICD10CM	Encounter for routine child health examination with abnormal findings
Z00.129	ICD10CM	Encounter for routine child health examination without abnormal findings
Z00.5	ICD10CM	Encounter for examination of potential donor of organ and tissue
Z00.8	ICD10CM	Encounter for other general examination
Z02.0	ICD10CM	Encounter for examination for admission to educational institution
Z02.1	ICD10CM	Encounter for pre-employment examination
Z02.2	ICD10CM	Encounter for examination for admission to residential institution
Z02.3	ICD10CM	Encounter for examination for recruitment to armed forces
Z02.4	ICD10CM	Encounter for examination for driving license
Z02.5	ICD10CM	Encounter for examination for participation in sport
Z02.6	ICD10CM	Encounter for examination for insurance purposes
Z02.71	ICD10CM	Encounter for disability determination
Z02.79	ICD10CM	Encounter for issue of other medical certificate
Z02.81	ICD10CM	Encounter for paternity testing
Z02.82	ICD10CM	Encounter for adoption services
Z02.83	ICD10CM	Encounter for blood-alcohol and blood-drug test
Z02.89	ICD10CM	Encounter for other administrative examinations
Z02.9	ICD10CM	Encounter for administrative examinations, unspecified

Concurrent Use of Opioids and Benzodiazepines

Methodology: IEHP-Defined Compliance Metric

Measure Description: The Concurrent Use of Opioids and Benzodiazepines measure specification is developed and maintained by the Pharmacy Quality Alliance (PQA). This measure examines the percentage of individuals 18 years and older with concurrent use of prescription opioids and benzodiazepines. The denominator includes individuals 18 years and older by the first day of the measurement year with two or more prescription claims for opioids filled on two or more separate days, for which the sum of the days supply is 15 or more days during the measurement period. The numerator includes individuals from the denominator with two or more prescription claims for benzodiazepines filled on two or more separate days, and concurrent use of opioids and benzodiazepines for 30 or more cumulative days.

Exclusion: Patients in hospice care and those with a cancer diagnosis are excluded.

Access to Care Needed Right Away

Methodology: Monthly Member Satisfaction Survey.

Measure Description: In the last six months, when you needed care right away, how often did you get care as soon as you needed it?

- Valid response: never, sometimes, usually, always
- Target response: usually, always

Measure Support: To help identify opportunities to improve customer service, IEHP conducts a monthly Member Satisfaction Survey between June-December annually. Member survey responses are analyzed and shared at the PCP level.

Coordination of Care

Methodology: Monthly Member Satisfaction Survey

Measure Description: In the last six months, how often did your Personal Doctor seem informed and up-to-date about the care you got from these doctors or other health providers?

- Valid response: never, sometimes, usually, always
- Target response: usually, always

Measure Support: To help identify opportunities to improve customer service, IEHP conducts a monthly Member Satisfaction Survey between June-December annually. Member Survey responses are analyzed and shared at the PCP level.

Rating of Access to Routine Care

Methodology: Monthly Member Satisfaction Survey

Measure Description: In the last six months, how often did you get an appointment for a check-up or routine care at a Doctor's office or clinic as soon as you needed it?

- Valid response: never, sometimes, usually, always
- Target response: usually, always

Measure Support: To help identify opportunities to improve customer service, IEHP conducts a monthly Member Satisfaction Survey between June-December annually. Member Survey responses are analyzed and shared at the IPA level.

INLAND EMPIRE HEALTH PLAN

HISTORICAL DATA FORM

The Historical Data form is for submissions of visits, procedures or services to close quality gaps in care as reflected on the Preventative Care Rosters that cannot be submitted via claims or encounters (e.g. services received prior to IEHP Membership, historical surgical procedures, etc.). **Any form submitted without appropriate proof of service documentation or any form that doesn't include Member name, DOB and date of service will NOT be processed.**

Results from LabCorp, Quest, BioData, RadNet, ARMC, RUHS, and Loma Linda **do not require submission** as IEHP receives this information directly.

Type of Historical Data:

- ☐ **PAP ONLY**
- ☐ **PAP AND HPV [co-testing]**
- ☐ **History of Total/Complete Hysterectomy [NO residual cervix]**
- ☐ **Mammogram**
- ☐ **History of Mastectomy**
- ☐ **Dilated Retinal Exam with Results**
- ☐ **Group A Streptococcus (Strep) Test – Throat**
- ☐ **HbA1c Results (for in-office Point of Care Testing)**
- ☐ **Other:**_____

For Immunizations - Please submit through CAIR2 website: https://cair.cdph.ca.gov

Member Information
Member Name: _____
IEHP ID #: _____ DOB: _____
Provider Information
Provider Name: _____
IEHP Provider #: _____ Address: _____
City: _____ State: _____ Zip: _____
Provider Phone #: _____ Provider Fax #: _____

This cover sheet MUST be accompanied with the *supporting medical record documentation*

PLEASE FAX TO: (909) 477-8568
Attn: Inland Empire Health Plan - Quality Informatics [HEDIS] Department

Last Rev: 3-09-2018

APPENDIX 4: *Member Satisfaction Survey*

IEHP A Public Entity
Inland Empire Health Plan

IEHP MEDI-CAL ADULT MEMBER SATISFACTION SURVEY 2017

Instructions: Answer each question by marking the box to the left of your answer.

You are sometimes told to skip over some questions in this survey. When this happens you will see an arrow with a note that tells you what question to answer next, like this: ☒ Yes ➔ **If Yes, go to #1 on page 1**
☐ No

Your Personal Doctor

1. **A personal doctor is the one you would see if you need a check-up, want advice about a health problem, or get sick or hurt. Do you have a personal doctor?**
   - ☐1 Yes
   - ☐2 No ➔ **If No, go to Question 14**

2. **In the last 6 months, how often did your personal doctor explain things in a way that was easy to understand?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

3. **In the last 6 months, how often did your personal doctor listen carefully to you?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

4. **In the last 6 months, how often did your personal doctor show respect for what you had to say?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

5. **In the last 6 months, how often did your personal doctor spend enough time with you?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

6. **In the last 6 months, how often did you and your personal doctor talk about all the prescribed medicines you take?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

7. **In the last 6 months, when you had a scheduled visit with your doctor, did he or she have your health records or other facts about your care?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

8. **In the last 6 months, did your doctor order a blood test, x-ray or other test for you?**
   - ☐1 Yes
   - ☐2 No ➔ **If No, go to Question 10**

9. **In the last 6 months, when your doctor ordered a blood test, x-ray or other test for you, how often did someone from your doctor's office give you those results?**
   - ☐1 Never
   - ☐2 Sometimes
   - ☐3 Usually
   - ☐4 Always

10. **Would you send a friend to see your doctor?**
    - ☐1 Yes
    - ☐2 No

11. **Using any number from 0 to 10, where 0 is the worst personal doctor possible and 10 is the best personal doctor possible, what number would you use to rate your "personal doctor"?**
    - ☐ 0 Worst personal doctor possible
    - ☐ 1
    - ☐ 2
    - ☐ 3
    - ☐ 4
    - ☐ 5
    - ☐ 6
    - ☐ 7
    - ☐ 8
    - ☐ 9
    - ☐ 10 Best personal doctor possible

Clerks and Receptionists at your Personal Doctor's Office

12. In the last 6 months, how often were clerks and receptionists at your personal doctor's office as helpful as you thought they should be?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

13. In the last 6 months, how often did clerks and receptionists at your personal doctor's office treat you with courtesy and respect?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

Your Access to Care in the Last 6 Months

These questions ask about your own health care. Do not include care you got when you stayed overnight in a hospital. Do not include the times you went for dental care visits.

14. In the last 6 months, did you have an illness, injury, or condition that needed care right away in a clinic, emergency room, or doctor's office?
    - 1 Yes
    - 2 No ➔ If No, go to Question 16

15. In the last 6 months, when you needed care right away, how often did you get care as soon as you needed?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

16. In the last 6 months, did you make any appointments for a check-up or routine care at a doctor's office or clinic?
    - 1 Yes
    - 2 No ➔ If No, go to Question 18

17. In the last 6 months, how often did you get an appointment for a check-up or routine care at a doctor's office or clinic as soon as you needed?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

18. In the last 6 months, did you need care after normal office hours?
    - 1 Yes
    - 2 No ➔ If No, go to Question 21

19. In the last 6 months, how often was it easy to get the after-hours care you thought you needed?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

20. In the last 6 months, when you needed after-hours care, what did you do?
    - 1 Called IEHP Nurse Advice Line
    - 2 Called my personal doctor's office
    - 3 Went to the Urgent Care
    - 4 Went to the Emergency Room
    - 5 Did not get care
    - 6 Other

21. In the last 6 months, did you take any prescribed medicine?
    - 1 Yes
    - 2 No ➔ If No, go to Question 24

22. In the last 6 months, how often was it easy to get your prescribed medicine?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

23. In the last 6 months, how often were your prescriptions not ready for you at the pharmacy due to an issue with IEHP's Prior Authorization process?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always
    - 5 Don't know

24. In the last 6 months, did you try to get information or help about prescriptions from IEHP's customer service?
    - 1 Yes
    - 2 No ➔ If No, go to Question 27

25. In the last 6 months, how often did IEHP's customer service give you the information or help you needed about prescription drugs?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

26. In the last 6 months, how often did IEHP's customer service staff treat you with courtesy and respect when you tried to get information or help about prescription drugs?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

27. In the last 6 months, did you get care from a doctor or other health provider besides your personal doctor?
    - 1 Yes
    - 2 No ➔ If No, go to Question 29

28. In the last 6 months, how often did your personal doctor seem informed and up-to-date about the care you got from these doctors or other health providers?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

29. Using any number from 0 to 10, where 0 is the worst health care possible and 10 is the best health care possible, what number would you use to rate all your health care in the last 6 months??
    - 0 Worst health care possible
    - 1
    - 2
    - 3
    - 4
    - 5
    - 6
    - 7
    - 8
    - 9
    - 10 Best health care possible

Your Health Plan: Inland Empire Health Plan (IEHP)

The next questions ask about your experience with your health plan.

30. In the last 6 months, did you get information or help from IEHP's customer service?
    - 1 Yes
    - 2 No ➔ If No, go to Question 33

31. In the last 6 months, how often did IEHP's customer service give you the information or help you needed?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

32. In the last 6 months, how often did IEHP's customer service staff treat you with courtesy and respect?
    - 1 Never
    - 2 Sometimes
    - 3 Usually
    - 4 Always

33. Using any number from 0 to 10, where 0 is the worst health plan possible and 10 is the best health plan possible, what number would you use to rate your health plan?
    - 0 Worst health plan possible
    - 1
    - 2
    - 3
    - 4
    - 5
    - 6
    - 7
    - 8
    - 9
    - 10 Best health plan possible

APPENDIX 5: *2018 IPA Global Quality P4P IPA Work Plan*

Review Check List – DRAFT

ITEM NUMBER	IPA CHECK LIST - ELEMENTS OF A QUALITY PROGRAM	TOTAL POSSIBLE POINTS
	Clinical Quality Domain	
1	Key Leadership Support for Clinical Quality Improvement	5
2	Tools and Resources for Clinical Quality Improvement	
	a. Evidence-Based Clinical Practice Guidelines (CPGs) for Prevention, Wellness and Chronic Condition Management (CCM)	5
	b. Toolkits for Team-Based Care including use of Targeted Member Lists from IEHP	5
3	Office and Practitioner Training Programs on Best Practices	5
4	Member Outreach and In-reach Activities to Address Care Gaps	5
5	Physician-level Reports and Monitoring of Clinical outcomes	5
6	Patient-centered Member Education Programs	5
7	Office Staff/ Practitioner Recognition Programs for High Performers	5
	Behavioral Health Integration Domain	
8	Evidenced Based CPG for Depression Screening and Management	5
9	Office and Physician Training Programs on Best Practices	5
10	Development of resources for follow-up	5
11	Physician-level Reports and Monitoring of Performance Metrics	5
	Encounter Data Domain	
12	Monthly Submission Volume Meeting IEHP Target Adequacy Rate	5
13	Monthly Submissions Accepted with <1% Error Rate	5
14	Tracking of Capitated Provider-Level Encounters	5
15	Use of Supplemental Data to improve data capture	5
16	Supplemental Data shared with IEHP timely and in agreed upon format	5
	Patient Experience Domain	
17	Physician-level Reports and Monitoring of Performance Metrics	5
18	Office Staff and Physician Education Programs to Improve Patient Experience	5
19	Office Staff/ Practitioner Recognition Programs for High Performers	5
OVERALL PROGRAM SCORE		**100**

APPENDIX 6: *Supplemental Claim File Data Dictionary*

The Claim file contains claims for medical services. It may also contain lab services that do not have an associated result, pharmaceuticals administered in the practitioners office (usually documented by J codes in the CPT Field), and medical encounter data. The Claim file should contain one record per unique claim line.

SUPPLEMENTAL CLAIM FILE DATA DICTIONARY			
Field Name	**Data Type**	**File Order**	**Notes**
MemberKey	Text (14)	1	IEHP Member ID.
ProviderKey	Text (25)	2	This should be the rendering provider's NPI.
ClaimNumber	Text (80)	3	Used to identify the claim source for Primary Source Verification.
DOS	Date	4	The beginning Date of Service for the claim in MM/DD/YYYY format.
DOSThru	Date	5	The ending Date of Service for the claim in MM/DD/YYYY format.
ICD9DxPri	Text (5)	6	ICD-9 diagnosis codes should contain all available digits (including all preceding zeros). Do not include the period that follows the third digit. If no fourth or fifth digit was coded, do not pad the missing spaces. For example, V42.0 should be loaded as V420. With the introduction of ICD-10 code set, IEHP will continue to support the ICD-9 code set as there are historical claims that rely on these codes (for HEDIS we recommend 3-4 years of historical claims data) in order to accurately calculate HEDIS rates.
ICD9DxSec1	Text (5)	7	
ICD9DxSec2	Text (5)	8	
ICD9DxSec3	Text (5)	9	
ICD9DxSec4	Text (5)	10	
ICD9DxSec5	Text (5)	11	
ICD9DxSec6	Text (5)	12	
ICD9DxSec7	Text (5)	13	
ICD9DxSec8	Text (5)	14	
ICD9DxSec9	Text (5)	15	
ICD9DxSec10	Text (5)	16	
ICD10DxPri	Text (7)	17	ICD-10 diagnosis codes should contain all available alphanumeric code. Do not include the decimal. For example, V39.00XS should be coded as V3900XS.
ICD10DxSec1	Text (7)	18	
ICD10DxSec2	Text (7)	19	
ICD10DxSec3	Text (7)	20	
ICD10DxSec4	Text (7)	21	
ICD10DxSec5	Text (7)	22	
ICD10DxSec6	Text (7)	23	
ICD10DxSec7	Text (7)	24	
ICD10DxSec8	Text (7)	25	
ICD10DxSec9	Text (7)	26	
ICD10DxSec10	Text (7)	27	
PCPFlag	Bit	28	Indicator for whether the claim provider serves as a PCP for the health plan. Refers to the provider's contractual relationship to the plan, rather than medical specialty. Valid values are 0 (no), or 1 (yes)
HCFAPOS	Text (2)	29	

SUPPLEMENTAL CLAIM FILE DATA DICTIONARY			
Field Name	**Data Type**	**File Order**	**Notes**
TOB	Text (4)	30	Must be converted to standard 4-digit length by adding leading zeros, if necessary.
UBRevenueCode	Text (4)	31	Must be converted to standard 4-digit length by adding leading zeros, if necessary.
UBOccurCode1	Text (2)	32	
UBOccurCode2	Text (2)	33	
UBOccurCode3	Text (2)	34	
UBOccurCode4	Text (2)	35	
HCPCSPx	Text (5)	36	
HCPCSMOD	Text (2)	37	
CPTPx	Text (5)	38	Level II CPT Codes are supported by HEDIS and should be placed in the same field as other CPT procedure codes.
CPTMOD1	Text (2)	39	
CPTMOD2	Text (2)	40	
ICD9Px1	Text (4)	41	ICD-9 procedure codes should contain all available digits (including all preceding zeros). Do not include the period that follows the third digit. With the introduction of ICD-10 code set, IEHP will continue to support the ICD-9 code set as there are historical claims that rely on these codes (for HEDIS we recommend 3-4 years of historical claims data) in order to accurately calculate HEDIS® rates.
ICD9Px2	Text (4)	42	
ICD9Px3	Text (4)	43	
ICD9Px4	Text (4)	44	
ICD9Px5	Text (4)	45	
ICD9Px6	Text (4)	46	
ICD9Px7	Text (4)	47	
ICD9Px8	Text (4)	48	
ICD9Px9	Text (4)	49	
ICD9Px10	Text (4)	50	
ICD10Px1	Text (7)	51	ICD-10 procedure codes should contain all available alphanumeric code. Do not include the decimal. For example, V39.00XS should be coded as V3900XS.
ICD10Px2	Text (7)	52	
ICD10Px3	Text (7)	53	
ICD10Px4	Text (7)	54	
ICD10Px5	Text (7)	55	
ICD10Px6	Text (7)	56	
ICD10Px7	Text (7)	57	
ICD10Px8	Text (7)	58	
ICD10Px9	Text (7)	59	
ICD10Px10	Text (7)	60	
ProviderSpecialty	Text (15)	61	Use Provider Specialties in the Provider Specialty Crosswalk Tab
POS	Text (2)	62	Place of Service. Also automatically built using a cross-reference. Valid values are: BC (Birthing Center), DN (Day/Night Hospitalization), ER (Emergency Room), IA (Inpatient Acute), IN (Inpatient Non-Acute), LA (Laboratory), OA (Outpatient/ Ambulatory), OC (Office/Clinic), OT (Other), RM (Mail Order Prescription Drugs), RR (Retail Pharmacy).

Supplemental Lab Claim File Data Dictionary

The LabClaim file contains claims for laboratory services and allows lab results to be stored. The LabClaim file should contain one record per unique lab service claim.

SUPPLEMENTAL LAB CLAIM FILE DATA DICTIONARY			
Field Name	**Data Type**	**File Order**	**Notes**
MemberKey	Text (30)	1	
ProviderKey	Text (25)	2	This should be the rendering provider's NPI.
ClaimNumber	Text (80)	3	Used to identify the claim source for Primary Source Verification.
DOS	Date	4	The Date of Service for the claim in MM/DD/YYYY format.
CPTPx	Text (5)	5	Level II CPT Codes are supported by HEDIS and should be placed in the same field as other CPT procedure codes.
LOINC	Text (7)	6	LOINC codes must contain the dash character that precedes the final digit.
HCPCSPx	Text (5)	7	Used for medical services, that comes in through lab claims. Only one HCPCS code per claim line is allowed. If the claim contains multiple HCPCS codes, load them as separate claims.
HCPCSMod	Text (2)	8	
Result	Decimal(28,10)	9	Used to document numeric lab results.
PosNegResult	Bit	10	Used to document positive/negative lab results. Valid values are 0 (negative), or 1 (positive).

APPENDIX 7: *Constructing the IPA Payment Amount per Member Point*

Using the formula below, the Payment Amount per Member Point is calculated as follows:

[Expected Global Quality Performance Score] x [Total Medi-Cal Membership as of 1/2018] =*
Total Member Points

[Total Incentive Dollars Available] / [Total Member Points] =
Payment Amount per Member Point

Final Payment Amount per Member Point Calculation:

EXPECTED GLOBAL QUALITY PERFORMANCE SCORE		TOTAL MEDI-CAL MEMBERSHIP AS OF 1/2018*		MEMBER POINTS
1.88	x	720,776	=	1,355,058.88

PROVIDER	TOTAL INCENTIVE DOLLARS AVAILABLE		MEMBER POINTS		PAYMENT PER MEMBER POINT
IPA	$20,000,000	÷	1,355,058.88	=	$14.76**

**Excludes IEHP Direct, Kaiser, Allied Pacific IPA, Heritage Provider Network and Pomona Valley Medical Group Medi-Cal membership. ** Payment per Member Point is not finalized. Payment Per Member Point will be included in published status reports beginning in the Spring.*

Rates will be shared with IPAs at least quarterly to track progress toward goals.
Initial IPA reports will be available in March 2018.

NOTES

A Public Entity

Inland Empire Health Plan

www.iehp.org

Provider Relations Team
909-890-2054
Monday-Friday, 8am - 5pm

Follow us:

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Quality Improvement

Provider Incentive Program

Welcome to California Health & Wellness

AGENDA

1. Medi-Cal Performance Measures
2. HEDIS Status Report vs. Care in Gap Report
3. Patient Level Compliance Bonus
   - "Critical" Measures
   - "Important" Measures
4. Provider Quality Performance Incentive
   - Star Ratings
5. Notice of Pregnancy Bonus
6. Frequently Asked Questions
7. Things to Remember
8. Quality Incentive Training Series

MEDI-CAL PERFORMANCE MEASURES

california health & wellness

HYBRID MEASURES

- Childhood Immunizations
- Adolescent Immunizations
- Well Child Visits
- Controlling High Blood Pressure
- Cervical Cancer Screening
- Weight Assessment and Counseling for Children/Adolescents *3 indicators
- Prenatal Care
- Postpartum Care
- Comprehensive Diabetes Care *6 indicators

ADMINISTRATIVE MEASURES

- Annual Monitoring for Patients on Persistent Medications *3 indicators
- Children and Adolescents Access to Primary Care Physicians *4 indicators based on age groups
- Medication Management for Asthma *2 indicators
- Avoidance of Antibiotic use for Bronchitis
- Use of imaging studies for low back pain
- Ambulatory Care *2 indicators
- All Cause Readmissions

NOTE: Compliance is based on NCQA HEDIS measure specifications and must be received aa a medical claim with the correct coding or by submission of the medical record with the correct documentation meeting measure compliance guidelines.

WHATS THE DIFFERENCE?

HEDIS STATUS REPORT vs. GAP IN CARE REPORT

california health & wellness

HEDIS STATUS REPORT

- Sent directly to provider location monthly
- Does not include all CHW membership
- Only includes patients/members that are identified for a specific measure
- Eligible for Provider Incentives
  - Patient Level Compliance Bonus
  - Provider Quality Performance Rating
  - Notice of Pregnancy Bonus

GAP IN CARE REPORT

- Located on the Provider Portal
- Includes all CHW membership assignment
- Not all patients/members on the GAP report are eligible for provider incentives

HEDIS Status Report

DR. SAMPLE	7/7/2015

YEAR TO DATE RATING: 0.2

$31,244

ID	Measure Name	OUR YEAR TO DATE PERFORMANC			Current count of patients need service or proof of service	# needed to reach 1 STAR	# needed to reach 2 STARS	# needed to reach 3 STARS	# needed to reach 4 STARS	Current RATING	Gap Closure Measures	Potential Payout
		Your Patients In Measure Population	Already Compliant	Year-to-Date Score								
CBP	Controlling High Blood Pressure	2	0	**0.00%**	**2**	1	2	2	2	**0**	$75	$150
CCS	Cervical Cancer Screening	7	2	**28.57%**	**5**	2	3	3	4	**0**	$75	$375
CDC-1	Diabetes Care - HbA1c Test	3	0	**0.00%**	**3**	3	3	3	3	**0**	$75	$225
CIS-3	Childhood Immunization Status	58	5	**8.62%**	**53**	34	37	41	42	**0**	$75	$3,975
W34	Well Child 3-6 Yrs	178	44	**24.72%**	**134**	74	84	94	104	**0**	$75	$10,050
CAP	Childrens and Adolescents Access to Primary Care Practitioners	813	588	**72.32%**	**225**	126	154	173	186	**0**	$25	$5,625
CDC-7	Diabetes Care - Eye Exam	3	0	**0.00%**	**3**	2	2	2	3	**0**	$25	$75
CDC-8	Diabetes Care - Nephropathy Attention	3	2	**66.67%**	**1**	1	1	1	1	**0**	$25	$25
IMA	Immunization Adolescents	49	12	**24.49%**	**37**	19	23	28	31	**0**	$25	$925
MPM	Annual Monitoring for People on Persistent Medications	1	0	**0.00%**	**1**	1	1	1	1	**0**	$25	$25
WCC	Weight Assessment and Counseling for Children/Adolescents	392	0	**0.00%**	**392**	197	238	272	304	**0**	$25	$9,800
AAB	Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis	1	1	**100.00%**	**0**				****	**4**	--	--
CDC-3	Diabetes Care - HbA1c <= 9	3	0	**0.00%**	**3**	1	2	2	2	**0**	--	--
CDC-9	Diabetes Care - BP < 140/90	3	0	**0.00%**	**3**	2	2	3	3	**0**	--	--
MMA	Medication Management for People with Asthma	17	0	**0.00%**	**17**	9	10	11	12	**0**	--	--
PPC-1	Prenatal Care	3	0	**0.00%**	**3**	3	3	3	3	**0**	--	--
PPC-2	Postpartum Care	3	1	**33.33%**	**2**	1	1	2	2	**0**	--	--

Patient Level Compliance Bonus

california health & wellness

Critical Measures = $75

- Childhood Immunizations
- Well Child Exam for Children Ages 3 to 6
- Controlling High Blood Pressure
- Diabetic Care: HbA1c Test
- Cervical Cancer Screening

Important Measures = $25

- Weight Assessment and Counseling for Children
- Diabetic Care: Eye Exam
- Diabetic Care: Medical Attention to Nephropathy
- Children Access to Primary Care Physicians
- Annual Monitoring for Patients on Persistent Medications
- Adolescent Immunizations

NOTE: Compliance is based on NCQA HEDIS measure specifications and must be received as a medical claim with the correct coding or by submission of the medical record with the correct documentation meeting measure compliance guidelines.

CRITICAL MEASURES

california health & wellness

Childhood Immunizations

- Received combination of vaccines before 2nd Birthday

Well Child Exam for Children ages 3- 6

- Annual "well child" exam - PM-160 Form in California

Prenatal Care

- Initial Prenatal Care visit in 1st Trimester, OR within 42 days of enrollment if enrolled after 1st trimester

Controlling High Blood Pressure

- Patients diagnosed with Hypertension in 1st half of year, need follow-up BP test and value < 140/90

Diabetic Care – Annual HbA1c Blood Test

- Blood test taken anytime in calendar year

Cervical Cancer Screening

- Ages (21-64): Pap test in past 3 years (2013 – 2015)
- Ages (30-64): Pap Test & HPV test in past 5 years (2011-2015)

NOTE: Compliance is based on NCQA HEDIS measure specifications and must be received aa a medical claim with the correct coding or by submission of the medical record with the correct documentation meeting measure compliance guidelines.

PROVIDER QUALITY "STAR" PERFORMANCE INCENTIVE

california health & wellness

Measure level star ratings (0 Stars to 4 Stars)

Star ratings based on NCQA Percentile levels for each measure

Below 25th Percentile	0 Stars
At or Above 25th Percentile	1 Star
At or Above 50th Percentile	2 Stars
At or Above 75th Percentile	3 Stars
At or Above 90th Percentile	4 Stars

The provider's overall rating is the average of their measure level star ratings

PROVIDER QUALITY PERFORMANCE RATING

DR. SAMPLE	7/7/2015

YEAR TO DATE RATING: 0.2

$31,244

		OUR YEAR TO DATE PERFORMANC										
ID	**Measure Name**	Your Patients In Measure Population	Already Compliant	Year-to-Date Score	**Current count of patients need service or proof of service**	# needed to reach **1 STAR**	# needed to reach **2 STARS**	# needed to reach **3 STARS**	# needed to reach **4 STARS**	**Current RATING**	**Gap Closure Measures**	**Potential Payout**
CBP	Controlling High Blood Pressure	2	0	**0.00%**	**2**	1	2	2	2	**0**	$75	$150
CCS	Cervical Cancer Screening	7	2	**28.57%**	**5**	2	3	3	4	**0**	$75	$375
CDC-1	Diabetes Care - HbA1c Test	3	0	**0.00%**	**3**	3	3	3	3	**0**	$75	$225
CIS-3	Childhood Immunization Status	58	5	**8.62%**	**53**	34	37	41	42	**0**	$75	$3,975
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MPM	Annual Monitoring for People on Persistent Medications	1	0	**0.00%**	**1**	1	1	1	1	**0**	$25	$25
WCC	Weight Assessment and Counseling for Children/Adolescents	392	0	**0.00%**	**392**	197	238	272	304	**0**	$25	$9,800
AAB	Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis	1	1	**100.00%**	**0**				****	**4**	--	--
CDC-3	Diabetes Care - HbA1c <= 9	3	0	**0.00%**	**3**	1	2	2	2	**0**	--	--
CDC-9	Diabetes Care - BP < 140/90	3	0	**0.00%**	**3**	2	2	3	3	**0**	--	--
MMA	Medication Management for People with Asthma	17	0	**0.00%**	**17**	9	10	11	12	**0**	--	--
PPC-1	Prenatal Care	3	0	**0.00%**	**3**	3	3	3	3	**0**	--	--
PPC-2	Postpartum Care	3	1	**33.33%**	**2**	1	1	2	2	**0**	--	--

NOTICE OF PREGNANCY BONUS

Improving Prenatal Care is a critical goal for CAHW and early identification of patients increases the likelihood of success. Providers are asked to complete an NOP – Notice of Pregnancy form for every patient with a new diagnosis of pregnancy. For every new NOP submitted for patients in their first trimester, you will receive a bonus of $75.00

Ongoing Bonus Payout: {Quarterly beginning October 2015}

FREQUENTLY ASKED QUESTIONS

Can I code for immunizations even if I am not charging for them?

- Yes. Coding for immunizations helps identify members that are compliant and those that still need additional vaccines.

Where can I find the Notice of Pregnancy (NOP) form?

- You can find the NOP as well as additional HEDIS information of our Provider Portal located on our website: **www.CAHealthWellness.com**

What if the doctor listed on the report is no longer practicing at this office/location?

- The HSR is reflective of membership assigned at your location . Although the provider is no longer at a particular site, the members are still assigned to that site.

Can I log the data into an Excel Spreadsheet and fax to you?

- Unfortunately no. In adherence to our audit and auditors, we are required to have the specific medical record

Will we get credit for submitting the NOP even if do not practice prenatal care at our facility?

- Yes. We need help identifying women that become pregnant so we can ensure great prenatal care. If a patient is identified as being pregnant, fill out the NOP and send in immediately. The NOP will be paid on a first submitted basis.

What does the "x" stand for on our report?

- The "x" means that the service is still needed for this measure. If the service has been completed already; please fax the medical record documentation to 877-278-9978.

Is this the same incentive program as last year?

- No. This provider incentive program is specific for this year. Each year we will tailor a provider incentive program that continues to improve the health and wellbeing of our members as well as rewarding our stakeholders.

THINGS TO REMEMBER

- 5 critical measures paid at $75 by turning non-compliant into compliant
  - Childhood Immunizations
  - Well Child Visits 3-6 years of age
  - Controlling High Blood Pressure
  - Diabetes Care: HbA1c Tests
  - Cervical Cancer Screening
- 6 important measures paid at $25 by turning non-compliant into compliant
  - Weight Assessment and Counseling for Nutrition and Physical Activity
  - Adolescent Immunizations
  - Diabetes Care: Eye Exam
  - Diabetes Care: Medical Attention for Nephropathy
  - Children and Adolescents Access to Primary Care Physician
  - Annual Monitoring for Patients on Persistent Medications

  ✓ **Bonus Payout: By October 31, 2015** for services in July, August, September

  ✓ **Bonus Payout: By March 31, 2016** for services in October, November, December

- Provider Quality Performance Ratings Payout

  ✓ **Bonus Payout: By March 31, 2016**

- Notice of Pregnancy (NOP) Bonus

  ✓ **Ongoing Bonus Payout starting October 2015**

- Make sure to use the “HEDIS STATUS REPORT” to change your patients from non-compliant to compliant

Please fax clinical documentation to our QI HEDIS Department: (877) 278-9978

QUALITY INCENTIVE PROGRAM PROVIDER TRAINING SERIES

california health & wellness

WEBINARS

Tuesday, July 21, 2015
• 7:30am - 8:30am PST – **Webinar Session**
Webinar: http://centene.adobeconnect.com/chwqip-72115/
For phone only access:
▪ Conference Line: (855) 351-5537
▪ Conference code: 314-647-3883

Thursday, July 23, 2015
• 12:30pm - 1:30pm PST – **Webinar Session**
Webinar: http://centene.adobeconnect.com/r658sefgf62/
For phone only access:
▪ Conference Line: (855) 351-5537
▪ Conference code: 314-647-3883

Tuesday, July 28, 2015
• 12:30pm - 1:30pm PST – **Webinar Session**
Webinar: http://centene.adobeconnect.com/chwqip-72815/
For phone only access:
▪ Conference Line: (855) 351-5537
▪ Conference code: 314-647-3883

Tuesday, July 30, 2015
• 7:30am - 8:30am PST – **Webinar Session**
Webinar: http://centene.adobeconnect.com/chwqip-73015/
For phone only access:
▪ Conference Line: (855) 351-5537
▪ Conference code: 314-647-3883

CONFERENCE CALLS

Tuesday, July 21, 2015
12:30pm - 1:30pm PST **– Conference Call**
▪ **Conference Line: (855) 351-5537**
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Thursday, July 23, 2015
7:30am - 8:30am PST **– Conference Call**
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Tuesday, July 30, 2015
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▪ Conference Line: (855) 351-5537
▪ Conference code: 314-647-3883

QUESTIONS

Blue Cross Blue Shield Blue Care Network of Michigan

Confidence comes with every card.®

2016 Performance Recognition Program

PROVIDER INCENTIVE PROGRAM FOR:

- **BCN Commercial HMO**
- **BCN Advantage℠ HMO-POS**
- **BCBSM Medicare Plus Blue℠ PPO**

CONTENTS

2016 PERFORMANCE RECOGNITION PROGRAM

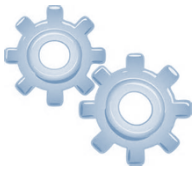
The Provider Performance Recognition Program rewards Blue Care Network Commercial providers and Medicare Advantage providers for both Blue Cross Blue Shield of Michigan and BCN for their role in helping Blue Cross and BCN achieve the objectives of the Healthcare Effectiveness Data and Information Set, or HEDIS®, and the Centers for Medicare & Medicaid Services' star ratings program. These objectives include:

- Better care
- Healthier people and communities
- Affordable care

Each program rewards providers who encourage their patients to get preventive screenings and procedures, such as eye exams and mammograms, and for achieving patient outcomes such as ensuring diabetic members have their blood sugar controlled.

Our philosophy is to use meaningful payments to encourage positive clinical results as well as increase HEDIS outcomes and CMS star ratings.

The components of the program, including the performance measures that are based on HEDIS benchmarks, are described in this booklet. Primary care physicians must have attributed or assigned members to participate in the program.



BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PHYSICIAN QUALITY INCENTIVE MEASURES

QUALITY INCENTIVE MEASURES	BCN COMMERCIAL HMO	BCN ADVANTAGE℠ HMO	BLUE CROSS MEDICARE ADVANTAGE PPO
Adult BMI assessment		●	●
Aspirin or antiplatelet therapy		■	
Breast cancer screening	●	●	●
Childhood immunizations — combo 10	●		
Colorectal cancer screening		●	●
Comprehensive diabetes care: HbA1c < 8%	●		
Comprehensive diabetes care: HbA1c ≤ 9%		●	●
Comprehensive diabetes care: monitoring for nephropathy	●	●	●
Controlling blood pressure		■	
Controlling high blood pressure for hypertension	●	●	●
Depression management — PHQ9 testing	●		
Disease modifying antirheumatic drug therapy for rheumatoid arthiritis		●	●
Medication adherence for diabetes medication		●	●
Medication adherence for hypertension medication		●	●
Medication adherence for cholesterol medications		●	●
Smoking/tobacco cessation counseling	●	■	
Weight assessment and counseling for children: BMI percentile, counseling for nutrition and physical activity	●		

Key

● = Performance Recognition Program
■ = CMS Million Hearts

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PAYOUT SUMMARY — BCN COMMERCIAL

BCN Commercial HMO payment calculation

Payments for each eligible provider are calculated using the following methodology, regardless of membership level.

1. Quality score: A quality score for each program measure is computed for each provider using the following formula:

   a) Numerator = Eligible members meeting criteria

   b) Denominator = Total members eligible

   c) Numerator ÷ Denominator: The individual provider's quality score for each program measure

2. Compare the individual provider's quality score to the plan goal for quality. The payment for services will be calculated once the plan goal is met, based upon the Numerator.

   For measures with no specific plan goal, a flat fee will be paid for each service completed.

BCN Commercial HMO payment table

QUALITY INCENTIVE MEASURES	PLAN GOAL	PAYOUT
Breast cancer screening	80%	$100
Childhood immunizations — combo 10	63%	$400
Weight assessment and counseling for children: BMI percentile, counseling for nutrition and physical activity	63%	$150
Comprehensive diabetes care: HbA1c < 8%	68%	$250
Comprehensive diabetes care: monitoring for nephropathy	90%	$125
Controlling high blood pressure for hypertension	75%	$100
Depression management — PHQ9 testing	Flat Fee	$200
Smoking/tobacco cessation counseling	Flat Fee	$30

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PAYOUT SUMMARY — MEDICARE

Medicare Advantage payment calculation

Program payments for each eligible provider are calculated using the following methodology.

1. Quality score: A quality score for each program measure is computed for each provider by determining:
   - Numerator = Eligible members meeting criteria
   - Denominator = Total members eligible
   - Numerator ÷ Denominator: The individual provider's quality score for each program measure
2. Compare the quality score for each measure to the **CMS star rating scale** for that measure to determine a star score for each measure.
3. Average the star scores for all measures to determine an overall star rating by provider.
4. Convert the overall star rating into a per-member-per-month payment using the **Medicare Advantage payment table**.

Note: Providers are scored separately for BCN Advantage and Medicare Advantage PPO products.
See next page for **CMS star rating scale** and **Medicare Advantage payment table**.

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PAYOUT SUMMARY — MEDICARE

CMS star rating scale

QUALITY INCENTIVE MEASURES	1 STAR	2 STAR	3 STAR	4 STAR	5 STAR	WEIGHT
Adult BMI assessment	< 70%	70 - 80.9%	81 - 89.9%	90 - 95.9%	≥ 96%	1
Breast cancer screening	< 39%	39 - 62.9%	63 - 73.9%	74 - 79.9%	≥ 80%	1
Colorectal cancer screening	< 51%	51 - 62.9%	63 - 70.9%	71 - 77.9%	≥ 78%	1
Comprehensive diabetes care: HbA1c ≤ 9%	< 49%	49 - 59.9%	60 - 70.9%	71 - 83.9%	≥ 84%	3
Comprehensive diabetes care: monitoring for nephropathy	< 85%	85 - 88.9%	89 - 92.9%	93 - 96.9%	≥ 97%	1
Controlling high blood pressure for hypertension	< 47%	47 - 61.9%	62 - 74.9%	75 - 81.9%	≥ 82%	1
Disease modifying anti-rheumatic drug therapy for rheumatoid arthiritis	< 64%	64 - 74.9%	75 - 81.9%	82 - 85.9%	≥ 86%	1
Medication adherence for diabetes medication	< 60%	60 - 68.9%	69 - 74.9%	75 - 81.9%	≥ 82%	3
Medication adherence for hypertension medication	< 58%	58 - 72.9%	73 - 76.9%	77 - 80.9%	≥ 81%	3
Medication adherence for cholesterol medications	< 50%	50 - 60.9%	61 - 72.9%	73 - 78.9%	≥ 79%	3

Medicare Advantage payment table

AVERAGE STAR	PMPM PAYOUT
5	$8
4.5 – 4.99	$7
4 – 4.49	$4
3.5 – 3.99	$2.50
< 3.5	$1 for each half-star improvement from 2015

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PAYOUT SUMMARY — MEDICARE

Medicare Advantage payment calculation
Example #1: "Dr. A"

DR. A QUALITY SCORES BY MEASURE:	NUMERATOR	DENOMINATOR	SCORE	STARS	WEIGHTED STARS
Adult BMI assessment	32	32	100%	5	5
Breast cancer screening	15	15	100%	5	5
Colorectal cancer screening	25	35	72%	4	4
Comprehensive diabetes care: HbA1c ≤ 9% (weighted x 3)	11	12	90%	5	5 5 5
Comprehensive diabetes care: monitoring for nephropathy	10	10	100%	5	5
Controlling high blood pressure for hypertension	0	0	n/a	n/a	n/a
Disease modifying anti-rheumatic drug therapy for rheumatoid arthritis	1	1	100%	5	5
Medication adherence for diabetes medications (weighted x 3)	5	6	83%	5	5 5 5
Medication adherence for hypertension medications (weighted x 3)	12	16	75%	3	3 3 3
Medication adherence for cholesterol medications (weighted x 3)	20	24	83%	5	5 5 5
Total stars					78
Number of measures with a star score for Dr. A					17
Average star rating					4.59
Per-member-per-month payment					$7.00
Dr. A's 2016 member months					1,000
Dr. A's total 2016 program dollars earned					**$7,000**

- Dr. A scored an average of 4.59 stars for 2016
- 4.59 stars places Dr. A in the 4.5 to 4.99 star range
- Dr. A will earn $7 per member per month for 2016

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2016 PAYOUT SUMMARY — MEDICARE

Medicare Advantage payment calculation
Example #2: "Dr. B"

	Scoring
Total stars	59
Number of measures with a star score for Dr. B	18
Average star rating 2016 for Dr. B	3.28
Average star rating 2015 for Dr. B	2.17
Dr. B star improvement 2015 – 2016	1.11
Per-member-per-month payment	$2.00
Dr. B's 2016 member months	500
Dr. B's total 2016 program dollars earned	**$1,000**

- Dr. B scored an average of 3.28 stars, below the 3.5 stars threshold for 2016
- Dr. B showed a 1.11 star improvement from 2015 to 2016
- The 1.11 star improvement is divided by 0.5 to determine how many half-star increments Dr. B improved
- 1.11/0.5 = 2.22, the 2.22 is rounded down to the nearest whole number which is 2
- Dr. B improved 2 half-star increments
- Dr. B will earn two times the improvement per member per month of $1
- Dr. B will earn $2 per member per month for 2016

Medicare Advantage payment calculation
Example #3: "Dr. C"

	Scoring
Total stars	31
Number of measures with a star score for Dr. C	12
Average star rating 2016 for Dr. C	2.58
Average star rating 2015 for Dr. C	3.08
Dr. C star improvement 2015 – 2016	None
Per-member-per-month payment (Dr. C showed no improvement)	$0
Dr. C's 2016 member months	750
Dr. C's total 2016 program dollars earned	**$0**

- Dr. C scored average of 2.58 stars, below the 3.5 stars threshold for 2016
- Dr. C showed no improvement from 2015 to 2016
- Dr. C does not qualify for a program payment for 2016

2016 PROGRAM SCHEDULE

JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG

Measurement period: January to December, 2016

HEB/Supplemental Date: January 2016 to Early/Mid-January 2017

Claim/EMR Submission: January 2016 to February 2017

Payment: May to August 2017

Note: See Page 24 for the schedule for the depression management quality measure.

PROGRAM QUALIFICATIONS

1. The primary care physician or physician organization must sign the BCN 2016 Medical Services Agreement to participate in the BCN Commercial and BCN Advantage Performance Recognition Programs and the Blue Cross Medicare Advantage PPO Provider Agreement to participate in the Blue Cross Medicare Plus Blue PPO Performance Recognition Program.

2. The primary care physician or physician organization must comply with all terms and conditions of those agreements, including:
   - Providing timely and accurate encounter, referral and claims data
   - Remitting any funds due for prior contract years

3. The primary care physician must be affiliated for the entire 2016 calendar year.

4. The primary care physician must be affiliated at the time of payment to be eligible for any program payments unless the PCP recently retired.

5. The primary care physician or PCP office must have a Health e-Blue℠ sign-on and actively use the program.

6. BCN and Blue Cross retain the right to modify the Performance Recognition Program for any reason and at any time. Modifications may include, but are not limited to:
   - Exclusion or removal of program measures
   - Changes to program calculation methodologies

7. Blue Care Network and Blue Cross conduct periodic random audits on provider data returns. If you are randomly selected to be audited for Health e-Blue data entry or electronic medical records, you must pass the audit in order to be eligible for payment.

PERFORMANCE MEASUREMENT GUIDELINES

- Each primary care physician will be credited for services completed through **Dec. 31, 2016,** to members who meet all measurement requirements, are continuously enrolled with the plan for the entire year and are assigned to a primary care physician whether or not the primary care physician was the member's primary care physician at the time services were provided.

- Credit will be granted to the primary care physician for each component measure only when the specific identified service is documented as provided to the member (by the primary care physician, the member's previous primary care physician or a specialist). Members may be excluded from measures under certain circumstances, such as bilateral mastectomy for breast cancer screening, which should be indicated to Blue Cross or BCN by the primary care physician offices via the Health e-Blue *Treatment Opportunities by Condition/Measure* screen.

- Blue Cross and BCN recognize that many primary care physician offices send reminder letters or may not see certain members in their offices who are identified by Blue Cross or BCN as needing certain services. Such occurrences will not count as credit toward the component measure.

- Each primary care physician's quality performance measurement data comes directly from Blue Cross or BCN's Health Management Program reporting database accessible through Health e-Blue. The Health e-Blue *Treatment Opportunities by Condition/Measure* for the Performance Recognition Program will include:
  - A list of the cohort member population for each component measure that needs a specific health promotion, disease prevention or health management service according to evidence-based medicine
  - **Intervention** opportunities for physicians to supplement Blue Cross or BCN's databases by providing service or exclusion data of which Blue Cross or BCN had no knowledge
  - **A Quality Summary Report or Performance Recognition Program composite score** that shows the monthly quality composite rates for the primary care physician and provider organizations

ADMINISTRATIVE DETAILS

Health e-Blue

Health e-Blue provides a valuable opportunity for provider offices to assess their current performance and return data to Blue Cross or BCN. We accept electronic submission of data through the Healthy e-Blue application, EMR, claims and HEDIS initiatives. Entering missing information will help reduce reporting errors. If your office needs assistance with or has a question about BCN Health e-Blue, please contact Health e-Blue technical support at healtheblue@bcbsm.com. For Blue Cross Health e-Blue questions please contact MAHealtheblue@bcbsm.com.

Please remember that all data entered into Health e-Blue must be for services you provide, not for services ordered, reminders sent or referrals provided.

Distribution of Blue Cross and BCN Performance Recognition Program Payment Reports and Payments

Blue Cross and BCN will make every effort to send the 2016 payment reports and payments by summer 2017.

BCN payments will be made according to BCN's incentive payment policy, subject to the requirements outlined in this document. The primary care physician's payment will be associated with the medical care group the primary care physician is affiliated with as of December 31, 2016.

Reconsideration

Blue Cross and BCN strongly encourage primary care physicians to focus on the ongoing review and data submission using Health e-Blue during each Performance Recognition Program year. In the event any future reconsideration process is provided based on extenuating circumstances, Blue Cross or BCN will notify the affected primary care physician of the terms, conditions and limitations of such a process.

QUESTIONS

If you have questions or concerns about the Performance Recognition Program, please contact your **provider consultant**. You can find contact information for your provider consultant by following these steps:

- Go to bcbsm.com/providers.
- Click on *Contact Us* in the upper right corner of the page.
- Under *Physicians and professionals*, click on *Blue Cross Blue Shield of Michigan* or *Blue Care Network provider contacts*.
- Click on *Provider consultants*.
- Find your provider consultant either on the *physician organization consultants* list or the applicable regional list.

Additional Blue Cross and BCN contacts

Provider Outreach HEDIS/stars/Risk
Laurie Latvis, director
313-225-7778

Network Performance Improvement
Tracy Nelsen, Southeast and East Michigan
734-332-2181

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HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

ADULT BMI ASSESSMENT						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS/CMS stars					
Description	Members 18-74 years of age who had an outpatient visit and whose weight and body mass index was documented during the measurement year or year prior to the measurement year					
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan for 2015-2016					
Age criteria	Members 18 years of age as of January 1, 2016 to 74 years as of December 31, 2016					
Numerator	Members as defined above					
Denominator	The eligible population					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 70%	70 – 80.9%	81 – 89.9%	90 – 95.9%	≥ 96%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

BREAST CANCER SCREENING						
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS/CMS stars					
Description	The percentage of women who had a mammogram to screen for breast cancer					
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan October 1, 2014 through December 31, 2016					
Age criteria	52 to 74 years of age as of December 31, 2016					
Exclusionary criteria	Women who have had a bilateral mastectomy The following criteria meets bilateral mastectomy: • Bilateral mastectomy • Unilateral mastectomy with bilateral modifier • Two unilateral mastectomies with services dates 14 days or more apart					
Numerator	A mammogram at any time on or between October 1, 2014, and December 31, 2016					
Denominator	The eligible population					
Level of measure	Provider level					
Target: COMM	80%					
Payout: COMM	$100 per service completed for each eligible member					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 39%	39 – 62.9%	63 – 73.9%	74 – 79.9%	≥ 80%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

CHILDHOOD IMMUNIZATIONS – COMBO 10	
Product lines	**BCN Commercial**
Source	HEDIS
Description	The percentage of children 2 years of age who meet the combination 10 criteria on or before their second birthday: • (4) DTaP* vaccinations • (3) IPV* vaccinations • (1) MMR vaccination • (1) VZV vaccination • (3) HiB* vaccinations • (3) Hepatitis B vaccinations • (4) PCV* vaccinations • (1) HepA vaccination • (2 or 3) RV* vaccinations • (2) Influenza** vaccinations *Vaccinations administered prior to 42 days after birth are not counted as a numerator hit. **Vaccinations administered prior to 180 days after birth are not counted as a numerator hit.
Continuous enrollment	Must be continuously enrolled 12 months prior to child's second birthday
Age criteria	Children who turn 2 years of age during 2016
Exclusionary criteria	Children who are documented with an anaphylactic reaction to the vaccine or its components
Numerator	The number of children who completed vaccinations as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: COMM	63%
Payout: COMM	$400 per Combo 10 completed for each eligible member

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

WEIGHT ASSESSMENT AND COUNSELING FOR CHILDREN: BMI PERCENTILE, COUNSELING FOR NUTRITION AND COUNSELING FOR PHYSICAL ACTIVITY	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Members 3 to 17 years of age who have an active BCN Commercial span through the end of 2016 and had an outpatient visit between January 1, 2016, and December 31, 2016, with a PCP or ObGyn, where BMI percentile, counseling for nutrition and counseling for physical activity were documented in the medical record. The member's outpatient visit was reflected on a claim and the BMI percentile, counseling for nutrition and counseling for physical activity was reflected on a claim, electronic data submission for an EMR or entered in Health e-Blue.
Continuous enrollment	Must be continuously enrolled with BCN for 2016
Age criteria	3 to 17 years of age as of December 31, 2016
Numerator	• BMI percentile documentation during the measurement period (January to December 2016). Documentation in the member's medical record must also include height and weight. • Counseling for nutrition during the measurement period (January to December 2016). • Counseling for physical activity during the measurement period (January to December, 2016).
Denominator	The eligible population
Level of measure	Provider level
Target: COMM	63%
Payout: COMM	$150 per eligible member for whom all services were complete

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

COLORECTAL CANCER SCREENINGS						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS/CMS stars					
Description	The percentage of members who had appropriate screening for colorectal cancer					
Continuous enrollment	Must be continuously enrolled with the same Blue Cross/BCN plan for 2015-2016					
Age criteria	51 to 75 years as of December 31, 2016					
Exclusionary criteria	Either of the following any time during the member's history through December 31, 2016 • Colorectal cancer • Total colectomy					
Numerator	One or more screenings for colorectal cancer. Any of the following meet criteria: • Fecal occult blood test during 2016 (digital rectal exams do not count) • Flexible sigmoidoscopy 2012 through 2016 • Colonoscopy 2007 through 2016					
Denominator	The eligible population					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 51%	51 – 62.9%	63 – 70.9%	71 – 77.9%	≥ 78%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

COMPREHENSIVE DIABETES CARE: CONTROLLED HbA1c < 8%	
Product lines	**BCN Commercial**
Source	HEDIS
Description	The percentage of members with diabetes (type 1 or 2) and a documented HbA1c < 8% using the latest lab conducted in 2016
Continuous enrollment	Members must be continuously enrolled with the same BCN plan for 2016
Age criteria	18 to 75 years as of December 2016
Exclusionary criteria	• Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2015 or 2016 and • Did not have a diagnosis of diabetes in 2015 or 2016
Numerator	The number of members with diabetes (type 1 or 2) with an HbA1c < 8.0%. This measure considers the most recent lab conducted in 2016. The member is not compliant if the most recent result is ≥ 8, if the member is missing a result or the test was not done during 2016.
Denominator	All members with diabetes as defined above
Level of measure	Provider level
Target: COMM	68%
Payout: COMM	$250 per service completed for each eligible member

COMPREHENSIVE DIABETES CARE: CONTROLLED HbA1c ≤ 9%						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS/CMS stars					
Description	The percentage of members with diabetes (type 1 or 2) and a documented HbA1c ≤ 9% using the latest lab conducted in 2016					
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	18 to 75 years as of December 2016					
Exclusionary criteria	• Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2015 or 2016 and • Did not have a diagnosis of diabetes in 2015 or 2016					
Numerator	The number of members with diabetes (type 1 or 2) with an HbA1c ≤9.0% This measure considers the most recent lab conducted in 2016. The member is not compliant if the most recent result is > 9, the member is missing a result or the test was not done during 2016.					
Denominator	All members with diabetes as defined above					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	**Weight**
	< 49%	49 – 59.9%	60 – 70.9%	71 – 83.9%	≥ 84%	**3**
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

COMPREHENSIVE DIABETES CARE: MONITORING FOR NEPHROPATHY						
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS/CMS stars					
Description	The percentage of members with diabetes (type 1 or 2) who have had one of the following: • A nephropathy screening or monitoring test (test for urine albumin or protein) in 2016 • Medical treatment for nephropathy in 2016 • Visit with a nephrologist in 2016 • At least one dispensing event of ACEI/ARB medication in 2016					
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	18 to 75 years as of December 2016					
Exclusionary criteria	• Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2015 or 2016 and • Did not have a diagnosis of diabetes in 2015 or 2016					
Numerator	Members with diabetes (type 1 or 2) who have had one of the following: • A nephropathy screening or monitoring test (test for urine albumin or protein) in 2016 • Medical treatment for nephropathy in 2016 • Visit with a nephrologist in 2016 • At least one dispensing event of ACEI/ARB medication in 2016					
Denominator	All members with diabetes as defined above					
Level of measure	Provider level					
Target: COMM	90%					
Payout: COMM	$125 per service completed for each eligible member					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 85%	85 – 88.9%	89 – 92.9%	93 – 96.9%	≥ 97%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

CONTROLLING HIGH BLOOD PRESSURE: HYPERTENSION						
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	BCN and Blue Cross clinical guidelines					
Description	Members 18 to 85 years of age who were diagnosed with hypertension anytime on or before June 30, 2016 Control is demonstrated by: • Members 18 to 59 years of age with BP < 140/90 mm Hg • Members 60 to 85 years of age with diagnosis of diabetes with BP < 140/90 mm Hg • Members 60 to 85 years of age without a diagnosis of diabetes with BP < 150/90 mm Hg The last blood pressure reading between July 1, 2016 and December 31, 2016, will be counted.					
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	Members 18 to 85 years as of December 31, 2016					
Numerator	Members as defined above					
Denominator	The eligible population					
Level of measure	Provider level					
Target: COMM	75%					
Payout: COMM	$100 per service completed for each eligible member					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 47%	47 – 61.9%	62 – 74.9%	75 – 81.9%	≥ 82%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

DISEASE-MODIFYING ANTI-RHEUMATIC DRUG THERAPY FOR RHEUMATOID ARTHRITIS						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	HEDIS					
Description	The percentage of members ages 18 years of age or older diagnosed with rheumatoid arthritis who were dispensed at least one ambulatory prescription for a disease-modifying anti-rheumatic drug					
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plans for 2016					
Age criteria	18 to 85 years of age or older as of December 31, 2016					
Numerator	Members as defined above					
Denominator	The eligible population					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	Weight
	< 64%	64 – 74.9%	75 – 81.9%	82 – 85.9%	≥ 86%	1
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

MEDICATION ADHERENCE FOR DIABETES MEDICATIONS						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	CMS stars					
Description	The percentage of adult Medicare members who adhere to their prescribed drug therapy across the following classes of oral diabetes medications; biguanides, sulfonylureas, thiazolidinediones, DPP-IV inhibitors, incretin mimetics, meglitinides, and SGLT2 inhibitors					
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	18 years of age by December 31, 2016					
Numerator	Number of adult members 18 years or older enrolled during 2016 with a proportion of days covered at 80 percent or more across the classes of oral diabetes medications Members are excluded if they have one or more fills for insulin during the measurement period.					
Denominator	Number of adult members 18 years or older enrolled during 2016 with at least two fills of medication across any of the drug classes					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	**Weight**
	< 60%	60 – 68.9%	69 – 74.9%	75 – 81.9%	≥ 82%	**3**
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

MEDICATION ADHERENCE FOR HYPERTENSION MEDICATIONS						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	CMS stars					
Description	The percentage of adult Medicare members who adhere to their prescribed drug therapy for ACEI or ARB medications					
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	18 years of age by December 31, 2016					
Numerator	Number of adult members 18 years of age or older enrolled during 2016 with a proportion of days covered at 80 percent or more for ACEI or ARB medications					
Denominator	Number of adult members 18 years or older enrolled during 2016 with at least two fills of either the same medication or medications with the same active ingredient					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	**Weight**
	< 58%	58 – 72.9%	73 – 76.9%	77 – 80.9%	≥ 81%	**3**
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

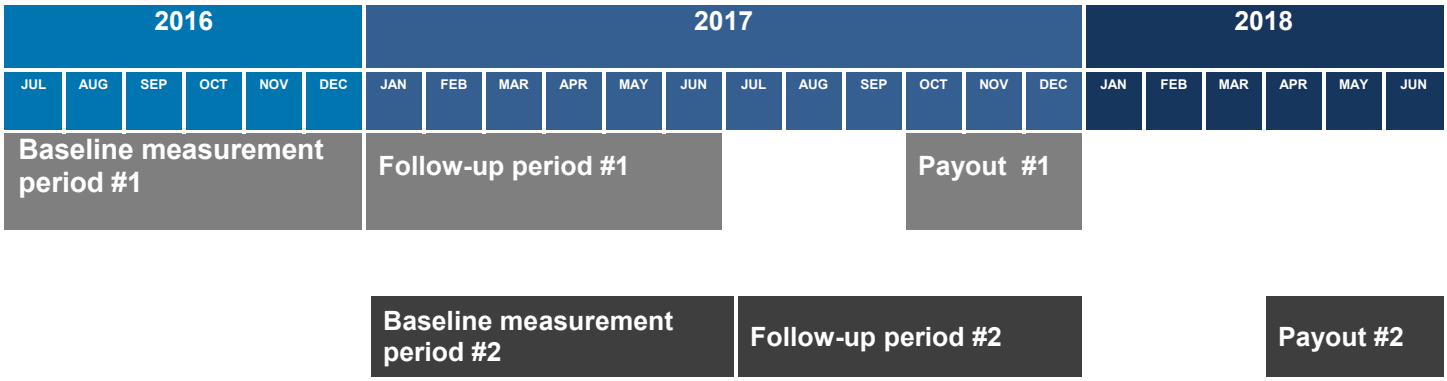
MEDICATION ADHERENCE FOR CHOLESTEROL MEDICATIONS						
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**					
Source	CMS stars					
Description	The percentage of adult Medicare members who adhere to their prescribed drug therapy for statin cholesterol medications					
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plan for 2016					
Age criteria	18 years of age by December 31, 2016					
Numerator	Number of adult members 18 years of age or older enrolled during the measurement period with a proportion of days covered at 80 percent or more for statin cholesterol medications					
Denominator	Number of adult members 18 years of age or older enrolled during 2016 with at least two fills of either the same statin medication or medications with the same active ingredient.					
Level of measure	Provider level					
Target: BCNA/MAPPO	1 star	2 stars	3 stars	4 stars	5 stars	**Weight**
	< 50%	50 – 60.9%	61 – 72.9%	73 – 78.9%	≥ 79%	**3**
Payout: BCNA/MAPPO	Per member, per month, based on overall average stars score for Medicare PRP measures					

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

SMOKING/TOBACCO CESSATION COUNSELING	
Product lines	**BCN Commercial**
Source	BCN Medical Administration
Description	Members who use tobacco and receive face-to-face cessation advice, information on medications and strategies to help them quit, and a follow-up letter from the physician to review the information discussed
Continuous enrollment	Not required
Age criteria	Members 18 years of age or older as of January 1, 2016
Numerator	Members as defined above who are smokers or tobacco users
Denominator	The eligible population
Level of measure	Provider level
Target: COMM	Flat fee per member who meets measure
Payout: COMM	$30 per service completed for each eligible member
Additional Details:	PCPs were provided with a sample member letter in the January-February 2016 *BCN Provider News* to send upon completion of an office visit that summarized the following that took place during the visit: • Face-to-face tobacco cessation advice • Information and medications that can assist the member in tobacco cessation • Tobacco cessation strategies to increase the member's chance of success These letters must be sent to the member upon completion of the visit and a copy must also be faxed to BCN at 1-**866-637-4972** to receive credit for this measure. The letter must be in the format provided by BCN in order to receive credit. A template for this letter can be found at **bcbsm.com**. 1. Login to Provider Secured Services. 2. Click on *BCN Provider Publications and Resources*. 3. Click on Forms and look under *Member materials*.

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

DEPRESSION MANAGEMENT: PHQ9 TESTING	
Product lines	**BCN Commercial**
Source	BCN Medical Administration
Description	Members who have any depressive condition and had a PHQ9 administered during the baseline period scoring greater than or equal to 10 and had a follow-up PHQ9 administered during the follow-up period, scoring below 5.
Continuous enrollment	Members must be continuously enrolled with the same BCN plan for the baseline and follow-up periods
Age criteria	12 years of age or older as of the first day of the baseline measurement period
Numerator	The last qualifying encounter (PHQ9 screening with a score < 5) in the follow-period determines the numerator events for the performance measure.
Denominator	The first qualifying encounter (PHQ9 Screening with a score ≥ 10) in the baseline determines the denominator events for the performance measure.
Level of measure	Provider level
Target: COMM	Flat fee per member who meets measure
Payout: COMM	$200 per service completed for each eligible member
Additional Details:	Measurement periods, follow-up periods and payouts will be on a rolling basis as outlined below:



CMS MILLION HEARTS INCENTIVE PROGRAM

Blue Care Network has implemented a program to prevent cardiovascular disease. The program is designed for BCN Advantage members, ages 40 and over, who have a history of cardiovascular disease or diabetes. The focus of the program is to reduce the morbidity and mortality related to cardiovascular disease in these members.

The program incorporates clinical practice guidelines for the management of ischemic heart disease and diabetes mellitus following the guiding principles behind the nation Million Hearts™ initiative. Million Hearts is a national initiative to prevent 1 million heart attacks and strokes over five years. It is led by the U.S. Department of Health and Human Services, the Centers for Disease Control and Prevention and the Centers for Medicare & Medicaid Services in partnership with other federal agencies.

CMS Million Hearts payment table

Quality incentive measures	Plan goal	Payout
Aspirin or antiplatelet therapy	Flat fee	$25
Blood pressure control	Flat fee	$25
Tobacco cessation counseling	Flat fee	$25

CMS Million Hearts payment calculation

CMS Million Hearts requires no specific plan goal. A flat fee is paid for each service completed.

CMS Million Hearts program qualifications

Providers must meet the Performance Recognition Program qualifications in order to be considered for a CMS Million Hearts incentive payment.

Providers can locate Million Hearts members in Health e-Blue under the Treatment Opportunity by Condition/Measures.

CMS Million Hearts data submission options

- Submit a claim with an appropriate CPT II code
- Health e-Blue entry
- Electronic medical record exchange

CMS MILLION HEARTS PROVIDER INCENTIVE
QUALITY INCENTIVE MEASURES

ASPIRIN OR ANTIPLATELET THERAPY	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2016, with a history of diabetes, cardiovascular disease or both who is prescribed or currently taking aspirin or antiplatelet therapy Report CPT II code 4086F for all patients meeting criteria
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

BLOOD PRESSURE CONTROL	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2016 who meet both the systolic and diastolic blood pressure reading requirements: • Members 18-59 years of age as of December 31, 2016 whose BP was < 140/90 mm Hg • Members 60-85 years of age as of December 31, 2016 with a diagnosis of diabetes whose BP was < 140/90 mm Hg • Members 60-85 years of age as of December 31, 2016 without a diagnosis of diabetes whose BP was < 150/90 mm Hg • Systolic blood pressure value report one of the systolic codes – 3074F – SBP < 130 – 3075F – SBP 130-139 – SBP > 140 and < 150 (Needs to be documented in EMR or in HEB. No CPT Cat II codes are available) • Diastolic blood pressure value report one of the diastolic codes – 3078F – DBP < 80 – 3079F – DBP 80-89
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

CMS MILLION HEARTS PROVIDER INCENTIVE
QUALITY INCENTIVE MEASURES

SMOKING/TOBACCO CESSATION COUNSELING	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2016 who are smokers and have been counseled on the importance of quitting smoking Providers can report 'Not a smoker' in Health e-Blue as an Exclusion Reason / Contra-Indication Report CPT II code 4000F or 4004F for each patient identified as a tobacco user and received tobacco cessation counseling
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

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2017 Performance Recognition Program

PROVIDER INCENTIVE PROGRAM FOR:

- **BCN Commercial HMO**
- **BCN Advantage℠ HMO-POS**
- **BCBSM Medicare Plus Blue℠ PPO**

CONTENTS

2017 PERFORMANCE RECOGNITION PROGRAM

The Provider Performance Recognition Program rewards Blue Care Network commercial providers and Medicare Advantage providers for both Blue Cross Blue Shield of Michigan and BCN for their role in helping Blue Cross and BCN achieve the objectives of the Healthcare Effectiveness Data and Information Set, or HEDIS®, and the Centers for Medicare & Medicaid Services' star ratings program. These objectives include:

- Better care
- Healthier people and communities
- Affordable care

Each program rewards providers who encourage their patients to get preventive screenings and procedures, such as eye exams and mammograms, and for achieving patient outcomes such as ensuring diabetic members have their blood sugar controlled.

Our philosophy is to use meaningful payments to encourage positive clinical results as well as increase HEDIS outcomes and CMS star ratings.

The components of the program, including the performance measures that are based on HEDIS benchmarks, are described in this booklet.

We encourage primary care physicians or PCP offices to have a Health e-Blue℠ sign-on and actively use the program.

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2017 PHYSICIAN QUALITY INCENTIVE MEASURES

QUALITY INCENTIVE MEASURES	BCN COMMERCIAL HMO	BCN ADVANTAGE℠ HMO	BLUE CROSS MEDICARE ADVANTAGE PPO
Aspirin or antiplatelet therapy		■	
Breast cancer screening	●	●	●
Colorectal cancer screening		●	●
Comprehensive diabetes care: eye examination	●	●	●
Comprehensive diabetes care: HbA1c < 8%	●		
Comprehensive diabetes care: HbA1c ≤ 9%		●	●
Comprehensive diabetes care: monitoring for nephropathy	●	●	●
Blood pressure control		■	
Controlling high blood pressure for hypertension		●	●
Depression management — PHQ9 testing	●		
Disease modifying antirheumatic drug therapy for rheumatoid arthritis		●	●
Influenza immunizations — pediatrics	●		
Follow-up after hospitalization, medical – 3 days		●	●
Follow up care for children with prescribed ADHD medication - initiation phase	●		
Osteoporosis management in women who had a fracture		●	●
Tobacco cessation counseling		■	
Use of imaging studies for low back pain	●		
Weight assessment and counseling for children: BMI percentile	●		
Weight assessment and counseling for children: counseling for nutrition	●		
Weight assessment and counseling for children: counseling for physical activity	●		
Well care visits – first 15 months	●		

Key

● = Performance Recognition Program
■ = CMS Million Hearts

BLUE CROSS BLUE SHIELD OF MICHIGAN AND BLUE CARE NETWORK
2017 PAYOUT SUMMARY

Payment calculation

Payments for each eligible provider are calculated using the following method.

For measures with a goal:

1. Quality score: A quality score for each program measure is computed for each provider using the following formula:
   a) Numerator = Eligible members meeting criteria
   b) Denominator = Total members eligible
   c) Numerator ÷ Denominator: The individual provider's quality score for each program measure

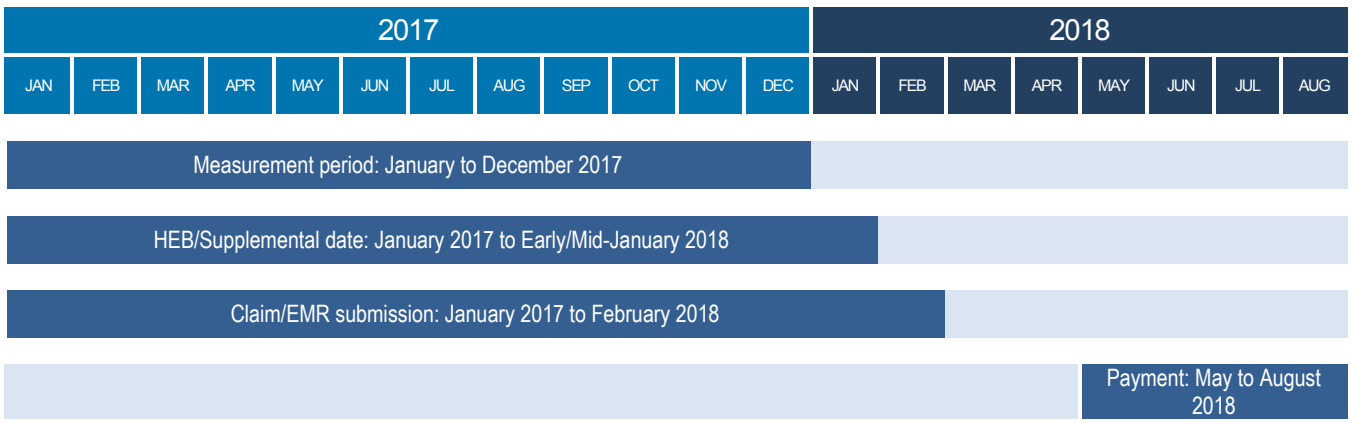
2. Compare the individual provider's quality score to the plan goal for quality. The payment for services will be calculated once the plan goal is met, based upon the numerator.

For measures with no specific goal, a flat fee will be paid for each service completed.

Payment table

QUALITY INCENTIVE MEASURES	BCN COMMERCIAL		MEDICARE ADVANTAGE℠	
	Goal	Payout	Goal	Payout
Breast cancer screening	80%	$125	76%	$50
Childhood immunizations — Influenza	flat fee	$50		
Colorectal cancer screening			78%	$50
Comprehensive diabetes care: eye examination	flat fee	$25	flat fee	$25
Comprehensive diabetes care: HbA1c < 8%	66%	$250		
Comprehensive diabetes care: HbA1c ≤ 9%			84%	$125
Comprehensive diabetes care: monitoring for nephropathy	93%	$150	97%	$75
Controlling high blood pressure for hypertension			86%	$25
Depression management — PHQ9 testing	flat fee	$200		
Disease-modifying anti-rheumatic drug therapy for rheumatoid arthritis			flat fee	$100
Follow-up after hospitalization, medical – 3 days			flat fee	$50
Follow-up care for children with prescribed ADHD medication - initiation phase	47%	$100		
Osteoporosis management in women who had a fracture			flat fee	$100
Use of imaging studies for low back pain	83%	$150		
Weight assessment and counseling for children: BMI percentile	83%	$50		
Weight assessment and counseling for children: counseling for nutrition	78%	$75		
Weight assessment and counseling for children: counseling for physical activity	63%	$100		
Well care visits – first 15 months	89%	$100		

2017 PROGRAM SCHEDULE



Note: See Page 16 for the depression management quality measure schedule.

BLUE CARE NETWORK COMMERCIAL
2017 MARKETPLACE MEMBERSHIP PAYOUT

To recognize the added effort required in managing the Marketplace population of members, BCN is offering a premium to providers who have a larger Marketplace membership and continue to meet performance goals. Providers whose assigned BCN Commercial membership is made up of ≥ 20 percent marketplace members will receive a 15 percent premium on Performance Recognition Program payments earned.

BCN will alert providers who qualify for this premium (based upon total 2016 BCN Commercial member months) at the start of the 2017 measurement year.

Example

Dr. A has 1,000 total BCN Commercial member months in 2016 and 250 of those member months were from the Marketplace population of members (25 percent of the total) and therefore qualifies for the Marketplace premium. Dr. A's performance by measure is outlined below.

QUALITY INCENTIVE MEASURES	Goal	Payout	Dr. A Score	Goal Met or Missed?	Dr. A Numerator	PRP Payment
Breast cancer screening	80%	$125	82%	Met	30	$3,750
Childhood immunizations — Influenza	flat fee	$50	n/a	n/a	2	$100
Comprehensive diabetes care: eye examination	flat fee	$25	n/a	n/a	2	$50
Comprehensive diabetes care: HbA1c < 8%	66%	$250	78%	Met	8	$2,000
Comprehensive diabetes care: monitoring for nephropathy	93%	$150	56%	Missed	5	$0
Depression management — PHQ9 testing	flat fee	$200	n/a	n/a	2	$400
Follow-up care for children with prescribed ADHD medication - initiation phase	47%	$100	50%	Met	1	$100
Use of imaging studies for low back pain	83%	$150	100%	Met	1	$150
Weight assessment & counseling for children: BMI percentile	83%	$50	83%	Met	10	$500
Weight assessment & counseling for children: counseling for nutrition	78%	$75	83%	Met	10	$750
Weight assessment & counseling for children: counseling for physical activity	63%	$100	67%	Met	8	$800
Well care visits – first 15 months	89%	$100	100%	Met	2	$200
Total base PRP payment						**$8,800**
15% Marketplace premium						**$1,320**
Total PRP payment with Marketplace premium						**$10,120**

Dr. A earned a 2017 base PRP payment of $8,800 plus a 15 percent premium of $1,320 to add up to a total payment of $10,120.

PROGRAM QUALIFICATIONS

1. The primary care physician or physician organization must sign the BCN 2017 Medical Services Agreement to participate in the BCN Commercial and BCN Advantage Performance Recognition Programs and the Blue Cross Medicare Advantage PPO Provider Agreement to participate in the Blue Cross Medicare Plus Blue PPO Performance Recognition Program.

2. The primary care physician or physician organization must comply with all terms and conditions of those agreements, including:
   - Providing timely and accurate encounter, referral and claims data
   - Remitting any funds due for prior contract years

3. The primary care physician must be affiliated for the entire 2017 calendar year.

4. Primary care physicians must have attributed or assigned members to participate in the program.

5. The primary care physician must be affiliated at the time of payment to be eligible for any program payments unless the PCP recently retired.

6. BCN and Blue Cross retain the right to modify the Performance Recognition Program for any reason and at any time. Modifications may include but are not limited to:
   - Exclusion or removal of program measures
   - Changes to program calculation methods

PERFORMANCE MEASUREMENT GUIDELINES

Measurement timeframe

Each primary care physician will be credited for services completed through **December 31, 2017** to members who meet all measurement requirements, are continuously enrolled with the plan for the entire year and are assigned to a primary care physician whether or not the primary care physician was the member's primary care physician at the time services were provided.

Exclusions

Members may be excluded from measures under certain circumstances such as bilateral mastectomy for breast cancer screening, which should be indicated to Blue Cross or BCN by the primary care physician offices via the Health e-Blue *Treatment Opportunities by Condition/Measure* screen.

Members in hospice during 2017 are excluded from the PRP program.

Qualifying Services

Credit will be granted to the primary care physician for each component measure only when the specific identified **service is documented as provided** to the member (by the primary care physician, the member's previous primary care physician or a specialist).

Blue Cross and BCN recognize that many primary care physician offices send **reminder letters** or may not see certain members in their offices who are identified by Blue Cross or BCN as needing certain services. Such occurrences **won't count** as credit toward the component measure.

Reporting

Each primary care physician's quality performance measurement data comes directly from Blue Cross or BCN's Health Management Program reporting database accessible through Health e-Blue. The Health e-Blue *Treatment Opportunities by Condition/Measure* for the Performance Recognition Program will include:

- A list of the cohort member population for each component measure that needs a specific health promotion, disease prevention or health management service according to evidence-based medicine
- **Intervention** opportunities for physicians to supplement Blue Cross or BCN's databases by providing service or exclusion data of which Blue Cross or BCN had no knowledge
- **A Quality Summary Report or Performance Recognition Program composite score** that shows the monthly quality composite rates for the primary care physician and provider organizations

ADMINISTRATIVE DETAILS

Health e-Blue℠

Health e-Blue provides a valuable opportunity for provider offices to assess their current performance and return data to Blue Cross or BCN. We accept electronic submission of data through the Healthy e-Blue application, EMR, claims and HEDIS initiatives. Entering missing information will reduce reporting errors. If your office has a question about BCN Health e-Blue, please contact Health e-Blue technical support at healtheblue@bcbsm.com. For Blue Cross Health e-Blue questions, contact MAHealtheblue@bcbsm.com.

Please remember that all data entered into Health e-Blue must be for services you provide, not for services ordered, reminders sent or referrals provided.

Distribution of Blue Cross and BCN Performance Recognition Program Payment Reports and Payments

Blue Cross and BCN will make every effort to send the 2017 payments and payment reports by **summer 2017**. BCN payments will be made according to BCN's incentive payment policy, subject to the requirements outlined in this document. The primary care physician's payment will be associated with the medical care group the primary care physician is affiliated with as of **December 31, 2017.**

Reconsideration

Blue Cross and BCN strongly encourage primary care physicians to focus on the ongoing review and data submission using Health e-Blue during each Performance Recognition Program year. In the event any future reconsideration process is provided based on **extenuating circumstances**, Blue Cross or BCN will notify the affected primary care physician of the terms, conditions and limitations of such a process.

QUESTIONS

If you have questions about the Performance Recognition Program, please contact your **provider consultant**. You can find contact information by following these steps:

- Go to bcbsm.com/providers.
- Click on *Contact Us* in the upper right corner of the page.
- Under *Physicians and professionals*, click on *Blue Cross Blue Shield of Michigan* or *Blue Care Network provider contacts*.
- Click on *Provider consultants*.
- Find your provider consultant either on the *physician organization consultants* list or the applicable regional list.

Additional Blue Cross and BCN contacts

Provider Outreach HEDIS/stars/Risk
Laurie Latvis, director
313-225-7778

Network Performance Improvement
Tracy Nelsen, Southeast and East Michigan
734-332-2181

Christine Wojtaszek, Mid and West Michigan
616-956-5769

Health e-Blue technical support

BCN Commercial and BCN Advantage
healtheblue@bcbsm.com

Blue Cross Medicare Plus Blue PPO
MAHealtheblue@bcbsm.com

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

BREAST CANCER SCREENING	
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS/CMS stars
Description	The percentage of women who had a mammogram to screen for breast cancer
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan October 1, 2015 through December 31, 2017
Age criteria	52 to 74 years of age as of December 31, 2017
Exclusionary criteria	Women who have had a bilateral mastectomy The following criteria meets bilateral mastectomy: • Bilateral mastectomy • Unilateral mastectomy with bilateral modifier • Two unilateral mastectomies with services dates 14 days or more apart
Numerator	A mammogram at any time on or between October 1, 2015 and December 31, 2017
Denominator	The eligible population
Target: COMM	80%
Payout: COMM	$125 per service completed for each eligible member
Target: BCNA/MAPPO	76%
Payout: BCNA/MAPPO	$50 per service completed for each eligible member

CHILDHOOD IMMUNIZATIONS – INFLUENZA	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Two influenza vaccinations with different dates of service, administered on or before the second birthday. Vaccinations administered prior to 180 days after birth are not counted as a numerator hit
Continuous enrollment	Must be continuously enrolled 12 months prior to child's second birthday
Age criteria	Children who turn 2 years of age during 2017
Exclusionary criteria	Children who are documented with an anaphylactic reaction to the vaccine or its components
Numerator	The number of children who completed vaccinations as defined above
Denominator	The eligible population
Target: COMM	Flat fee per member who meets measure
Payout: COMM	$50 per eligible member for whom all services were complete (not payable per vaccination)

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

COLORECTAL CANCER SCREENINGS	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS/CMS stars
Description	The percentage of members who had appropriate screening for colorectal cancer
Continuous enrollment	Must be continuously enrolled with the same Blue Cross/BCN plan for 2016-2017
Age criteria	51 to 75 years as of December 31, 2017
Exclusionary criteria	Either of the following any time during the member's history through December 31, 2017 • Colorectal cancer • Total colectomy
Numerator	One or more screenings for colorectal cancer. Any of the following meet criteria: • Fecal occult blood test during 2017 (digital rectal exams do not count) • Flexible sigmoidoscopy 2013 through 2017 • Colonoscopy 2008 through 2017 • FIT-DNA (Cologuard®) 2015 through 2017 • CT Colonography 2013 through 2017
Denominator	The eligible population
Target: BCNA/MAPPO	78%
Payout: BCNA/MAPPO	$50 per eligible member for whom all services were complete

WEIGHT ASSESSMENT AND COUNSELING FOR CHILDREN: BMI PERCENTILE	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Members 3 to 17 years of age who have an active BCN Commercial span through the end of 2017 and had an outpatient visit between January 1, 2017, and December 31, 2017, with a PCP or OB-GYN, where BMI percentile was documented in the medical record The member's outpatient visit was reflected on a claim and the BMI percentile was reflected on a claim, electronic data submission for an EMR or entered in Health e-Blue
Continuous enrollment	Must be continuously enrolled with BCN for 2017
Age criteria	3 to 17 years of age as of December 31, 2017
Exclusionary criteria	Members who have a diagnosis of pregnancy during the measurement year
Numerator	BMI percentile documentation during the measurement period (January to December 2017) Documentation in the member's medical record must also include height and weight
Denominator	The eligible population
Target: COMM	83%
Payout: COMM	$50 per eligible member for whom all services were complete

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

WEIGHT ASSESSMENT AND COUNSELING FOR CHILDREN: COUNSELING FOR NUTRITION	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Members 3 to 17 years of age who have an active BCN Commercial span through the end of 2017 and had an outpatient visit between January 1, 2017 and December 31, 2017, with a PCP or OB-GYN, where BMI counseling for nutrition was documented in the medical recordThe member's outpatient visit was reflected on a claim and the counseling for nutrition was reflected on a claim, electronic data submission for an EMR or entered in Health e-Blue
Continuous enrollment	Must be continuously enrolled with BCN for 2017
Exclusionary criteria	Members who have a diagnosis of pregnancy during the measurement year
Age criteria	3 to 17 years of age as of December 31, 2017
Numerator	Counseling for nutrition during the measurement period — January to December 2017
Denominator	The eligible population
Target: COMM	78%
Payout: COMM	$75 per eligible member for whom all services were complete

WEIGHT ASSESSMENT AND COUNSELING FOR CHILDREN: COUNSELING FOR PHYSICAL ACTIVITY	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Members 3 to 17 years of age who have an active BCN Commercial span through the end of 2017 and had an outpatient visit between January 1, 2017 and December 31, 2017 with a PCP or OB-GYN, where counseling for physical activity was documented in the medical record The member's outpatient visit was reflected on a claim and the counseling for physical activity was reflected on a claim, electronic data submission for an EMR or entered in Health e-Blue
Continuous enrollment	Must be continuously enrolled with BCN for 2017
Age criteria	3 to 17 years of age as of December 31, 2017
Exclusionary criteria	Members who have a diagnosis of pregnancy during the measurement year
Numerator	Counseling for physical activity during the measurement period (January to December, 2017)
Denominator	The eligible population
Target: COMM	63%
Payout: COMM	$100 per eligible member for whom all services were complete

HEALTH CARE OUTCOMES: PREVENTIVE HEALTH

WELL CARE VISITS – FIRST 15 MONTHS	
Product lines	**BCN Commercial**
Source	HEDIS
Description	Percentage of children with 6 or more well-child visits in the first 15 months of life
Continuous enrollment	Must be continuously enrolled 31 days of age through 15 months
Age criteria	Children who turn 15 months during 2017
Numerator	The number of children who completed six or more well-care visits with a primary care physician in the first 15 months of life with different dates of service
Denominator	The eligible population
Target: COMM	89%
Payout: COMM	$100 per eligible member for whom all services were complete

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

COMPREHENSIVE DIABETES CARE: RETINAL EYE EXAMS	
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS
Description	The percentage of members with diabetes (Type 1 or 2) and a documented retinal eye exam
Continuous enrollment	Members must be continuously enrolled with the same BCN plan for 2017
Age criteria	18 to 75 years as of December 2017
Exclusionary criteria	Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2016 or 2017
Numerator	The number of members with diabetes (Type 1 or 2) with a retinal eye exam during 2017 or a retinal eye exam with negative results during 2016
Denominator	All members with diabetes as defined above
Target: COMM	Flat fee per member who meets measure
Payout: COMM	$25 per service completed for each eligible member
Target: BCNA/MAPPO	Flat fee per member who meets measure
Payout: BCNA/MAPPO	$25 per service completed for each eligible member
Additional Details	This measure is payable to the provider who performs the service (if an eye care professional performs the service, he or she is eligible for the incentive, not the PCP). All results must be submitted in order to qualify for this incentive

COMPREHENSIVE DIABETES CARE: CONTROLLED HbA1c < 8%	
Product lines	**BCN Commercial**
Source	HEDIS
Description	The percentage of members with diabetes (Type 1 or 2) and a documented HbA1c < 8% using the latest lab conducted in 2017
Continuous enrollment	Members must be continuously enrolled with the same BCN plan for 2017
Age criteria	18 to 75 years as of December 2017
Exclusionary criteria	Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2016 or 2017
Numerator	The number of members with diabetes (Type 1 or 2) with an HbA1c < 8.0%. This measure considers the most recent lab conducted in 2017. The member isn't compliant if the most recent result is ≥ 8, if the member is missing a result or the test was not done during 2017
Denominator	All members with diabetes as defined above
Target: COMM	66%
Payout: COMM	$250 per service completed for each eligible member

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

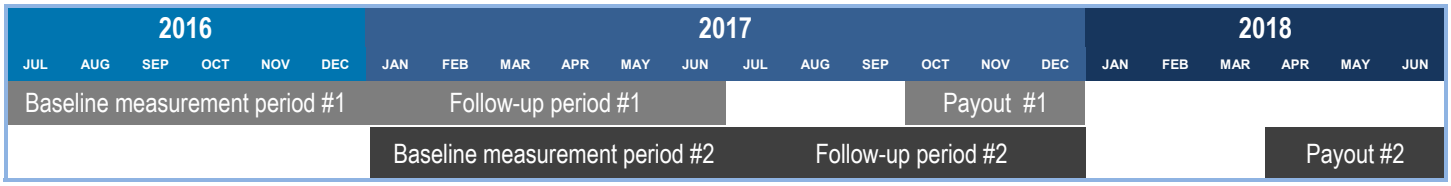
COMPREHENSIVE DIABETES CARE: CONTROLLED HbA1c ≤ 9%	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS/CMS stars
Description	The percentage of members with diabetes (Type 1 or 2) and a documented HbA1c ≤ 9% using the latest lab conducted in 2017
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan for 2017
Age criteria	18 to 75 years as of December 2017
Exclusionary criteria	Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2016 or 2017
Numerator	The number of members with diabetes (Type 1 or 2) with an HbA1c ≤9.0% This measure considers the most recent lab conducted in 2017. The member isn't compliant if the most recent result is > 9, the member is missing a result or the test wasn't done during 2017
Denominator	All members with diabetes as defined above
Target: BCNA/MAPPO	84%
Payout: BCNA/MAPPO	$125 per service completed for each eligible member

COMPREHENSIVE DIABETES CARE: MONITORING FOR NEPHROPATHY	
Product lines	**BCN Commercial, BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS/CMS stars
Description	The percentage of members with diabetes (Type 1 or 2) who have had one of the following: • A nephropathy screening or monitoring test (test for urine albumin or protein) in 2017 • Medical treatment for nephropathy in 2017 • Visit with a nephrologist in 2017 • At least one dispensing event of ACEI/ARB medication in 2017
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plan for 2017
Age criteria	18 to 75 years as of December 2017
Exclusionary criteria	Diagnosis of gestational or steroid-induced diabetes, in any setting, during 2016 or 2017
Numerator	Members with diabetes (Type 1 or 2) who have had one of the following: • A nephropathy screening or monitoring test (test for urine albumin or protein) in 2017 • Medical treatment for nephropathy in 2017 • Visit with a nephrologist in 2017 • At least one dispensing event of ACEI/ARB medication in 2017
Denominator	All members with diabetes as defined above
Target: COMM	93%
Payout: COMM	$150 per service completed for each eligible member
Target: BCNA/MAPPO	97%
Payout: BCNA/MAPPO	$75 per service completed for each eligible member

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

CONTROLLING HIGH BLOOD PRESSURE: HYPERTENSION	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	BCN and Blue Cross clinical guidelines
Description	Members 18 to 85 years of age who were diagnosed with hypertension anytime on or before June 30, 2017 Control is demonstrated by: • Members 18 to 59 years of age with BP < 140/90 mm Hg • Members 60 to 85 years of age with diagnosis of diabetes with BP < 140/90 mm Hg • Members 60 to 85 years of age without a diagnosis of diabetes with BP < 150/90 mm Hg The last blood pressure reading prior to December 31, 2017 will be counted The last controlled blood pressure must occur after the date of diagnosis
Continuous enrollment	Must be continuously enrolled with the same Blue Cross or BCN plan for 2017
Age criteria	Members 18 to 85 years as of December 31, 2016
Exclusionary Criteria	For exclusions, please refer to the HEDIS 2017 Specification Document
Numerator	Members as defined above
Denominator	The eligible population
Target: BCNA/MAPPO	86%
Payout: BCNA/MAPPO	$25 per service completed for each eligible member

DEPRESSION MANAGEMENT: PHQ9 TESTING	
Product lines	**BCN Commercial**
Source	BCN Medical Administration
Description	Members who have a PHQ9 administered during the baseline period, scoring greater than or equal to 10 and had a follow-up PHQ9 administered during the follow-up period, scoring below 5 or with a reduction of 50% from the original score
Continuous enrollment	Members must be continuously enrolled for the baseline and follow-up periods
Age criteria	12 years of age or older as of the first day of the baseline measurement period
Numerator	The last qualifying encounter (PHQ9 screening with a score < 5 or a 50% reduction from the original score, to indicate remission) in the follow-up period determines the numerator events for the performance measure
Denominator	The first qualifying encounter (PHQ9 Screening with a score ≥ 10) in the baseline determines the denominator events for the performance measure. Only those scoring ≥ 10 will appear in the Treatment Opportunities panel
Target: COMM	Flat fee per member who meets measure
Payout: COMM	$200 per service completed for each eligible member
Additional Details:	See Appendix 2 for a step-by-step guide on how to enter data to qualify for this measure. We *will not* display the PHQ-9 testing rate on the HEB QSRs when the data become available Measurement periods, follow-up periods and payouts will be on a rolling basis as outlined below:



DISEASE-MODIFYING ANTI-RHEUMATIC DRUG THERAPY FOR RHEUMATOID ARTHRITIS	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS, CMS Stars
Description	The percentage of members 18 years of age or older diagnosed with rheumatoid arthritis who were dispensed at least one ambulatory prescription for a disease-modifying anti-rheumatic drug
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plans for 2017
Age criteria	18 to 85 years of age or older as of December 31, 2017
Numerator	Members as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: BCNA/MAPPO	Flat fee per member who meets measure
Payout: BCNA/MAPPO	$100 per service completed for each eligible member

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

FOLLOW-UP AFTER HOSPITALIZATION WITHIN 3 DAYS OF A MEDICAL DISCHARGE	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	BCN and BCBSM Medical Administration
Description	The percentage of members who had a follow-up visit with their PCP or specialist within three days of a medical hospital discharge
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plans for 2017
Age criteria	18 to 85 years of age or older as of December 31, 2017
Numerator	Members as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: BCNA/MAPPO	Flat fee per member who meets measure
Payout: BCNA/MAPPO	$50 per service completed for each eligible member
Additional Information	The goal of this measure is to aid in medication reconciliation, post discharge and to avoid member readmissions

FOLLOW-UP CARE FOR CHILDREN WITH PRESCRIBED ADHD MEDICATION – INITIATION PHASE	
Product lines	**BCN Commercial**
Source	HEDIS
Description	The percentage of members 6 to 12 years of age as of the Index Prescription Start Date with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with practitioner with prescribing authority during the 30-day Initiation Phase
Continuous enrollment	Members must be continuously enrolled for 120 days prior to the IPSD through 30 days after the IPSD
Age criteria	6 to 12 years of age as of December 31, 2017
Exclusionary criteria	Exclude from the denominator for both rates, members with a diagnosis of narcolepsy any time during their history through December 31, 2017
Numerator	Members as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: COMM	47%
Payout: COMM	$100 per service completed for each eligible member
Additional Information	This measure doesn't match HEDIS timeframes. This measure will consider IPSD from January 1, 2017 through December 31, 2017 and will allow for a 30-day runout into 2018 to track follow-up visits for IPSD occurring in the last month of 2017

HEALTH CARE OUTCOMES: DISEASE MANAGEMENT

OSTEOPOROSIS MANAGEMENT IN WOMEN WHO HAD A FRACTURE	
Product lines	**BCN Advantage, Blue Cross Medicare Plus Blue PPO**
Source	HEDIS, CMS Stars
Description	The percentage of women 67 to 85 years of age who suffered a fracture and who had EITHER a bone mineral density test or a prescription for a drug to treat or to prevent osteoporosis in the six months after the fracture The member has to be negative for a diagnosis of fracture for 60 days (two months) prior to the IESD and have appropriate testing or treatment for osteoporosis after the fracture defined by any of the following criteria: • A BMD test on the initial fracture date (IESD) or in the 180-day period after the initial fracture date - OR - • A BMD test during the inpatient stay for the fracture (applies only to fractures requiring hospitalization) - OR - • A dispensed prescription to treat osteoporosis on the initial fracture date or in the 180-day period after the initial fracture date
Continuous enrollment	12 months before the initial fracture date through six months after the initial fracture date
Age criteria	Women 67 to 85 years of age as of December 31, 2017
Exclusionary criteria	Exclude members who had a BMD 730 days prior to IESD, or a claim/encounter for osteoporosis therapy or received a dispensed prescription to treat osteoporosis during the 365 days prior to the IESD
Numerator	Members as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: BCNA/MAPPO	Flat fee per member who meets measure
Payout: BCNA/MAPPO	$100 per service completed for each eligible member

USE OF IMAGING STUDIES FOR LOW BACK PAIN	
Product lines	**BCN Commercial**
Source	HEDIS
Description	The percentage of members with a primary diagnosis of low back pain who didn't have an imaging study (plain X-ray, MRI, CT scan) within 28 days of the diagnosis
Continuous enrollment	Members must be continuously enrolled with the same Blue Cross or BCN plans for 2017
Age criteria	18 to 85 years of age or older as of December 31, 2017
Numerator	Members as defined above
Denominator	The eligible population
Level of measure	Provider level
Target: COMM	83%
Payout: COMM	$150 per service completed for each eligible member
Additional Information	This measure will be based on HEDIS 2016 specifications, not the adjusted, new HEDIS specifications

CMS MILLION HEARTS INCENTIVE PROGRAM

Blue Care Network has implemented a program to prevent cardiovascular disease. The program is designed for BCN Advantage members, ages 40 and older, who have a history of cardiovascular disease or diabetes. The focus of the program is to reduce the morbidity and mortality related to cardiovascular disease in these members.

The program incorporates clinical practice guidelines for the management of ischemic heart disease and diabetes mellitus following the guiding principles of the nation Million Hearts™ initiative. Million Hearts is a national initiative to prevent one million heart attacks and strokes over five years. It is led by the U.S. Department of Health and Human Services, the Centers for Disease Control and Prevention and the Centers for Medicare & Medicaid Services in partnership with other federal agencies.

CMS Million Hearts payment table

Quality incentive measures	Plan goal	Payout
Aspirin or antiplatelet therapy	Flat fee	$25
Blood pressure control	Flat fee	$25
Tobacco cessation counseling	Flat fee	$25

CMS Million Hearts payment calculation

CMS Million Hearts requires no specific plan goal. A flat fee is paid for each service completed.

CMS Million Hearts program qualifications

Providers must meet the Performance Recognition Program qualifications to be considered for a CMS Million Hearts incentive payment.

Providers can locate Million Hearts members in Health e-Blue under the Treatment Opportunity by Condition/Measures.

CMS Million Hearts data submission options

- Submit a claim with an appropriate CPT II code
- Health e-Blue entry
- Electronic medical record exchange

CMS MILLION HEARTS PROVIDER INCENTIVE
QUALITY INCENTIVE MEASURES

ASPIRIN OR ANTIPLATELET THERAPY	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2017 with a history of diabetes, cardiovascular disease or both who are prescribed or currently taking aspirin or antiplatelet therapy Report CPT II code 4086F for all patients meeting criteria
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

BLOOD PRESSURE CONTROL	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2017 who meet both the systolic and diastolic blood pressure reading requirements: • Members 18 to 59 years of age as of December 31, 2017 whose BP was < 140/90 mm Hg • Members 60 to 85 years of age as of December 31, 2017 with a diagnosis of diabetes whose BP was < 140/90 mm Hg • Members 60 to 85 years of age as of December 31, 2017 without a diagnosis of diabetes whose BP was < 150/90 mm Hg • Systolic blood pressure value report one of the systolic codes – 3074F – SBP < 130 – 3075F – SBP 130-139 – SBP > 140 and < 150 (Needs to be documented in EMR or in HEB. No CPT Cat II codes are available) • Diastolic blood pressure value report one of the diastolic codes – 3078F – DBP < 80 – 3079F – DBP 80-89
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

CMS MILLION HEARTS PROVIDER INCENTIVE
QUALITY INCENTIVE MEASURES

SMOKING/TOBACCO CESSATION COUNSELING	
Product lines	**BCN Advantage**
Source	CMS Million Hearts
Description	Members age 40 and over as of December 31, 2017 who are smokers and have been counseled on the importance of quitting smoking Providers can report 'Not a smoker' in Health e-Blue as an Exclusion Reason/Contra-Indication Report CPT II code 4000F or 4004F for each patient identified as a tobacco user and received tobacco cessation counseling
Level of measure	Provider level
Target: BCNA	Flat fee per member who meets measure
Payout: BCNA	$25 per service completed for each eligible member

APPENDIX 1:
COMPARISON SUMMARY OF PHYSICIAN RECOGNITION PROGRAM AND BLUE CROSS COMMERCIAL PPO VALUE-BASED REIMBURSEMENT MEASURES

Based on feedback from our provider partners, the PRP team has worked with the Blue Cross Value Partnerships team to develop a comprehensive list of quality measures that are included in each program. Our hope is that this document will aid in administration of the Blue Cross Blue Shield and Blue Care Network quality incentive programs.

	Physician Recognition Program			Blue Cross Commercial PPO Clinical Quality Value-Based Reimbursement			
				Blue Cross Commercial PPO QRS			Medicare Advantage Stars
QUALITY MEASURES	BCN Commercial HMO	BCN Advantage℠ HMO	Blue Cross Medicare Advantage PPO	Adult Practices	Family Practices	Pediatric Practices	Adult/Family Practices
Adult BMI assessment				•	•		•
Annual monitoring for patients on persistent medications				•	•		
Antidepressant medication management: acute phase	⌘			•	•		
Antidepressant medication management: continuation phase	⌘			•	•		
Appropriate glucose monitoring for members prescribed an antipsychotic drug	⌘						
Appropriate testing for children with pharyngitis					•	•	
Appropriate treatment for children with upper respiratory infection					•	•	
Aspirin or antiplatelet therapy		■					
Avoidance for antibiotic treatment in adults with acute bronchitis				•	•		
Breast cancer screening	•	•	•	•	•		•
Cervical cancer screening				•	•		
Adolescent immunization — combo 1					•	•	

Key

• = Performance Recognition Program/PGIP
■ = CMS Million Hearts
⌘ = BCN Behavioral Health Incentive Program

SUMMARY OF PRP AND BLUE CROSS PGIP MEASURES (continued)

	Physician Recognition Program			Blue Cross Commercial PPO Clinical Quality Value-Based Reimbursement			
QUALITY MEASURES	BCN Commercial HMO	BCN Advantage℠ HMO	Blue Cross Medicare Advantage PPO	Blue Cross Commercial PPO QRS			Medicare Advantage Stars
				Adult Practices	Family Practices	Pediatric Practices	Adult/Family Practices
Childhood immunizations — combo 10					•	•	
Childhood immunizations – influenza	•						
Chlamydia screening				•	•		
Colorectal cancer screening		•	•	•	•		•
Comprehensive diabetes care: HbA1c < 8%	•			•	•		
Comprehensive diabetes care: HbA1c ≤ 9%		•	•				•
Comprehensive diabetes care: HbA1c testing				•	•		
Comprehensive diabetes care: monitoring for nephropathy	•	•	•	•	•		•
Comprehensive diabetes care: retinal eye exam	•	•	•	•	•		•
Controlling blood pressure		■		•	•		•
Controlling high blood pressure for hypertension		•	•	•	•		•
Depression management — PHQ9 testing	•						
Disease-modifying anti-rheumatic drug therapy for rheumatoid arthritis		•	•				
Follow-up after hospitalization, medical – 3 days		•	•				
Follow-up after hospitalization, mental health – 7 days	⌘						
Follow-up care for children prescribed ADHD medication: continuation and maintenance phase					•	•	

Key

• = Performance Recognition Program
■ = CMS Million Hearts
⌘ = BCN Behavioral Health Incentive Program

SUMMARY OF PRP AND BLUE CROSS PGIP MEASURES (continued)

	Physician Recognition Program			Blue Cross Commercial PPO Clinical Quality Value-Based Reimbursement			
QUALITY MEASURES	**BCN Commercial HMO**	**BCN Advantage℠ HMO**	**Blue Cross Medicare Advantage PPO**	**Blue Cross Commercial PPO QRS**			**Medicare Advantage Stars**
				Adult Practices	**Family Practices**	**Pediatric Practices**	**Adult/Family Practices**
Follow-up care for children prescribed ADHD medication: initiation phase	●				●	●	
HPV vaccine for adolescents – male and female					●	●	
Medication adherence for cholesterol medications				●	●		●
Medication adherence for diabetes medication				●	●		●
Medication adherence for hypertension medication				●	●		●
Medication management for people with asthma				●	●	●	
Osteoporosis management in women who had a fracture		●	●				
PCP contact from behavioral health provider	⌘						
Pharmacotherapy adherence for bipolar disorder	⌘						
Smoking/tobacco cessation counseling		■					
Therapeutic alliance for behavioral health counseling	⌘						
Use of imaging studies for low back pain	●			●	●		
Weight assessment and counseling for children: BMI percentile, counseling for nutrition and physical activity (three unique measures)	●				●	●	
Well-child visits in the 3rd, 4th, 5th and 6th years of life					●	●	
Well-child visits in the first 15 months of life (6 or more)	●				●	●	

Key

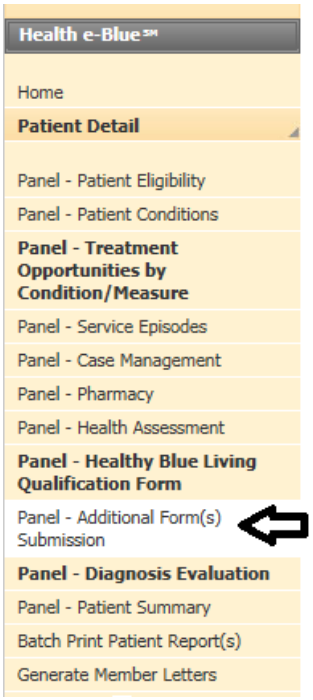
● = Performance Recognition Program
■ = CMS Million Hearts
⌘ = BCN Behavioral Health Incentive Program

APPENDIX 2:
DEPRESSION MANAGEMENT – PHQ9 TESTING
HEALTH E-BLUE MEASURE ENTRY GUIDE
BCN Commercial Measure

To qualify for the 2017 PRP Depression Management measure, Health e-Blue users must report Blue Care Network Commercial members' Depression Management PHQ9 results using *Panel - Additional Form (s) Submission*.

This guide will walk users through a step-by-step process to enter the required information.

STEP 1: LOGIN
Log in to Blue Care Network - Health e-Blue and click on *Panel- Additional Form (s) Submission* from the left navigation menu.



STEP 2: LOCATE COMMERCIAL PHQ PANEL MEMBERS

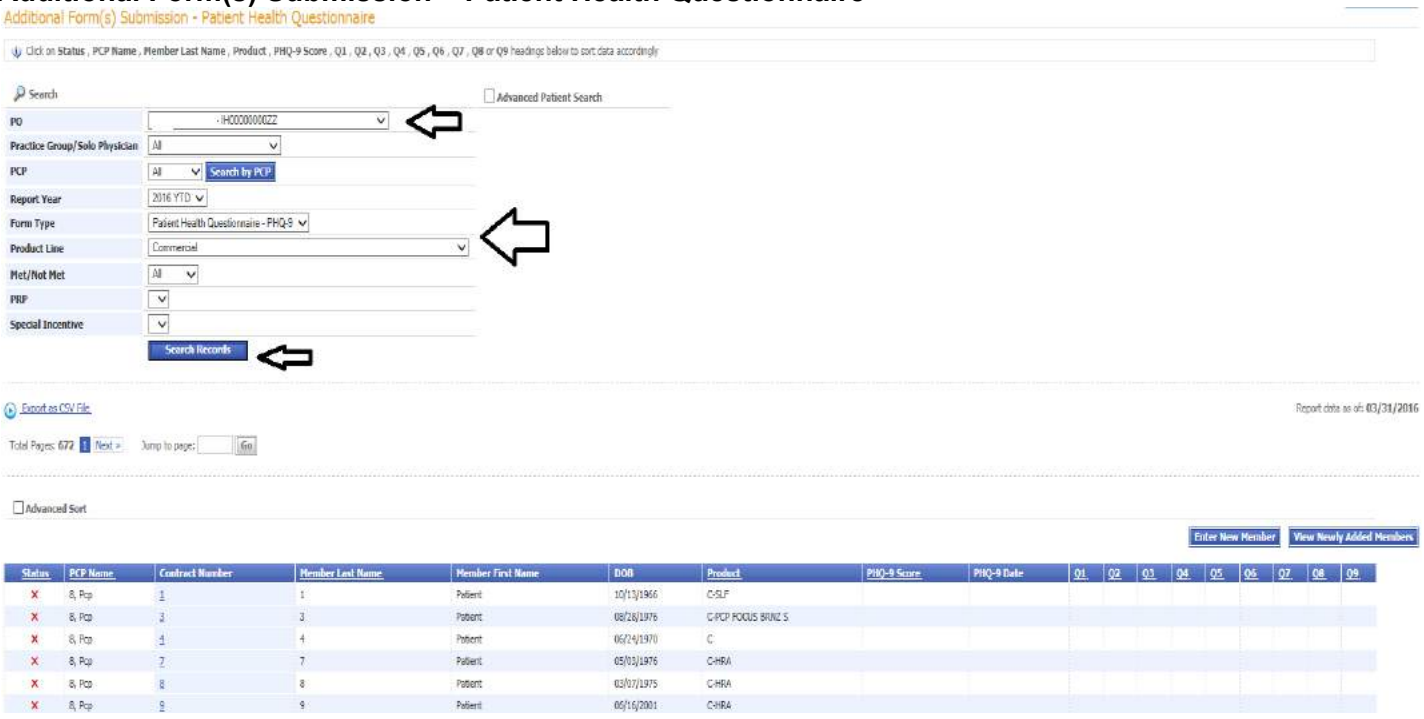
Select the appropriate physician organization, practice group and PCP from the dropdown menus.

In the Form Type dropdown menu, select ***Patient Health Questionnaire – PHQ-9***.

Select ***Commercial*** from the Product Line dropdown menu**.**

Click ***Search Records***.

Additional Form(s) Submission – Patient Health Questionnaire



Note: if you aren't able to find your member, skip down to **STEP 5**.

STEP 3: SELECT COMMERCIAL PHQ PANEL MEMBERS

Select the commercial member in the panel by clicking the ***Contract Number*** and the Patient Health Questionnaire – PHQ9 form will appear.

STEP 4: ENTER PHQ MEMBER RESULTS

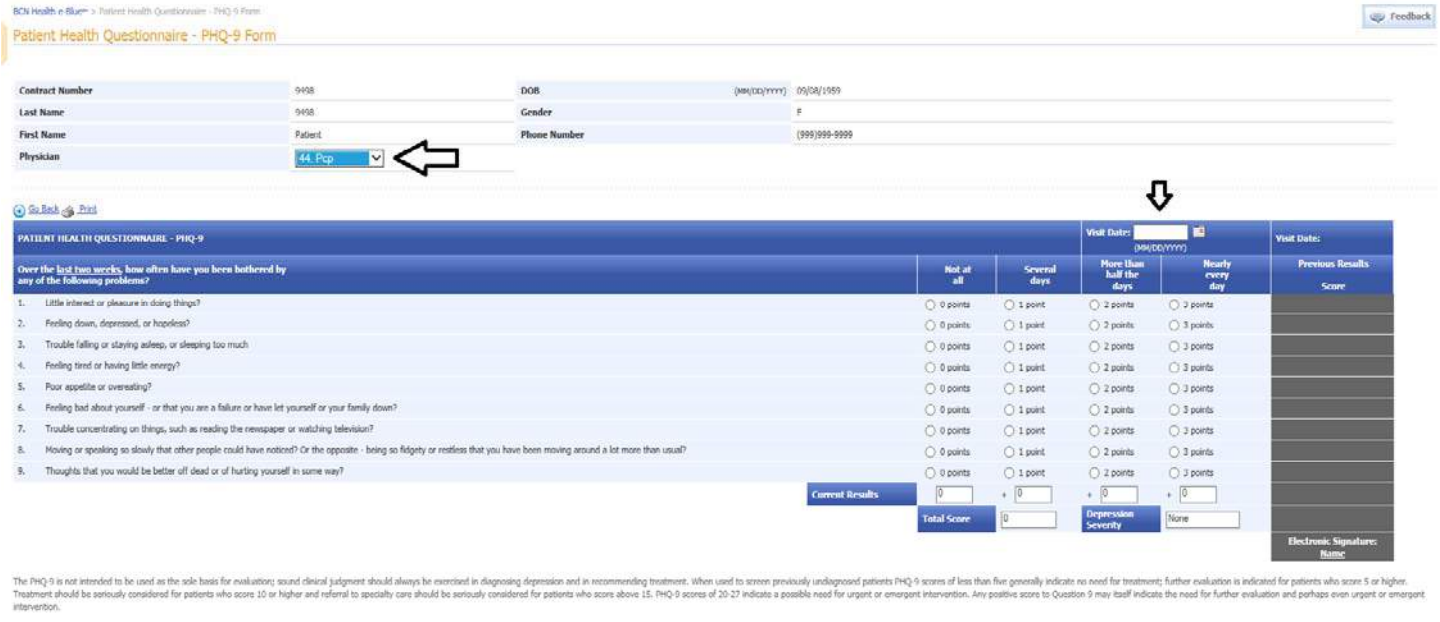
The member information will prepopulate in the PHQ-9 form.

Select the ***Physician*** name from the dropdown menu. The physician name will prepopulate in the PHQ-9 form near the bottom.

Enter the member ***Visit Date*****.**

Enter PHQ-9 results**.**

Patient Health Questionnaire - PHQ-9 Form – data entry screen



STEP 5: ADDING NEW MEMBERS - COMMERCIAL PHQ PANEL MEMBERS

How to add a new member and view newly added members
If you need to add a commercial member, select the appropriate physician organization, practice group and PCP information in the dropdown menus.

In the Form Type dropdown menu, select ***Patient Health Questionnaire – PHQ-9***.

Select ***Commercial*** from the Product Line dropdown menu**.**

Click ***Search Records***.

Scroll to the far right of your screen. Just above the blue header, you will see **Enter New Member**. Click on the box and a blank Patient Health Questionnaire - PHQ-9 form will appear.

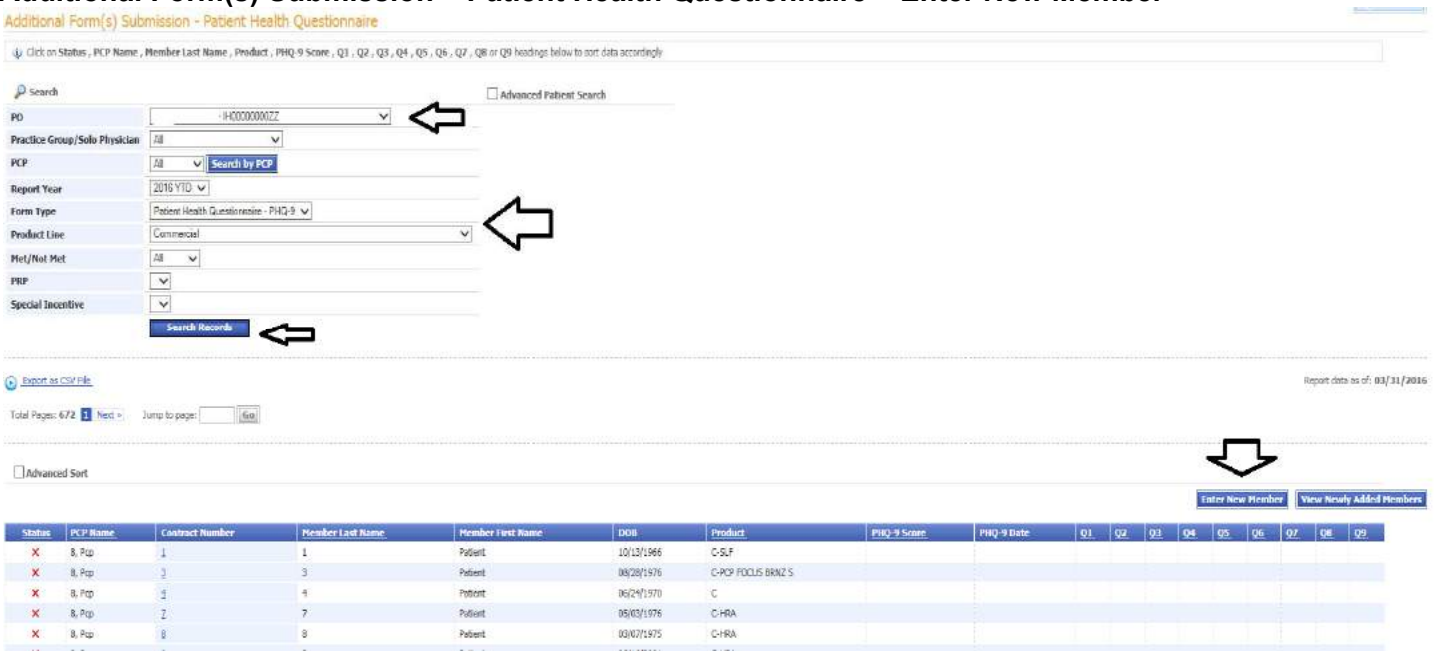
Enter the Commercial member numeric contract number that appears on the Blue Cross or BCN ID card.

Enter all demographic information for the member.

Enter the PHQ9 results.

Save and print the form for your records.

Additional Form(s) Submission – Patient Health Questionnaire – Enter New Member



Please reference the Health e-Blue homepage for the 2017 Performance Recognition Program PDF document for 2017 and 2017 Baseline and follow-up measurement periods.

Blue Cross
Blue Shield
Blue Care Network
of Michigan

R060544

2017 MHS Pay for Performance (HEDIS)

mhs

Hoosier Healthwise | Healthy Indiana Plan | Hoosier Care Connect

AGENDA

- MHS Pay For Performance (P4P)
- Secure Web Reporting
- Patient Analytics
- My Health Direct
- Question and Answer

WHAT YOU WILL LEARN

1. Measure Overviews & Specifications
2. Documentation Requirements
3. Administrative Measures
4. Secure Web Reports
5. My Health Direct
6. How Payout is Calculated

2017 P4P

- Bonus Pay for Performance (P4P) fund written into Primary Medical Provider contracts
- Measures are different for each product line
- Measures aligned with HEDIS® and NCQA
- Annual payout

2017 HOOSIER HEALTHWISE P4P

P4P SCHEDULE A-2A-1
Hoosier Healthwise

Pay-For-Performance Measures		Goal Rate	Minimum Number of Covered Persons	Points
Children's Care (Quality)				***42 points***
Childhood Immunization Status (CIS)COMBO 10	% of 2 year old Covered Persons who had the following immunizations by their second birthday: 4 DTaP, 3 IPV, 1 MMR, 3 Hib, 3 Hep B, 1 VZV, 4 PCV, 1 Hep A, 2 or 3 RV (depending on dose schedule), 2 Flu	HEDIS 75th percentile	10	7 points
Follow-Up Care for Children Prescribed ADHD Medication – Initiation Phase	% of members 6–12 years of age as of the IPSD with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with practitioner with prescribing authority during the 30-day Initiation Phase	HEDIS 75th percentile	5	7 points
Follow-Up Care for Children Prescribed ADHD Medication – continuation phase	% of members 6–12 years of age as of the IPSD with an ambulatory prescription dispensed for ADHD medication, who remained on the medication for at least 210 days and who, in addition to the visit in the Initiation Phase, had at least two follow-up visits with a practitioner within 270 days (9 months) after the Initiation Phase ended	HEDIS 75th percentile	5	7 points
Well-Child Visits in the First 15 Months of Life (W15)	% of Covered Persons turning 15 mos within the current year who had 6 or more visits with PMP before turning 15 mos old	HEDIS 75th percentile	10	7 points
Well-Child Visits in the Third, Fourth, Fifth and Sixth Years of Life (W34)	% of Covered Persons who turned 3-6 years old within the year who had 1 or more well child visits within the current year	HEDIS 75th percentile	10	7 points
Adolescent Well-Care Visits (AWC)	% of Covered Persons 12-21 years old who had at least 1 comprehensive well care visit with PMP or OB within the current year	HEDIS 75th percentile	10	7 points

2017 HOOSIER HEALTHWISE P4P

Maternal Care (Quality)				*20 points*
Prenatal and Postpartum Care (PPC)	Timeliness of Prenatal Care - % of deliveries that received a prenatal care visit in the first trimester or within 42 days of enrollment	HEDIS 75th percentile	5	7 points
Prenatal and Postpartum Care (PPC)	Postpartum Care - % of deliveries that had a postpartum visit on or between 21 and 56 days after delivery	HEDIS 75th percentile	5	7 points
Frequency of Ongoing Prenatal Care (FPC)	81+ Percent - % of Covered Persons that received 81% or more of expected prenatal visits from time of enrollment based on ACOG recommendations	HEDIS 75th percentile	5	6 points

2017 HOOSIER HEALTHWISE P4P

Women's Care (Quality)					***7 points***
	Chlamydia Screening in Women (CHL)	% of female Covered Persons age 16-24 years identified as sexually active who had at least one Chlamydia test in the current year	HEDIS 75th percentile	5	7 points
Respiratory Care					***14 points***
	MED Management for People With Asthma (Med 75% rate)	% of members 5–64 years of age during the measurement year who were identified as having persistent asthma and were dispensed appropriate medications and remained on an asthma controller medication for at least 75% of their treatment period	HEDIS 75th percentile	5	7 points
	Asthma Medication Ratio (AMR) - total	% of members 5–64 years of age who were identified as having persistent asthma and had a ratio of controller medications to total asthma medications of 0.50 or greater during the measurement year	HEDIS 75th percentile	5	7 points
Ambulatory Measures					***7 points***
	Ambulatory Care (AMB) – ER utilization	utilization of ambulatory care in the ED - # visits per 1,000 member months	HEDIS 10th percentile	10	7 points
Provider Outreach (Administrative) Credit given for use of any 3 of the following 5:					***10 points****
	Provider-Initiated Preventive Health Outreach	Selected outreach condition must be applicable to at least 20% of total panel, i.e. telephonic campaign, Covered Person mailing campaign, special well-child health check day at your office. Report of Outreach must be received by MHS by December 31 of the measurement year. At a minimum, the outreach must be described and a list of Covered Persons who received the outreach must be included.			
	Panel Size Increase	Increase panel size by 10%			
	Training Attendance or Use of Bright Futures	Physician or Office Manager attendance in one MHS training/orientation sessions during the calendar year or documented use of the AAP Bright Futures program			
	Use of Patient Satisfaction Survey	Use of a practice-level patient satisfaction survey, such as the American Academy of Family Physicians model questionnaire			
	Use of EMR or MHS Well Visit Form	Use of Electronic Medical Record or the MHS Child or Adult Health Maintenance Form for well-visits			

*Use of 1 = 3 points
Use of 2 = 6 points
Use of 3 or more = 10 points

2017 HOOSIER HEALTHWISE P4P MEASURES

- Child and adolescent well-care
  - Childhood immunization status (CIS)
  - Well-child visits 0-15 months (W15)
  - Well-child visits 3-6 years (W34)
  - Well-adolescent visits 12-21 years (AWC)
  - Follow-up care for children prescribed ADHD medication – Acute and Continuation phases (ADD)

- Maternal care
  - Timeliness/initiation of prenatal care (PPC)
  - Frequency of prenatal care (FPC)
  - Postpartum care (PPC)

2017 HOOSIER HEALTHWISE P4P MEASURES

- Women's care
  - Chlamydia screening (CHL)

- Respiratory care
  - MED Management for Asthmatics (MMA)
  - Asthma Medication Ratio (AMR) - total

- Ambulatory Measures
  - Ambulatory Care (AMB) – ER utilization

2017 HIP P4P

P4P SCHEDULE A-2B-1
Healthy Indiana Plan (HIP)

Pay-For-Performance Measures			Goal Rate	Minimum Number of Covered Persons	Points
Women's Care (Quality)					***21 points***
	Chlamydia Screening in Women (CHL)	% of female Covered Persons age 16-24 years identified as sexually active who had at least one Chlamydia test in the current year	HEDIS 75th percentile	5	7 points
	Cervical Cancer Screening (CCS)	% of female Covered Persons age 24-64 years who received 1 or more Pap tests to screen for cervical cancer in the current year	HEDIS 75th percentile	5	7 points
	Breast Cancer Screening (BCS)	% of women 50–74 years of age who had a mammogram to screen for breast cancer	HEDIS 75th percentile	5	7 points
Maternal Care (Quality)					***20 points***
	Prenatal and Postpartum Care (PPC)	Timeliness of Prenatal Care - % of deliveries that received a prenatal care visit in the first trimester or within 42 days of enrollment	HEDIS 75th percentile	5	7 points
	Prenatal and Postpartum Care (PPC)	Postpartum Care - % of deliveries that had a postpartum visit on or between 21 and 56 days after delivery	HEDIS 75th percentile	5	7 points
	Frequency of Ongoing Prenatal Care (FPC)	81+ Percent - % of Covered Persons that received 81% or more of expected prenatal visits from time of enrollment based on ACOG recommendations	HEDIS 75th percentile	5	6 points

2017 HIP P4P

Respiratory Care					***14 points***
	MED Management for People With Asthma (Med 75% rate)	% of members 5–64 years of age during the measurement year who were identified as having persistent asthma and were dispensed appropriate medications and remained on an asthma controller medication for at least 75% of their treatment period	HEDIS 75th percentile	5	7 points
	Pharmacotherapy Management of COPD Exacerbation (PCE) - systemic corticosteroid	% of COPD exacerbations for members 40 years of age and older who had an acute inpatient discharge or ED visit on or between January 1–November 30 of the measurement year and who were dispensed a systemic corticosteroid (or there was evidence of an active prescription) within 14 days of the event	HEDIS 75th percentile	5	7 points

2017 HIP P4P

Behavior Health Care					***7 points***
	Antidepressant Medication Management (AMM) – Acute Phase	% of members who remained on an antidepressant medication for at least 84 days (12 weeks)	HEDIS 75th percentile	5	7 points
Diabetes Care					***14 points***
	Diabetes Care - Eye exam (retinal) performed	% of members 18–75 years of age with diabetes (type 1 and type 2) who had an eye exam (retinal) performed	HEDIS 75th percentile	5	7 points
	Diabetes Care - Medical attention for nephropathy	% of members 18–75 years of age with diabetes (type 1 and type 2) who had medical attention for nephropathy	HEDIS 75th percentile	5	7 points
Ambulatory Measures					***14 points***
	Ambulatory Care (AMB) – ER utilization	utilization of ambulatory care in the ED - # visits per 1,000 member months	HEDIS 10th percentile	10	7 points
	Adults' Access to Preventive/Ambulatory Health Services (AAP)	% of members 20 years and older who had an ambulatory or preventive care visit	HEDIS 75th percentile	10	7 points
Provider Outreach (Administrative) Credit given for use of any 3 of the following 5:					***10 points****
	Provider-Initiated Preventive Health Outreach	Selected outreach condition must be applicable to at least 20% of total panel, i.e. telephonic campaign, Covered Person mailing campaign, special well-child health check day at your office. Report of Outreach must be received by MHS by December 31 of the measurement year. At a minimum, the outreach must be described and a list of Covered Persons who received the outreach must be included.			
	Panel Size Increase	Increase panel size by 10%			
	Training Attendance or Use of Bright Futures	Physician or Office Manager attendance in one MHS training/orientation session during the calendar year or documented use of the AAP Bright Futures program			
	Use of Patient Satisfaction Survey	Use of a practice-level patient satisfaction survey, such as the American Academy of Family Physicians model questionnaire			
	Use of EMR or MHS Well Visit Form	Use of Electronic Medical Record or the MHS Adolescent or Adult Health Maintenance Form for well-visits			
	P4P Scoring Key for Provider Outreach • Complete one activity above to earn 3 Points. (30% payment for this section) • Complete two activities above to earn 6 Points. (60% payment for this section) • Complete three or more activities above and earn 100% payment for this section.				

2017 HIP P4P Measures

- Maternal care
  - Timeliness/initiation of prenatal care (PPC)
  - Frequency of prenatal care (FPC)
  - Postpartum care (PPC)

- Women's Care
  - Chlamydia Screening (CHL)
  - Cervical Cancer Screening (CCS)
  - Breast Cancer Screening (BCS)

2017 HIP P4P Measures

- Respiratory care
  - MED Management for Asthmatics (MMA)
  - Pharmacotherapy Management of COPD Exacerbation (PCE) - systemic corticosteroid

- Behavior Health Care
  - Antidepressant Med Management (AMM) – Acute Phase

2017 HIP P4P Measures

- Diabetes Care (CDC)
  - Diabetes Care - Eye exam (retinal) performed
  - Diabetes Care - Medical attention for nephropathy

- Ambulatory Measures
  - Ambulatory Care (AMB) – ER utilization
  - Adults' Access to Preventive/Ambulatory Health Services (AAP)

2017 HOOSIER CARE CONNECT P4P

P4P SCHEDULE 2C-1A
Hoosier Care Connect

Pay-For-Performance Measures		Goal Rate	Minimum Number of Covered Persons	Points
Children's Care (Quality)				***28 points***
Childhood Immunization Status (CIS)COMBO 10	% of 2 year old Covered Persons who had the following immunizations by their second birthday: 4 DTaP, 3 IPV, 1 MMR, 3 Hib, 3 Hep B, 1 VZV, 4 PCV, 1 Hep A, 2 or 3 RV (depending on dose schedule), 2 Flu	HEDIS 75th percentile	10	7 points
Well-Child Visits in the First 15 Months of Life (W15)	% of Covered Persons turning 15 months within the current year who had 6 or more visits with PMP before turning 15 months old	HEDIS 75th percentile	10	7 points
Well-Child Visits in the Third, Fourth, Fifth and Sixth Years of Life (W34)	% of Covered Persons who turned 3-6 years old within the year who had 1 or more well child visits within the current year	HEDIS 75th percentile	10	7 points
Adolescent Well-Care Visits (AWC)	% of Covered Persons 12-21 years old who had at least 1 comprehensive well care visit with PMP or OB within the current year	HEDIS 75th percentile	10	7 points
Respiratory Care				***27 points***
MED Management for People With Asthma (Med 75% rate)	% of members 5–64 years of age during the measurement year who were identified as having persistent asthma and were dispensed appropriate medications and remained on an asthma controller medication for at least 75% of their treatment period	HEDIS 75th percentile	5	7 points
Asthma Medication Ratio (AMR) - total	% of members 5–64 years of age who were identified as having persistent asthma and had a ratio of controller medications to total asthma medications of 0.50 or greater during the measurement year	HEDIS 75th percentile	5	7 points

2017 HOOSIER CARE CONNECT P4P

	Pharmacotherapy Management of COPD Exacerbation (PCE) - systemic corticosteroid	% of COPD exacerbations for members 40 years of age and older who had an acute inpatient discharge or ED visit on or between January 1– November 30 of the measurement year and who were dispensed a systemic corticosteroid (or there was evidence of an active prescription) within 14 days of the event	HEDIS 75th percentile	5	7 points
	Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis	% of adults 18 – 64 years of age with a diagnosis of acute bronchitis who were not dispensed an antibiotic prescription on or within three days after the diagnosis. [Members with chronic respiratory disorders such as COPD and Cystic Fibrosis are excluded from this measure.]	HEDIS 75th percentile	5	6 points
Diabetes Care					***14 points***
	Diabetes Care - Eye exam (retinal) performed	% of members 18–75 years of age with diabetes (type 1 and type 2) who had an eye exam (retinal) performed	HEDIS 75th percentile	5	7 points
	Diabetes Care - Medical attention for nephropathy	% of members 18–75 years of age with diabetes (type 1 and type 2) who had medical attention for nephropathy	HEDIS 75th percentile	5	7 points
Ambulatory Measures					***14 points***
	Ambulatory Care (AMB) – ER utilization	utilization of ambulatory care in the ED - # visits per 1,000 member months	HEDIS 10th percentile	10	7 points
	Adults' Access to Preventive/Ambulatory Health Services (AAP)	% of members 20 years and older who had an ambulatory or preventive care visit	HEDIS 75th percentile	10	7 points
Behavioral Health Care					***7 points***
	Antidepressant Medication Management (AMM) – Acute Phase	% of members who remained on an antidepressant medication for at least 84 days (12 weeks)	HEDIS 75th percentile	5	7 points

2017 HOOSIER CARE CONNECT P4P

Provider Outreach (Administrative) Credit given for use of any 3 of the following 5:		*10 points**
Provider-Initiated Preventive Health Outreach	Selected outreach condition must be applicable to at least 20% of total panel, i.e. telephonic campaign, Covered Person mailing campaign, special well-child health check day at your office. Report of Outreach must be received by MHS by December 31 of the measurement year. At a minimum, the outreach must be described and a list of Covered Persons who received the outreach must be included.	
Panel Size Increase	Increase panel size by 10%	
Training Attendance or Use of Bright Futures	Physician or Office Manager attendance in one MHS training/orientation session during the calendar year or documented use of the AAP Bright Futures program	
Use of Patient Satisfaction Survey	Use of a practice-level patient satisfaction survey, such as the American Academy of Family Physicians model questionnaire	
Use of EMR or MHS Well Visit Form	Use of Electronic Medical Record or the MHS Child or Adult Health Maintenance Form for well-visits	
P4P Scoring Key for Provider Outreach • Complete one activity above to earn 3 Points. (30% payment for this section) • Complete two activities above to earn 6 Points. (60% payment for this section) • Complete three or more activities above and earn 100% payment for this section.		

2017 HOOSIER CARE CONNECT P4P Measures

- Child and adolescent well-care
  - Childhood immunization status (CIS)
  - Well-child visits 0-15 months (W15)
  - Well-child visits 3-6 years (W34)
  - Well-adolescent visits 12-21 years (AWC)

- Behavior Health Care
  - Antidepressant Medication Management (AMM) – Acute Phase

2017 HOOSIER CARE CONNECT P4P Measures

- Diabetes Care (CDC)
  - Diabetes Care - Eye exam (retinal) performed
  - Diabetes Care - Medical attention for nephropathy

- Ambulatory Measures
  - Ambulatory Care (AMB) – ER utilization
  - Adults' Access to Preventive/Ambulatory Health Services (AAP)

2017 HOOSIER CARE CONNECT P4P Measures

- Respiratory Care
  - MED Management for People With Asthma (MMA)
  - Asthma Medication Ratio (AMR) – total
  - Pharmacotherapy Management of COPD Exacerbation (PCE) - systemic corticosteroid
  - Avoidance of Antibiotic Treatment in Adults with Acute Bronchitis (AAB)

Administrative Measures

Credit given for use of any 3 of the following 5 measures:

- Provider-Initiated Preventive Health Outreach
- Panel Size Increase by 10%
- Physician or Office Manager attendance at one MHS training/orientation session during the calendar year or documented use of the AAP Bright Futures program
- Use of Patient Satisfaction Survey
- Use of EMR or MHS Well Visit Form

Measure Requirements and Coding

- You can find additional information on the measurement requirements and some tips for coding on our website at the link below located under HEDIS

- https://www.mhsindiana.com/providers/resources/guides-and-manuals.html

Secure Web Portal Reporting and MyHealthDirect

P4P Scorecards

Reports updated regularly on secure portal

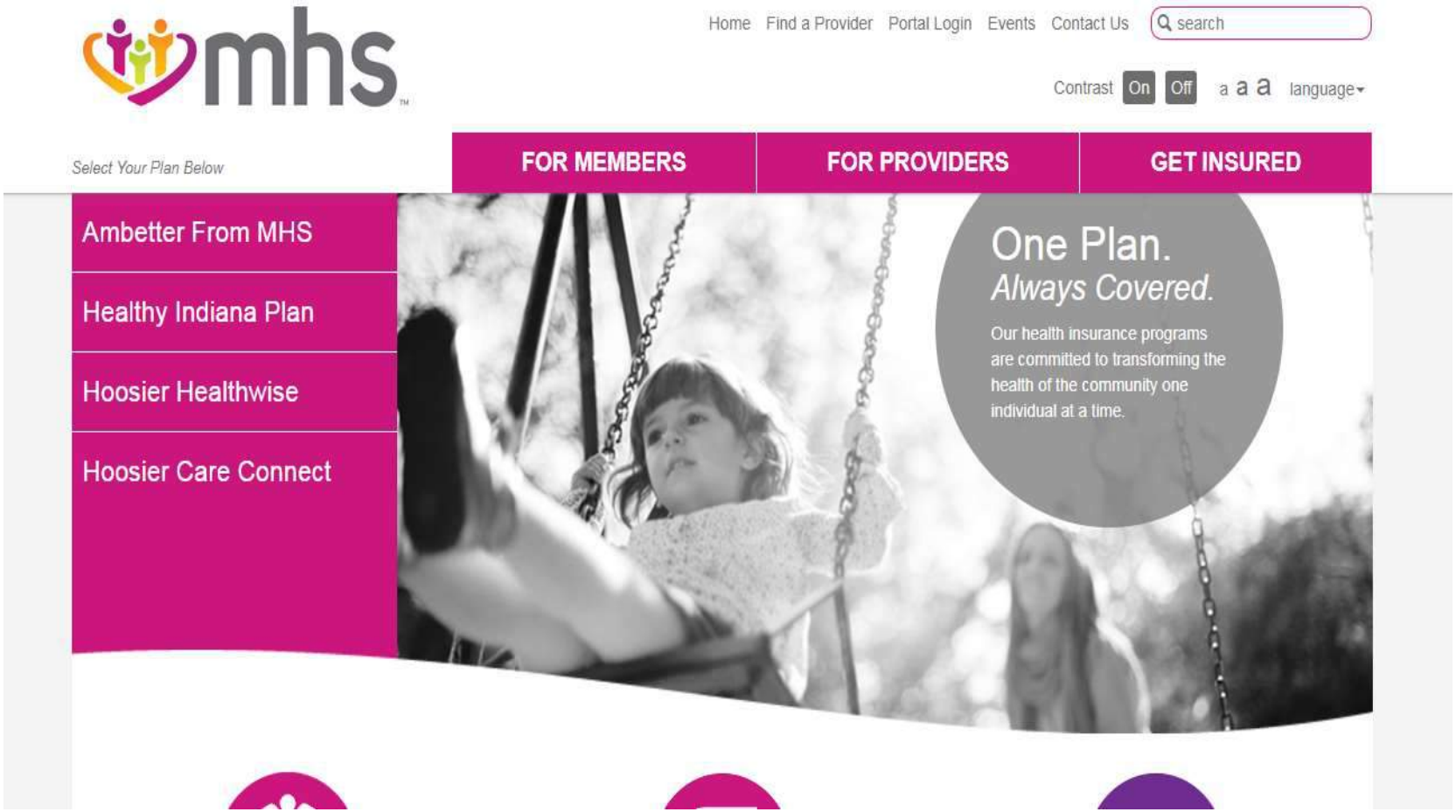
- Group scorecards
- Individual scorecards
- Members in Need of Services lists

Scorecards (cont.)

Updated measurement rates on scorecards include:

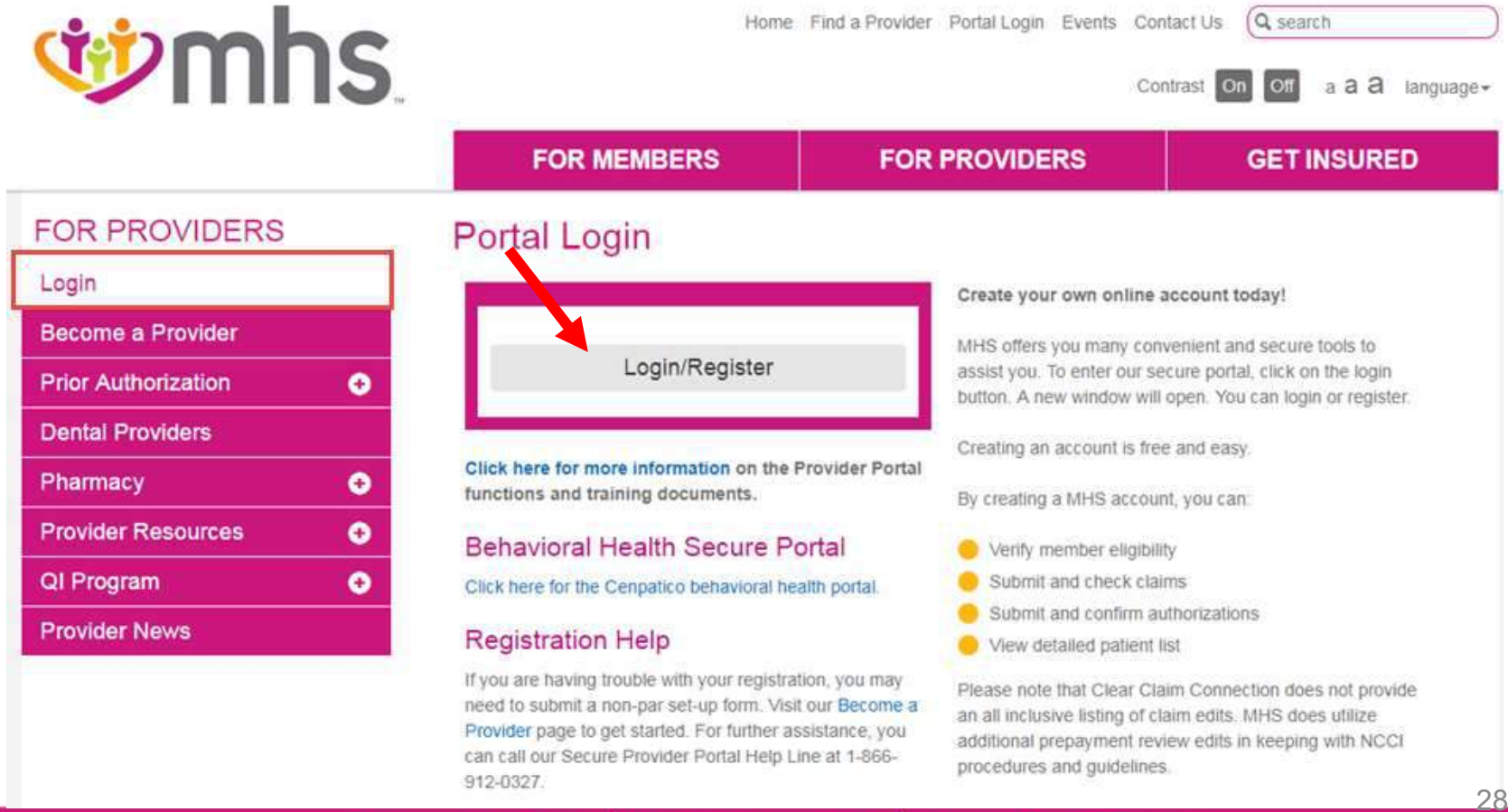
- Claims data (pharmacy, encounter/medical)
- CHIRP / Lab results
- Medical record documentation
- Collected annually

MHS Public Website

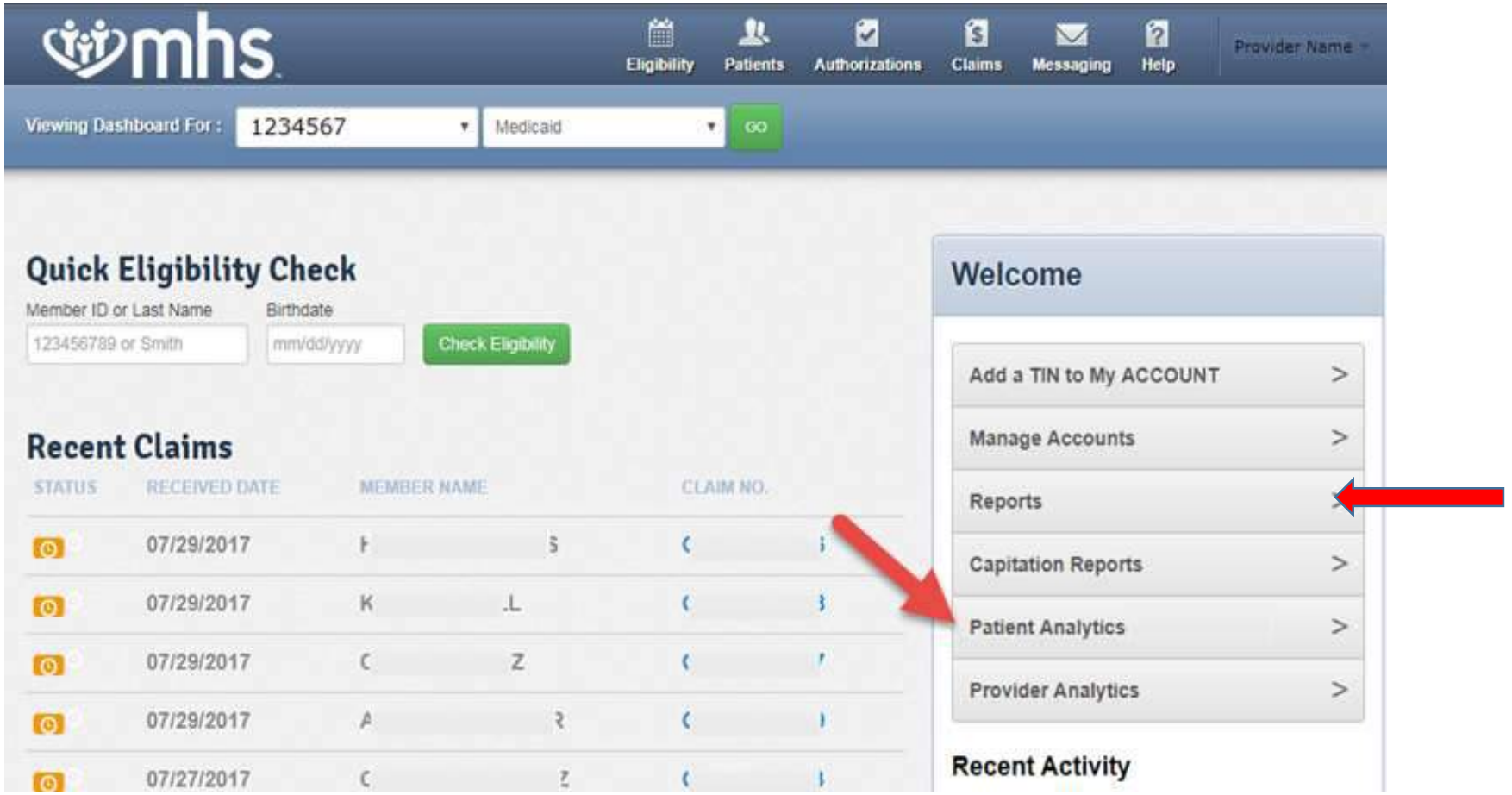


Public Website

At MHSIndiana.com click on For Providers, Login and then Login/Register



MHS Secure Portal



Group Scorecard Example

Group name:

Time period covered by this report: YTD 2015 - 1/1/2015 thru 11/30/2015

Group Performance Metrics

Prod	Measure	Minimun applicable members needed for measurement	Number of applicable Members in your practice	Number of Members who comply with the applicable criteria	Group average percentage of members who comply with the criteria	NCQA 75th percentile of members who comply with the criteria (MHS GOAL)	Members needed to reach MHS GOAL
HHW	Adolescent Well Care	10	32	10	31.25%	59.98%	10
HHW	Cervical Cancer	8	1	0	0.00%	67.88%	1
HHW	Childhood Imm - Combo 2	10	1	0	0.00%	79.40%	1
HHW	Chlamydia Screening - Total	10	1	0	0.00%	61.98%	1
HHW	Lead Screening	10	1	0	0.00%	79.67%	1
HHW	Well Child 3-6 Years	10	11	4	36.36%	78.46%	5
HIP	CDC All - Eye Exam	0	3	2	66.67%	62.30%	0
HIP	CDC All - LDL Test	0	3	3	100.00%	79.52%	0
HIP	Cervical Cancer	0	25	9	36.00%	72.99%	10
HIP	Chlamydia Screening - Total	0	1	0	0.00%	61.81%	1
HIP	Colorectal Cancer	0	1	1	100.00%	61.90%	0

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Provider Scorecard Example

Physician name
Group name
Address

Time period covered by this report: YTD 2015 - 1/1/2015 thru 11/30/2015

Physician Performance Metrics

Product	Measure	Number of applicable Members assigned to you	Number of Members who comply with the applicable criteria	Your average percentage of members who comply with the criteria	NCQA 75th percentile of members who comply with the criteria MHS GOAL	Members Needed to reach MHS Goal
HHW	Adolescent Well Care	119	45	37.82%	59.98%	27
HHW	CDC All - LDL Test	1	1	100.00%	80.18%	0
HHW	Cervical Cancer	3	1	33.33%	67.88%	2
HHW	Childhood Imm - Combo 2	8	2	25.00%	79.40%	5
HHW	Chlamydia Screening - Tot	17	13	76.47%	61.98%	0
HHW	Lead Screening	8	2	25.00%	79.67%	5
HHW	Use App Meds Asthma	4	3	75.00%	87.50%	1
HHW	Well Child 15 Months - 6 vi	13	6	46.15%	66.24%	3
HHW	Well Child 3-6 Years	91	54	59.34%	78.46%	18
HIP	CDC All - Eye Exam	14	7	50.00%	62.30%	2
HIP	CDC All - LDL Test	14	12	85.71%	79.52%	0
HIP	Cervical Cancer	84	41	48.81%	72.99%	21
HIP	Chlamydia Screening - Tot	11	6	54.55%	61.81%	1
HIP	Colorectal Cancer	13	6	46.15%	61.90%	3

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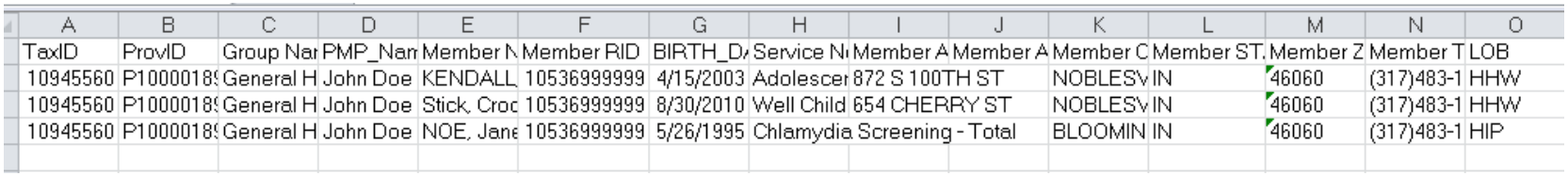
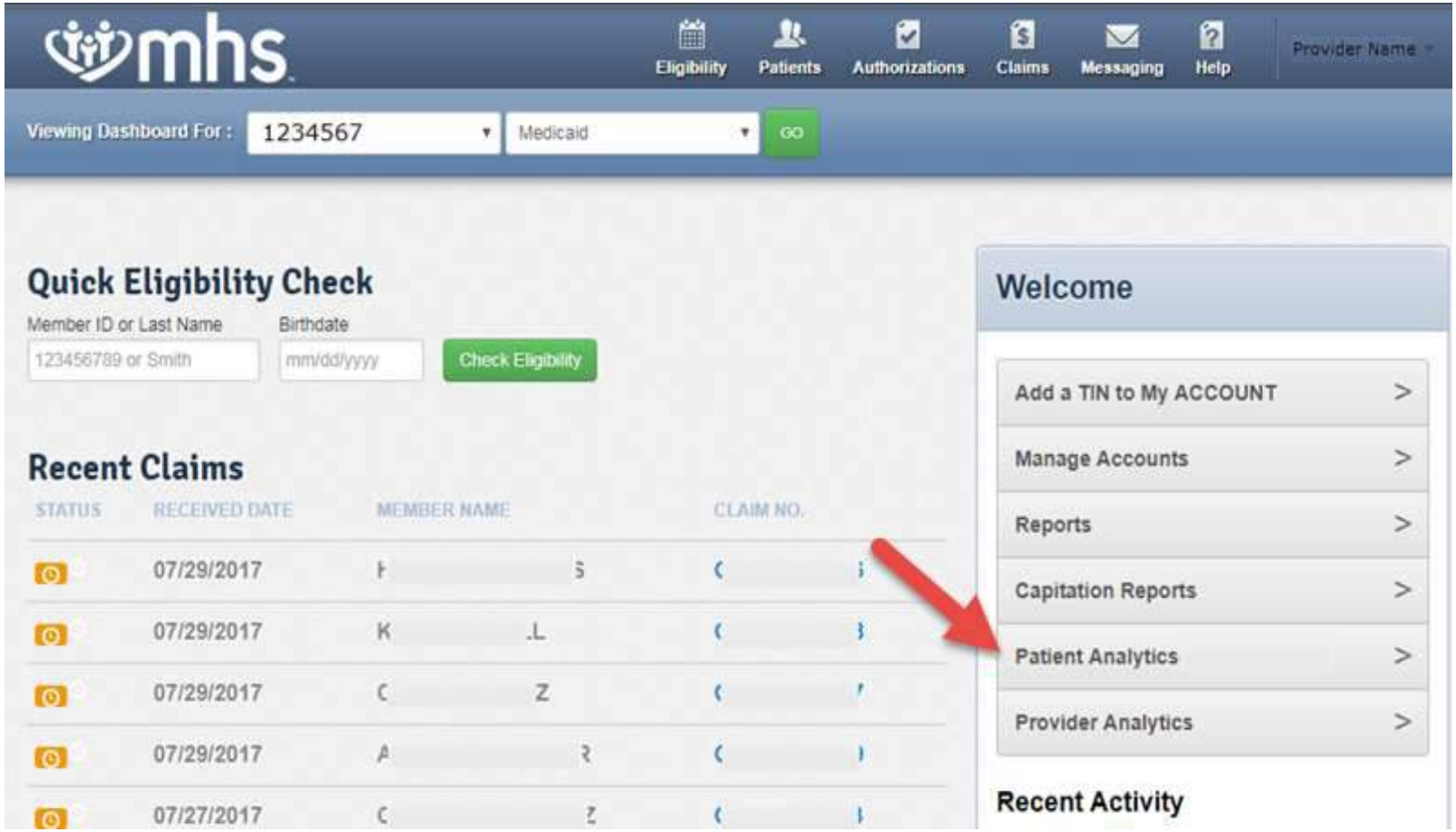
Member Gap List Example



A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
TaxID	ProvID	Group Nar	PMP_Nam	Member N	Member RID	BIRTH_D/	Service Nı	Member A	Member A	Member C	Member ST.	Member Z	Member T	LOB
10945560	P1000018	General H	John Doe	KENDALL,	10536999999	4/15/2003	Adolescer	872 S 100TH ST		NOBLESV	IN	46060	(317)483-1	HHW
10945560	P1000018	General H	John Doe	Stick, Croc	10536999999	8/30/2010	Well Child	654 CHERRY ST		NOBLESV	IN	46060	(317)483-1	HHW
10945560	P1000018	General H	John Doe	NOE, Jane	10536999999	5/26/1995	Chlamydia	Screening - Total		BLOOMIN	IN	46060	(317)483-1	HIP

- Excel file
- Sortable
- Filterable

MHS Secure Portal



Patient Analytics

What is Patient Analytics?

- Patient Analytics is a web-based patient care platform that uses claims data to create a detailed patient- and population-level reporting

Patient Analytics

Why Was Patient Analytics Created?

- Patient Analytics was created to enable providers to make more informed patient care decisions based on health histories, current diagnoses, and prescription regimens, which also supports population health views and outreach initiatives

Patient Analytics

What Does Patient Analytics Do?

- Within Patient Analytics, each patient has a detailed clinical profile. Patients with the most care gaps are identified allowing providers to take a proactive approach to managed care

Key Benefits

- **Population Health:** Providers are able to manage member's information using patient registries. The information can easily be accessed online and many elements can be printed
- **Medical History** – Patient Analytics contains up to 24 months of medical, pharmacy, and lab claims
- **Increased Visibility** – Primary Care Physicians (PCPs) will have access to claims history submitted by other providers
- **Improved Outcomes:** Patient Analytics helps providers improve patient care, performance, outcomes and adherence to quality measures

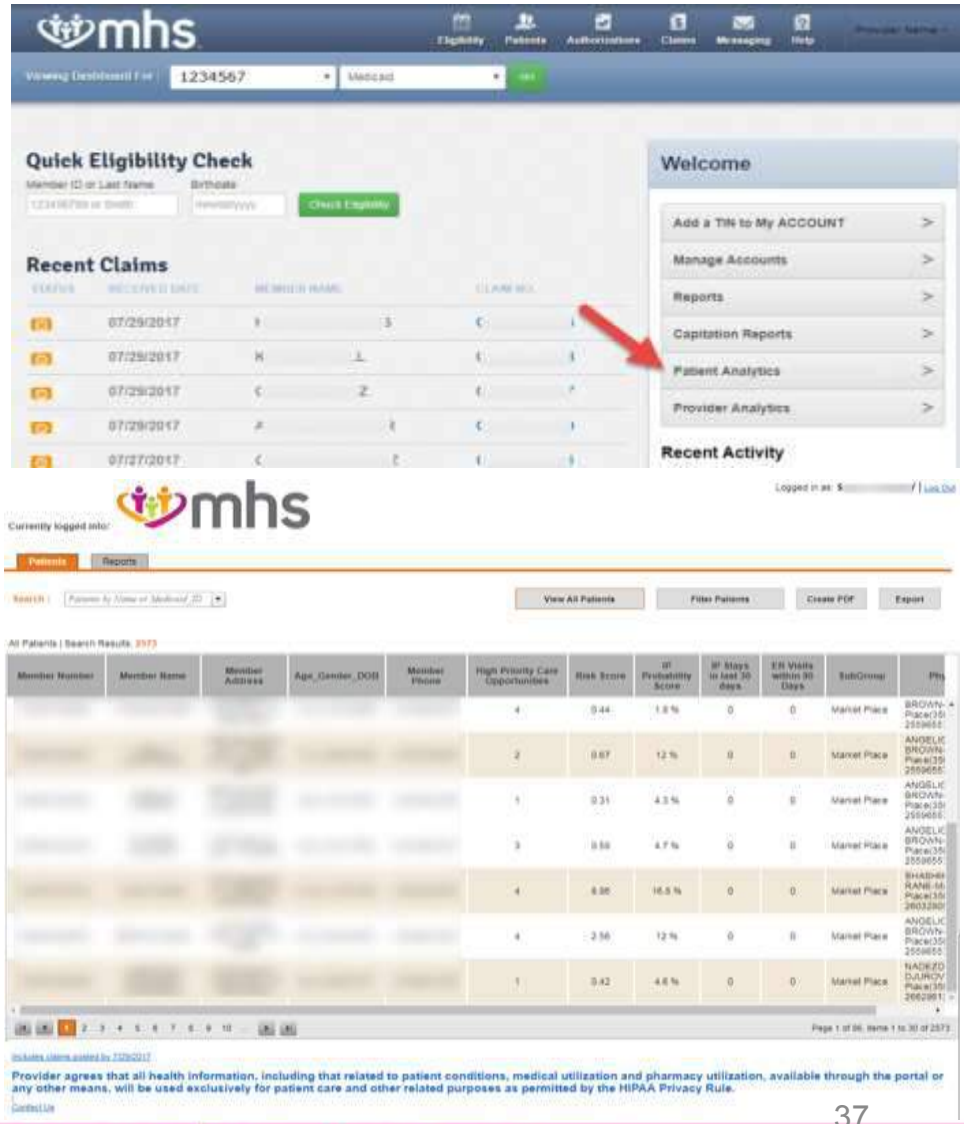
Accessing Patient Analytics

- When logging into Patient Analytics, the user is presented with the Patients tab as the main landing page. Across the top of the screen are the following buttons:

- View All Patients – This button will remove any filter options and display all patients for which the user has access
- Filter Patients – By selecting this button, an info window generates allowing the user to select patients that fit a specific criteria

  Manage Filters: Filter the patient list by business rules, subgroups, and physicians.

- Create PDF – Generate a .pdf document or printer friendly version of the patient list
- Export – Exports the Patient List to an Excel worksheet

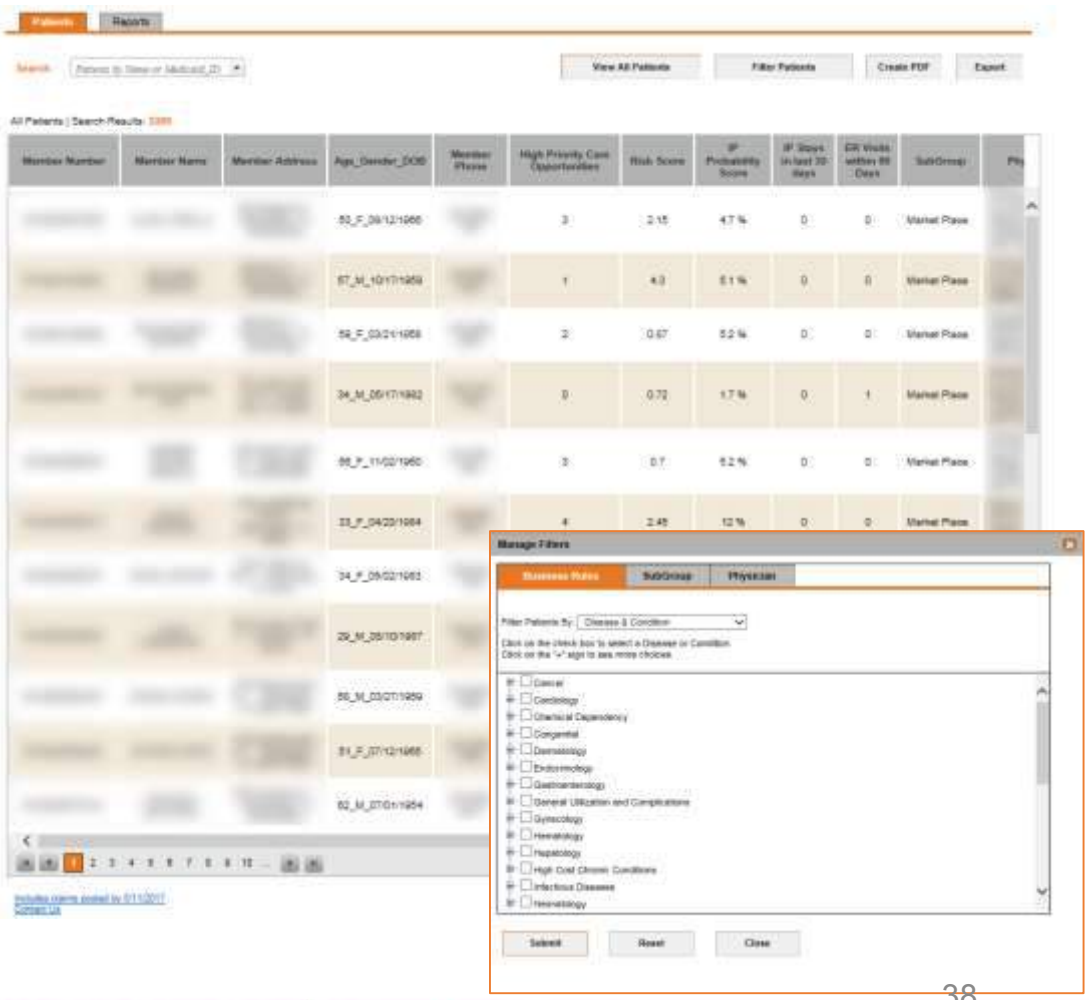


Patients Tab

1. **Tabs:** Allows the providers to choose between the Patients information and Reports
2. **Logout Button:** For security purposes, logout to protect patient information. Not shown, in upper right hand corner
3. **Search:** Allows providers to search by the patient's name, Medicaid, Medicare or Marketplace ID number
4. **Filters and Export Features:** Allows users to view all patients or filter by multiple criteria. The users will also have the ability to create a PDF document or export a detailed patient profile

    4a. Manage Filters: Filter the patient list by business rules, subgroups, and physicians

5. **Timeframe:** Provides the date when claims have been posted, followed by a link to contact for questions or concerns



Search Results

Patient Demographics


All Patients | Search Results: 3089

Member Number	Member Name	Member Address	Age_Gender_DOB	Member Phone	High Priority Care Opportunities	Risk Score	IP Probability Score	IP Stays in last 30 days	ER Visits within 90 Days	SubGroup	Phy

High Priority Care Opportunities: Displays a count of care opportunities deemed to be of the highest importance

Risk Score: Identifies the likelihood that the patient will incur cost and services in the next 12 months when compared to an average patient. An average patient has a health of 1.0. Higher values indicate the patient is more likely to need services in the future

IP Probability: A percentage indicating the likelihood that a patient will have one or more inpatient confinements in the next 12 months

Inpatient Stays in the Last 30 Days: A metric that captures the number of distinct inpatient hospitalizations in the last 30 days based on processed claims

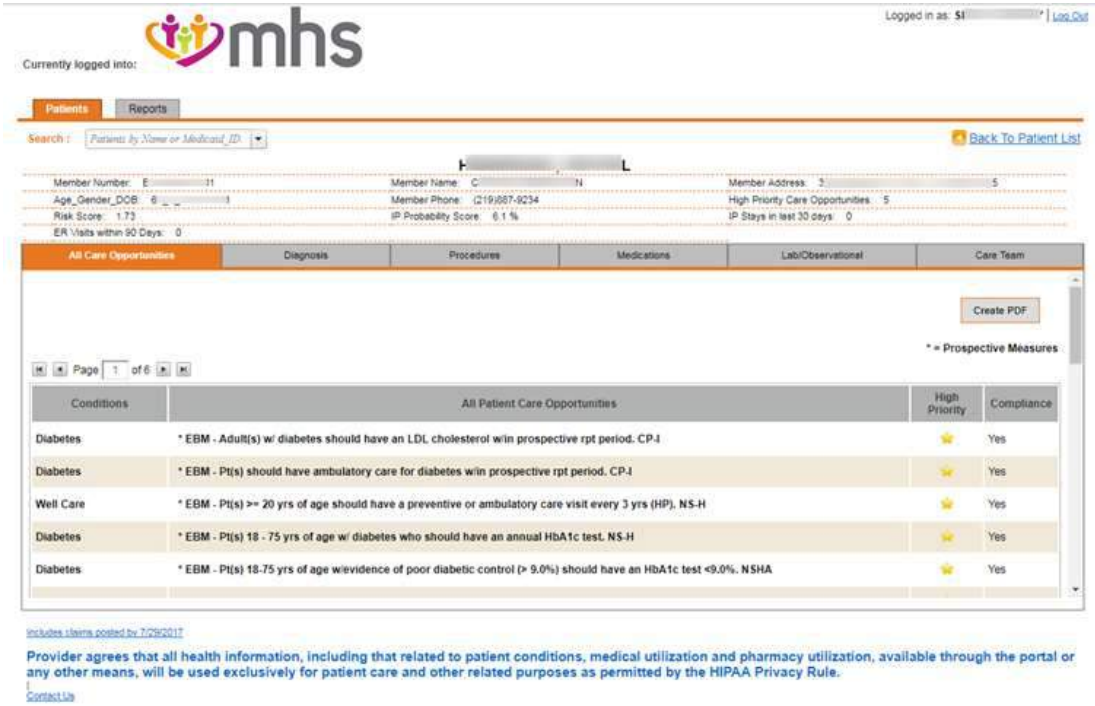
Emergency Room Visits within 90 Days: A metric that shows the number of distinct emergency room visits within 90 days based on processed claims

Subgroup: Medicaid, Medicare, or Marketplace

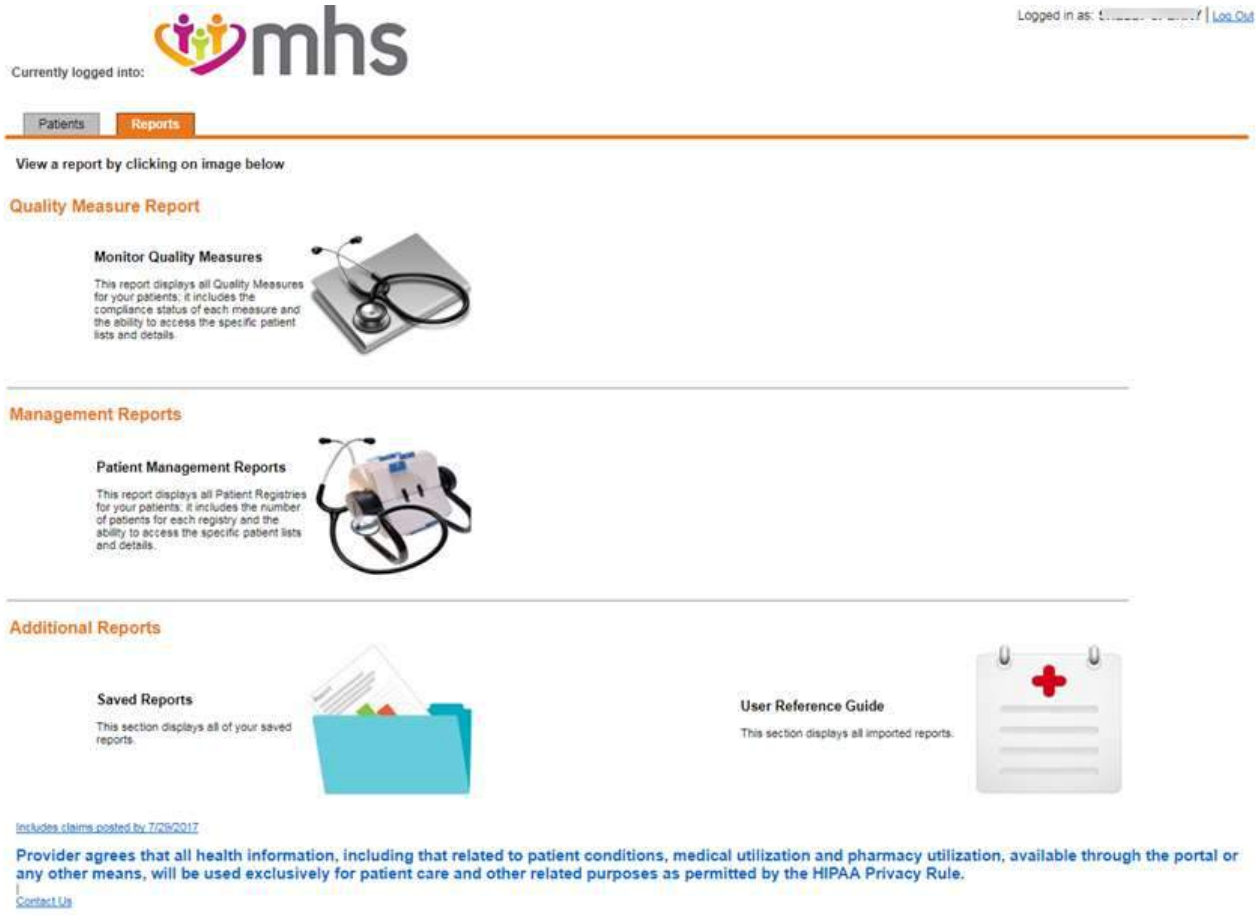
Physician: Displays the provider's name and credentials

Patient Profile

1. **Member Demographics:** Displays information about the member
2. **All Care Opportunities**: The default landing page for patient details. Displays care opportunities or measures that indicate if a patient has or has not received treatment for a health condition
3. **Diagnosis:** Shows primary and secondary diagnoses from claims data
4. **Procedures:** Shows patient procedures associated with primary and secondary diagnoses
5. **Medications:** Displays a list of medications prescribed to the patient
6. **Lab/Observational:** Shows lab values, interpretations, and trends
7. **Care Team:** Allows users to view the patient's providers. Providers are labeled as Managing Doctor or Other Doctor



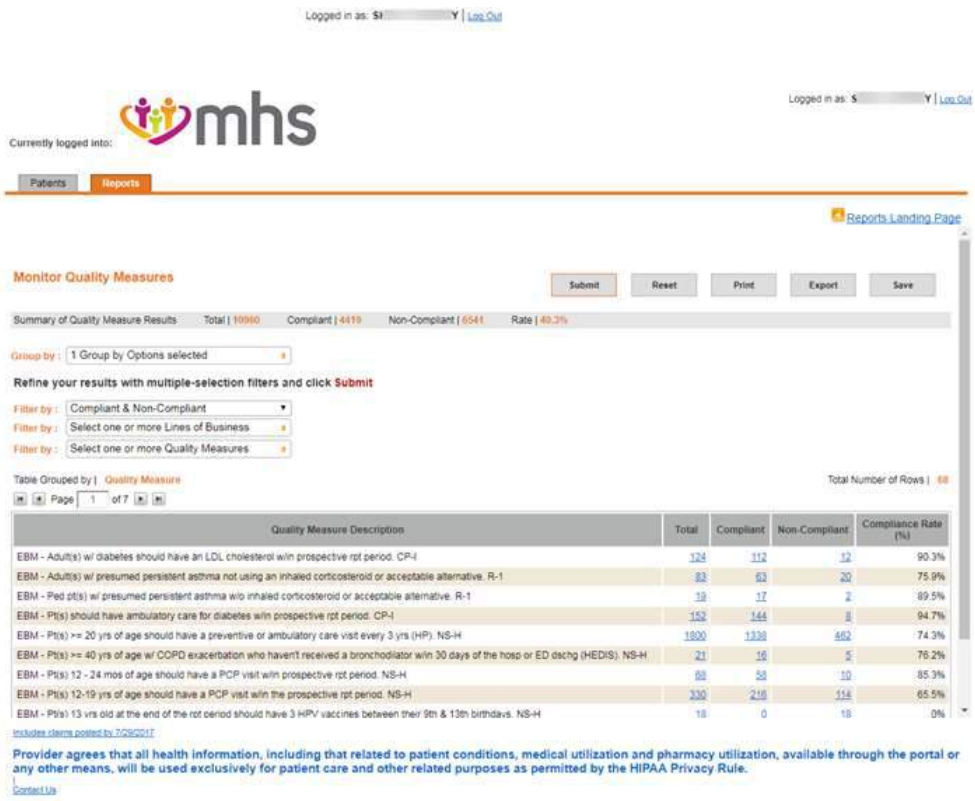
Reports


Currently logged into:
mhs
Logged in as: [redacted] | Log Out
Patients
Reports
View a report by clicking on image below
Quality Measure Report
Monitor Quality Measures
This report displays all Quality Measures for your patients; it includes the compliance status of each measure and the ability to access the specific patient lists and details.
Management Reports
Patient Management Reports
This report displays all Patient Registries for your patients; it includes the number of patients for each registry and the ability to access the specific patient lists and details.
Additional Reports
Saved Reports
This section displays all of your saved reports.
User Reference Guide
This section displays all imported reports.
Includes claims posted by 7/28/2017
Provider agrees that all health information, including that related to patient conditions, medical utilization and pharmacy utilization, available through the portal or any other means, will be used exclusively for patient care and other related purposes as permitted by the HIPAA Privacy Rule.
Contact Us

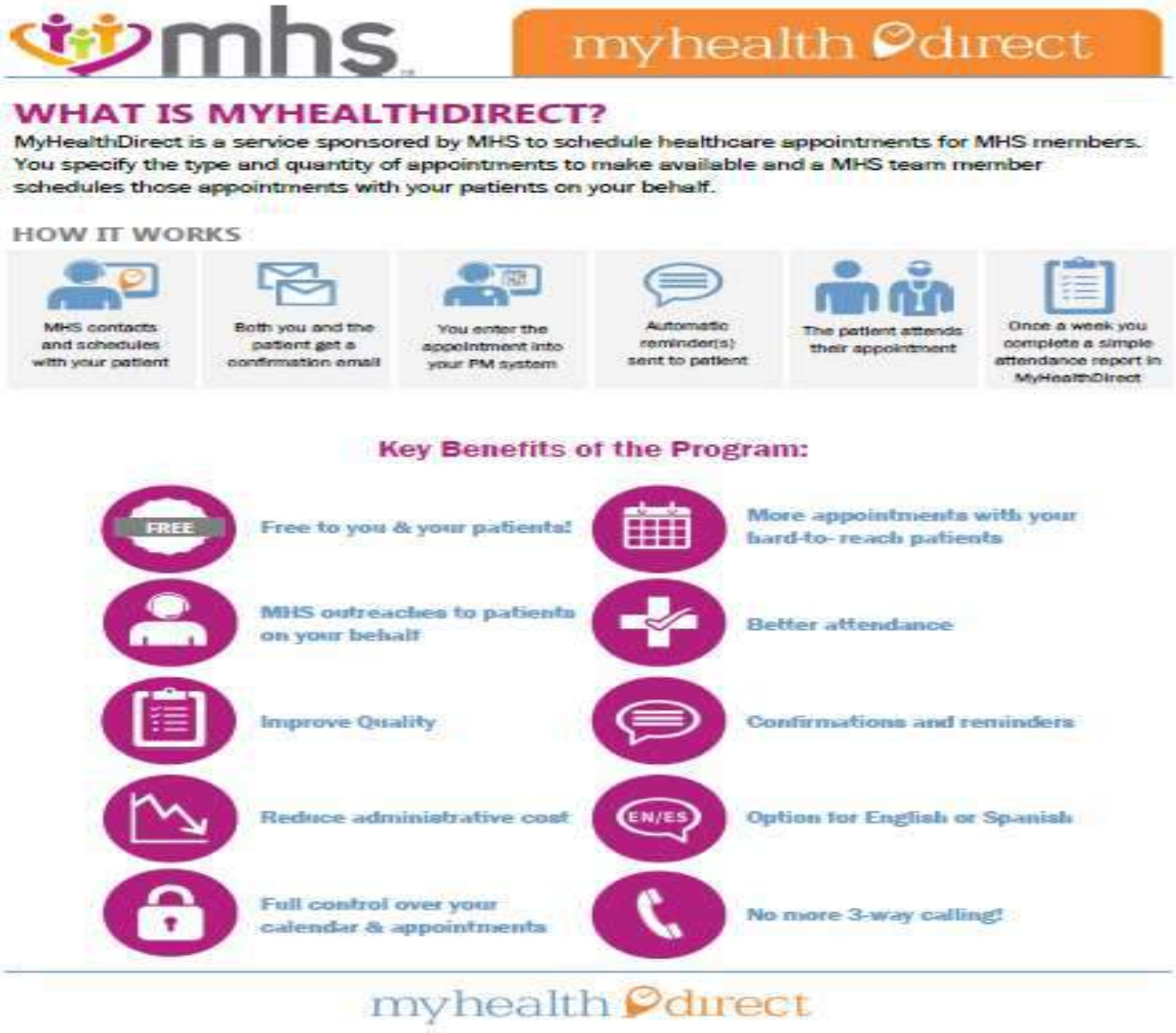
Quality Measure Report

Monitor Quality Measures Report

- Users are able to view reports by selected grouping and filtering options



MYHEALTHDIRECT



mhs

FREQUENTLY ASKED QUESTIONS

1 How do I get started?

One time:

1. Complete the Clinic Setup Form and User Agreements
2. Activate your user account
3. Schedule and complete the training webinar (est. 45 minutes)

Ongoing Responsibilities:

1. Enter appointments promptly as you receive the confirmations
2. Report attendance weekly
3. Keep your calendar up to date

2 How do I keep from double booking?

You always have full control over your calendar. You make appointments available in MyHealthDirect and then block them in your practice management system. When an appointment comes in through MyHealthDirect, you enter the information and change the blocked slot to a scheduled appointment. If you want to schedule an appointment for a blocked slot, it's easy to remove that slot from your MyHealthDirect inventory so it isn't double-booked.

3 I don't want appointments to go unused

All appointments have a give-back rule known as a "restriction." We recommend setting your appointment restrictions at 72 hours. If an appointment is still unbooked 72 hours out, it will automatically become unavailable in MyHealthDirect and your staff can fill it without concern for double-booking.

4 Can I get appointment confirmations other ways?

Confirmation emails can be sent by email, fax, or both. Additionally, a connector is available for practices with a high volume of appointments. This connector allows MyHealthDirect to update your practice management system directly. Please contact your MyHealthDirect Account Executive for more information.

More Questions? *Please feel free to contact your Provider Representative or MyHealthDirect at any time!*

Danielle Curran
Account Manager, MyHealthDirect
dcurran@myhealthdirect.com | 832.818.9080

Caroline Larsen
Account Specialist, MyHealthDirect
clarsen@myhealthdirect.com | 615.588.7110

myhealthdirect

P4P Payout Calculations

Payout calculations based on final HEDIS admin rates and paid at contract level.

Factors include –

- Panel size
- Required number of members qualified per measure
- Funds from measures without enough members get rolled into other qualifying measures

MHS Provider Relations Team

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What you learned today

1. Review of P4P measures
2. The Documentation Requirements
3. Reporting tools that are available for providers to review.
4. New Patient Analytics tool
5. Benefits of My Health Direct
6. How Payout is Calculated

Questions

Thank you for partnering with MHS

Increasing Awareness and Uptake of Influenza Immunization

Glen Nowak, Ph.D.
Acting Director of Media Relations, CDC
Associate Director for Communications, NIP/CDC

"Warning"

- Good (i.e., effective) communication is a necessary but usually only partially sufficient condition for achieving desired behaviors.
- Facts, figures, and statistics, in and of themselves, don't equate to good communication (nor does more information equal good communication).

Question

"It strikes 2 million Americans each year. And complications from this kill up to 200,000 people a year--more people than breast cancer, car crashes, and AIDS combined. The good news is, in most cases, this can be prevented."

What is it that causes this harm? (And does having this information change your behavior?)

IntelligenceReport®

By Lyric Wallwork Winik

Stop A Deadly Killer

Skater Tara Lipinski suffered from DVT.

It strikes 2 million Americans each year and kills more people than breast cancer, car crashes and AIDS combined, yet most of us do not even know its name. The condition is called deep vein thrombosis, or DVT. It begins with a blood clot in the leg that can travel to the lungs, causing a pulmonary embolism and often death. Many of us are at risk—just sitting for a long time on a plane can produce DVT. But older people, pregnant women, smokers, the obese and others with a condition that limits mobility are at increased risk. Symptoms include leg tenderness, pain, swelling, discoloration or redness. If you suspect DVT, call a doctor immediately: There are quick, noninvasive tests to identify it, plus options ranging from blood thinners to simple exercises. National DVT Awareness Month begins tomorrow. Go to www.preventdvt.org to learn more.

A magnetic scan shows a leg blockage (white line), indicating deep vein thrombosis. Its clots can be fatal.

There are tests to identify DVT, and simple solutions.

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"Recipe" for Fostering Public Interest and High Vaccine Demand (1)

1. Influenza's arrival coincides with immunization "season" (i.e., when people can take action)
2. Dominant strain and/or initial cases of disease are:
   - Associated with severe illness and/or outcomes
   - Occur among people for whom influenza is not generally perceived to cause serious complications (e.g., children, healthy adults, healthy seniors)
   - In cities and communities with significant media outlets (e.g., daily newspapers, major TV stations)

"Recipe" for Fostering Public Interest and High Vaccine Demand (2)

3. Medical experts and public health authorities publicly (e.g., via media) state concern and alarm (and predict dire outcomes)– and urge influenza vaccination.
4. The combination of '2' and '3' result in:
   A. Significant media interest and attention
   B. Framing of the flu season in terms that motivate behavior (e.g., as "very severe," "more severe than last or past years," "deadly")

"Recipe" for Fostering Public Interest and High Vaccine Demand (3)

5. Continued reports (e.g., from health officials and media) that influenza is causing severe illness and/or affecting lots of people– helping foster the perception that many people are susceptible to a bad case of influenza.
6. Visible/tangible examples of the seriousness of the illness (e.g., pictures of children, families of those affected coming forward) and people getting vaccinated (the first to motivate, the latter to reinforce)
7. References to, and discussions, of pandemic influenza– along with continued reference to the importance of vaccination.

Implications of the "Recipe"

- A large component of consumer demand for flu vaccination is contingent upon things we can't control (e.g., timing, severity, extent, duration of the disease and resulting illness).
- Fostering demand, particularly among people who don't routinely receive an annual influenza vaccination, requires creating concern, anxiety, and worry. For example:
  - A perception or sense that many people are falling ill;
  - A perception or sense that many people are experiencing bad illness;
  - A perception or sense of vulnerability to contracting and experiencing bad illness.

Additional (Pandemic) Influenza Communication Challenges

- Recommendations and perceptions regarding influenza vaccination are not "universal" (and achieving consensus by "fiat" is difficult)
- "Mass media" doesn't effectively reach "the mass"
- Mixed messages and advice are hard to avoid

Influenza Immunization Recommendations and Perceptions

- Until recently, influenza vaccination recommended primarily for 65 and older and people with certain chronic medical conditions– fostering perception that vaccination was for "elderly" and "frail"
- Now recommended for 50-64 year olds and 6-23 month olds– to many, implying a) its helpful primarily for older people and b) we have data that supports such precision
- Experts "nuance" recommendations, but the public (as well as many healthcare providers) don't similarly nuance their perceptions (e.g., "recommend" vs. "encourage," 6-23 month olds vs. 2 year olds)

Three Likely Population Segments

- **People who routinely receive an annual influenza vaccination, including those we recommend do so**
  - Primarily 65 years old and older
  - Primarily get vaccinated in Sept-November
- **People who sometimes receive an annual influenza vaccination, including those we recommend do so**
  - Interest is often contingent on perceptions of severity of the strain, likelihood they or someone they know will contract it, their belief they will experience or transmit a severe case
  - Appear to get vaccinated later (November, early December)
- **People who choose not to get an influenza vaccination, including those we recommend do so:**
  - Inversely related to age (e.g., most likely 18-49)
  - Among older people, often based on a firmly held belief/conviction

"Mass Media" Less Helpful

- Most people have 10 or so options when it comes to television viewing– many have 50-100 or more
- Hundreds of websites offer medical and health information
- Daily newspaper readership has been declining, particularly among 18-49 year olds
- Cultural and ethnic diversity is greater than ever
- Health literacy is a growing problem
- Belief that today you need to expose people to your message 10-12 times to achieve attention

The Challenge of Avoiding "Mixed Messages and Advice"

- Often arise when expert actions and behaviors don't seem to match or be consistent with policies and recommendations (e.g., healthcare providers not getting annual influenza vaccinations)
- Often fostered by a desire to improve our ability to provide services should large numbers of people act upon our advice
- Often recognized primarily in hindsight– and in contexts outside our own area of expertise

Tom Toles

Washington Post May 2004

Tom Toles ***(Modified)***

Washington Post May 2004

Some Recommendations

- Adopt more sophisticated approach to influenza-related communication:
  - Greater investment in communication research
  - Greater appreciation of need for a) less nuanced messages/advice and b) development/use of a portfolio of messages and materials
  - Plans that extend beyond news media reliance
- Recognition that the kind of communication activities envisioned (e.g., broad scope, high visibility, message frequency) require significant investment
- Greater understanding and use of risk communication principles (e.g., dilemma sharing, acknowledging uncertainty, providing coping strategies and advice)

Thank You

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Global Vaccine Market Features and Trends

Miloud Kaddar

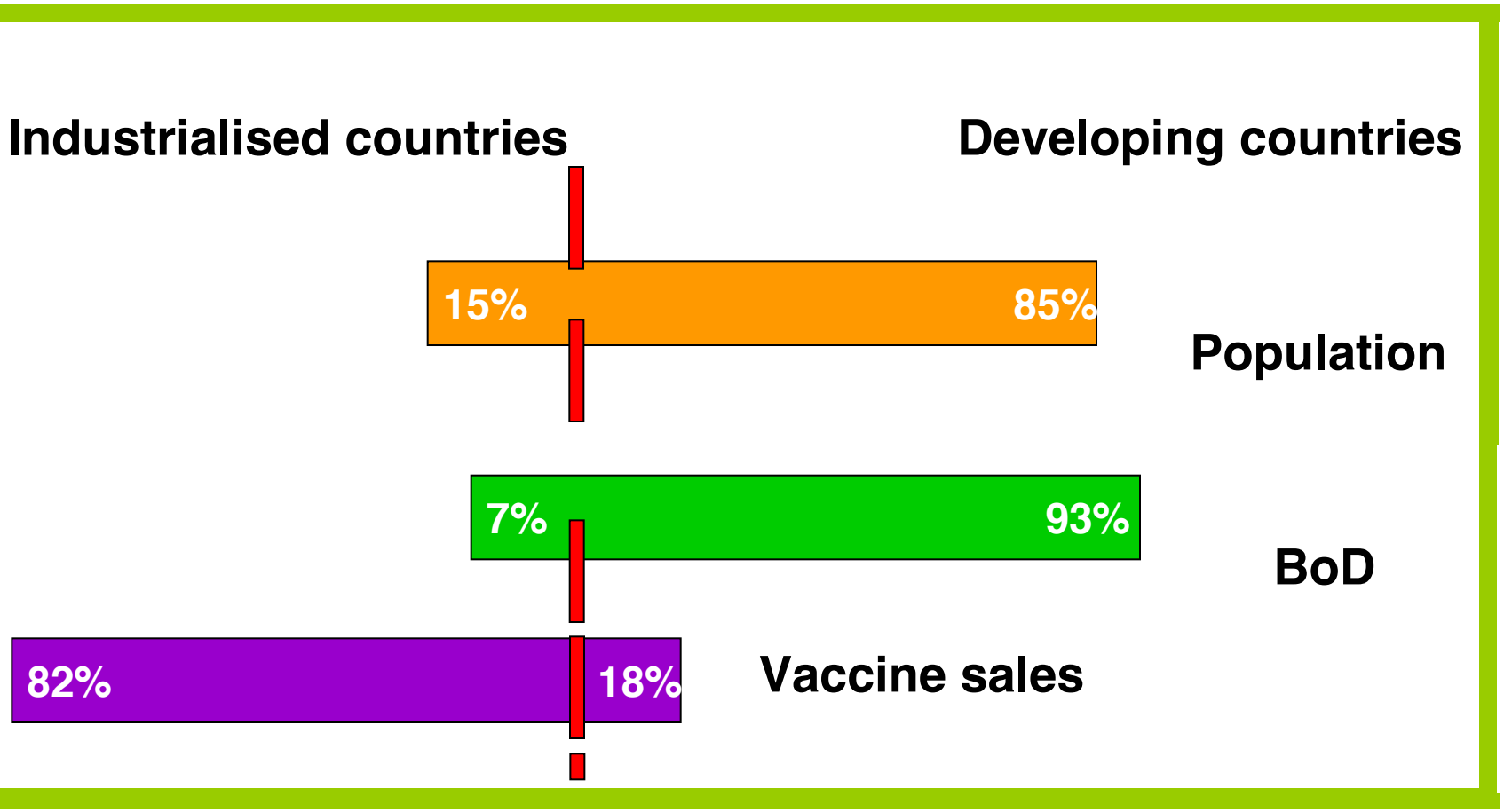
Senior Adviser, Health Economist

WHO, IVB, Geneva

GLOBAL VACCINE MARKET

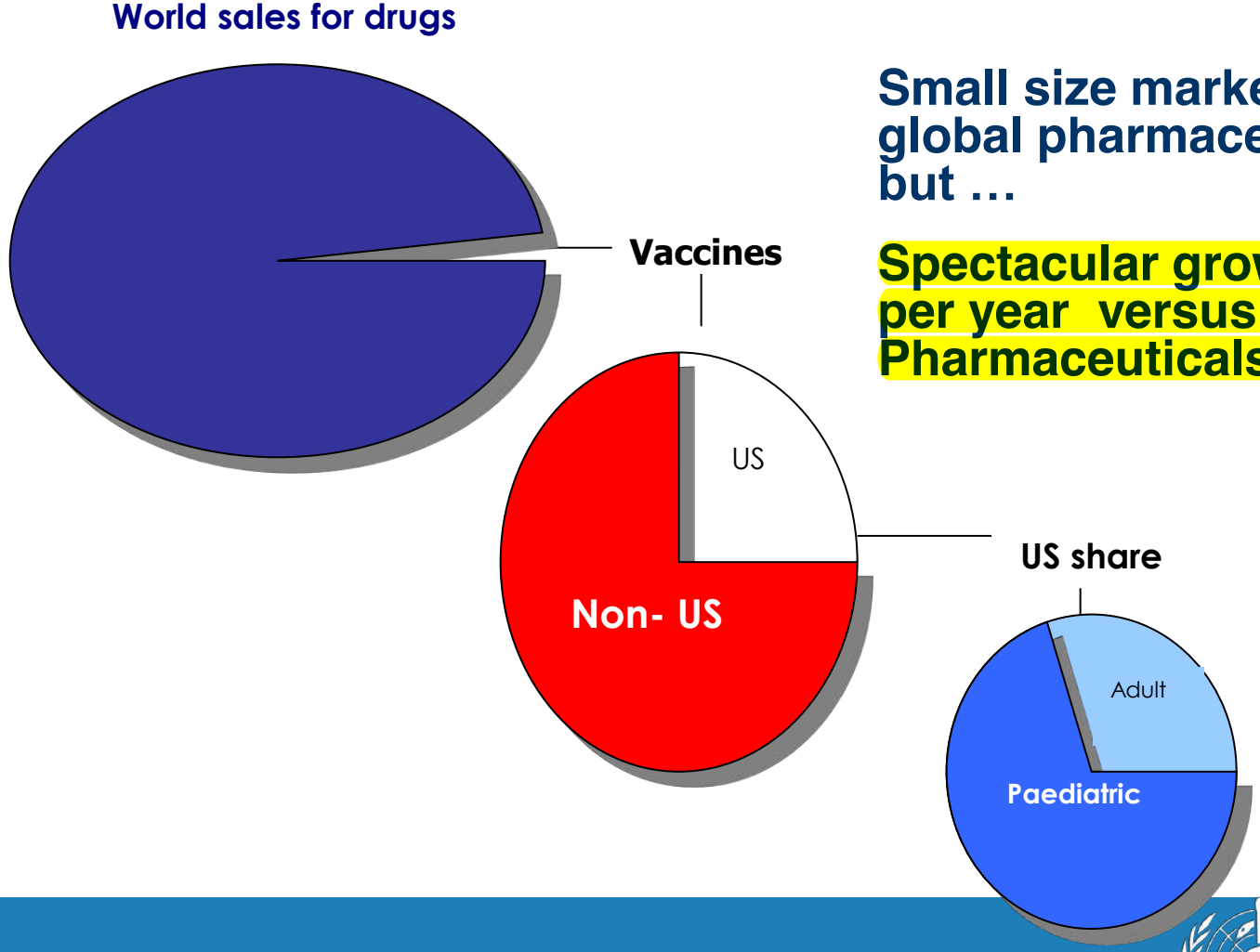
- MAIN FEATURES OF THE VACCINE MARKET ?
- NEW TRENDS SINCE 2000 ?
- IMPLICATIONS ?

Vaccine Market
North – South GAP



World Health Organization

VACCINE MARKET STRUCTURE 2010

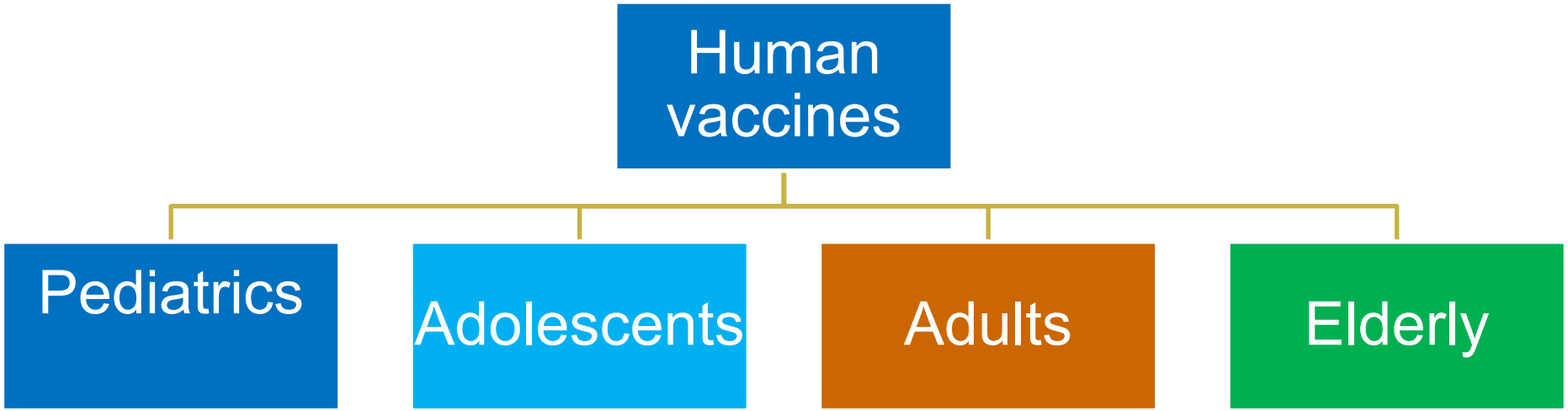


Small size market : 2/3% of the global pharmaceutical market but …

Spectacular growth rate : 10 - 15% per year versus 5-7 % for Pharmaceuticals

World Health Organization

Vaccine segments



World Health Organization

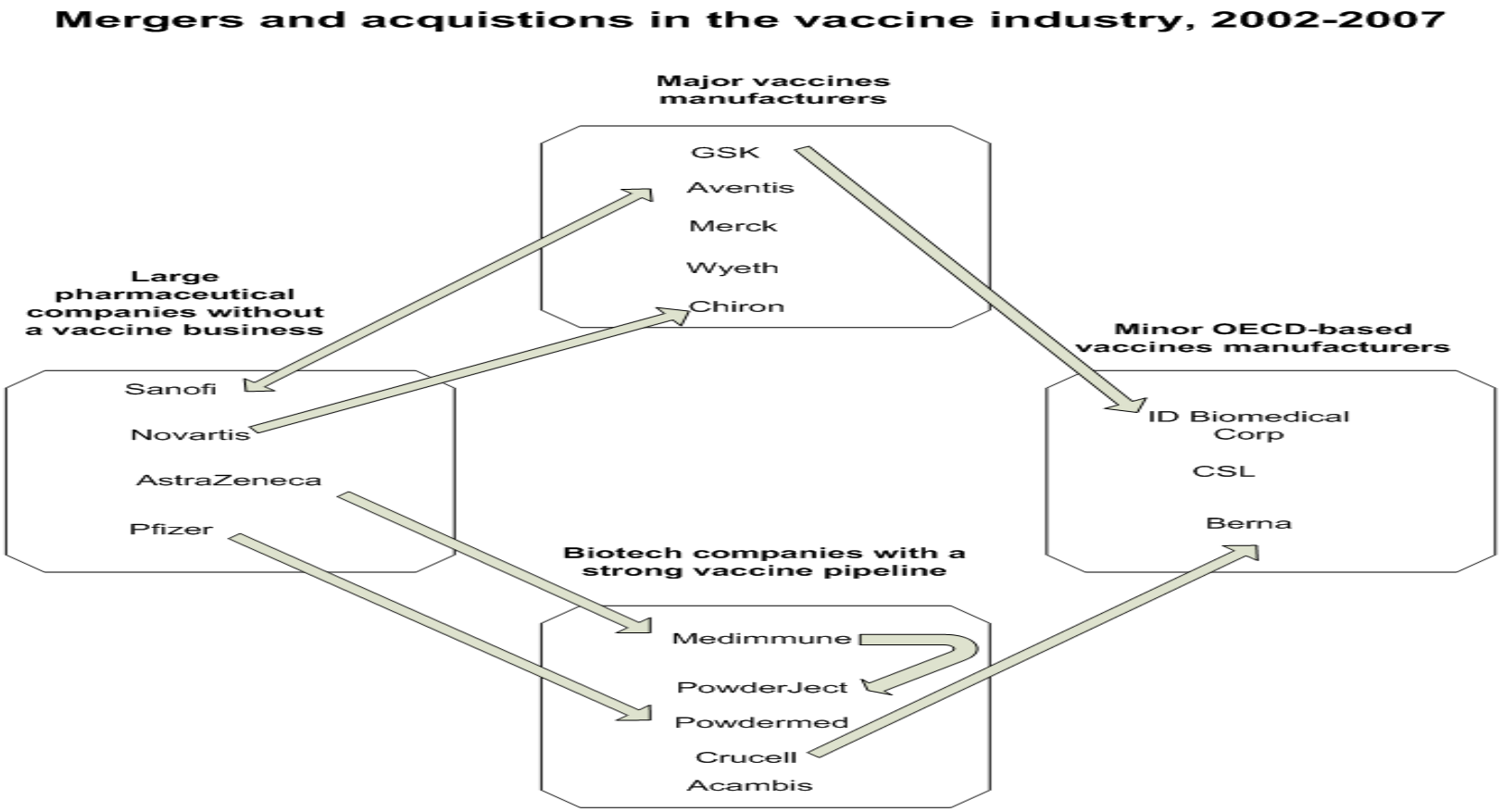
GLOBAL VACCINE MARKET: RAPID GROWTH and CHANGING STATUS

- Tripled in value from USD 5B in 2000 to almost USD 24 B in 2013
  - Influenza vaccine market: estimated at $2.9 billion in 2011 to $3.8 billion by 2018
  - US : $1.6 billion in 2011 to $2.2 billion in 2018
- Global market projected to rise to USD 100 B by 2025
- More than 120 new products in the development pipeline
- 60 are of importance for developing countries
- Vaccines: becoming an engine for the pharmaceutical industry
- Changing status of the vaccines within the pharmaceutical industry
- New business model for vaccines is emerging?

Main features of Vaccine market (2)

- Newer and more expensive vaccines are coming into the market faster than ever before
- Growing concentration in OECD countries but also newcomers (Pfizer, J&J,..)
- Vaccine development: increasing investment

MERGERS AND ACQUISITIONS 2002-2007: Illustration



Note. Double arrows denote mergers, single arrows denote acquisitions where the origin of the arrow is the buyer. Headings (such 'large pharmaceutical companies without a vaccine business') and company names refer to the situation in 2002.

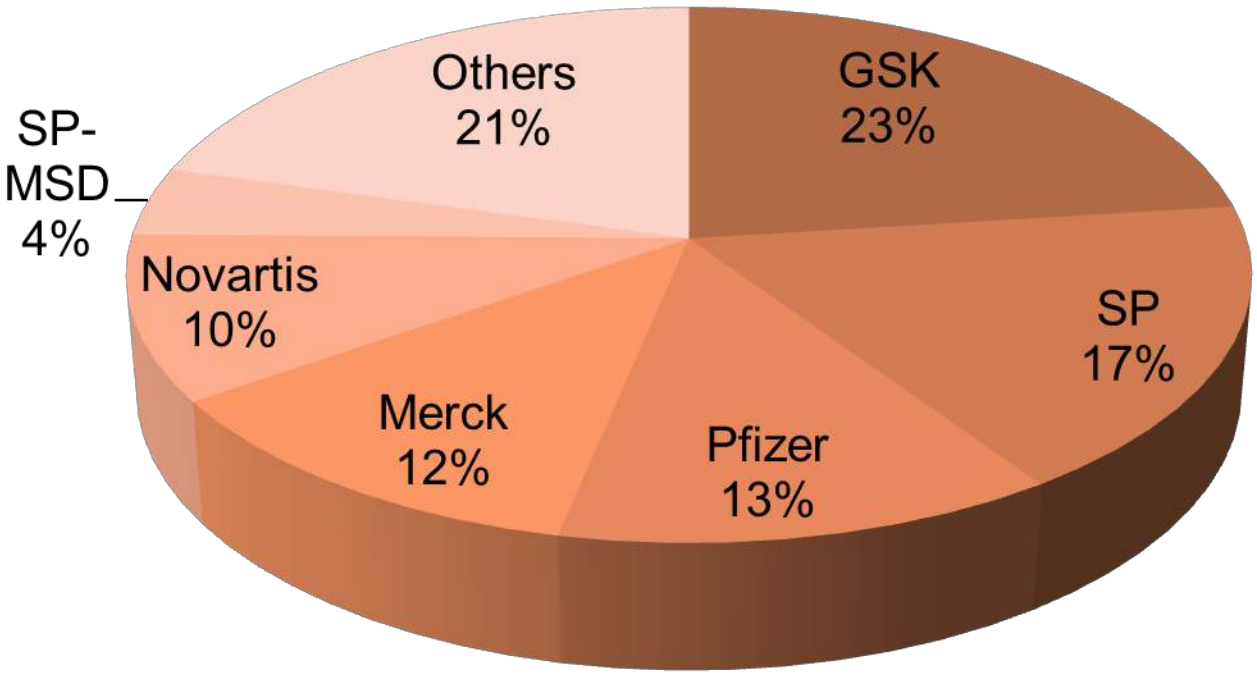
World Health Organization

Overview of major vaccine related acquisitions (2005-2012)

Target Company	Acquiring Company	Investment Made	Date Announced
1.Bilthoven Bio of Netherlands	Serum Institute of India Ltd	Euros 80M	July 2012
2.Zhejiang Tianyuan Bio	Novartis	$ 125 M?	March 2011
3.Wyeth	Pfizer	$68 bn	Jan 2009
4.MedImmune	AstraZenecea	$15.6 bn	April 2007
5.Chiron	Novartis	$5.1 bn	Oct 2005
6.Crucell	Johnson & Johnson	$2.6 bn	Sep 2009
7. ID Biomedical	GSK	$1.4 bn	Sep 2005
8.Shantha Bio	Sanofi Aventis	$781 mn	July 2009
9.Acambis	Sanofi Aventis	$549 mn	July 2008
10. Intercell	Novartis	$363 mn	July 2007
11. Corixa	GSK	$300 mn	May 2005
12. PowderMed	Pfizer	$230 mn	Oct 2006
13. Coley	Pfizer	$214 mn	Nov 2007

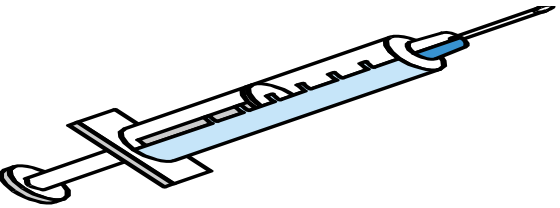
Source:VacZine Analytics + Fierce vaccine

Global vaccine leaders



- 5 large multi-national corporations make up 80% of the global market
- Major focus on new vaccine development for industrialised country markets

World Health Organization



Top product sales in 2010

Brand name (producer)	Type/composition	2010 sales (US$)
Prevnar-13 (Pfizer)	13-valent pnenumococcal conjugate vaccine	$2.4 billion
Proquad (Merck/Sanofi-Aventis)	Measles-mumps-rubella and varicella combination vaccine (MMR-V)	$1.4 billion
Gardasil (Merck)	HPV	$1.35 billion
Prevnar (Pfizer)	7-valent pnenumococcal conjugate vaccine	$1.2 billion
Fluzone (Sanofi Pasteur)	Influenza (seasonal and H1N1 strains)	$1.2 billion
Infanrix and Pediarix) (GSK)	Infanrix = DTaP Pediarix = DTap-HepB-IPV (combination DPT-based vaccines with acellular pertussis)	$1.2 billion

Source: Krishan Maggon knoll (http://knol.google.com/k/krishan-maggon/global-vaccine-market-2010/3fy5eowy8suq3/152….)

Total sales First half 2012

	Vaccine	Company	H1 Sales	Use
1	Prevnar 13	Pfizer	$1.847 billion	Pneumococcal infection
2	PENTAct-HIB	Sanofi	$672 million	Diphtheria, Pertussis/whooping cough; Tetanus; Polio; Haemophilus influenza type b
3	Gardasil	Merck & Co	$608 million	human papillomavirus (HPV)
4	Pediarix	GlaxoSmithKline	$535 million	Diphtheria; Tetanus; Pertussis/whooping cough; Hepatitis B; Polio
5	Hepatitis Vaccine Franchise	GlaxoSmithKline	$500 million	Hepatitis A; Hepatitis B
6	Celtura	Novartis	$441 million	Swine flu
7	Varivax	Merck & Co.	$392 million	Varicella virus
8	Cervarix	GlaxoSmithKline	$285 million	HPV
9	RotaTeq	Merck & Co.	$284 million	Rotaviral gastroenteritis
10	Synflorix	GlaxoSmithKline	$274 million	Pneumococcal infection; Otitis media
11	Rotarix	GlaxoSmithKline	$266 million	Rotaviral gastroenteritis

Total sales First half 2012 (2)

	Vaccine	Company	H1 Sales	Use
12	Zostavax	Merck & Co.	$224 million	Shingles; Herpes
13	Prevnar 7	Pfizer	$222 million	Pneumococcal infection; Otitis media
14	Fluzone/Vaxigrip	Sanofi	$219 million	Influenza
15	Menactra	Sanofi	$217 million	Meningitis
16	Pneumovax	Merck & Co.	$213 million	Pneumococcal infection
17	Adacel	Sanofi	$207 million	Diphtheria; Pertussis/whooping cough; Tetanus
18	MMR-II	Merck & Co.	$180 million	Measles, Mumps, Rubella
19	Boostrix	GlaxoSmithKline	$165 million	Diphtheria; Tetanus; Pertussis/whooping cough
20	Biothrax	Emergent BioSolutions	$88 million	Anthrax

Sources: EvaluatePharma; Fiercevaccines, Sep 2012

VACCINE MARKET : GROWTH FACTORS ?

Combination of :

- Importance of communicable diseases and new threats
- Cost effectiveness of immunizations
- New funding opportunities (Gov, PPP, donors, Foundations,..)
- New research techniques and manufacturing technologies
- Increasing demand, new target population, larger emerging markets
- Higher prices, improved profitability for the industry (blockbuster vaccines..)

Developing countries: vaccine market share and trends

Developing country market

80 % of population / less than 20% of global market

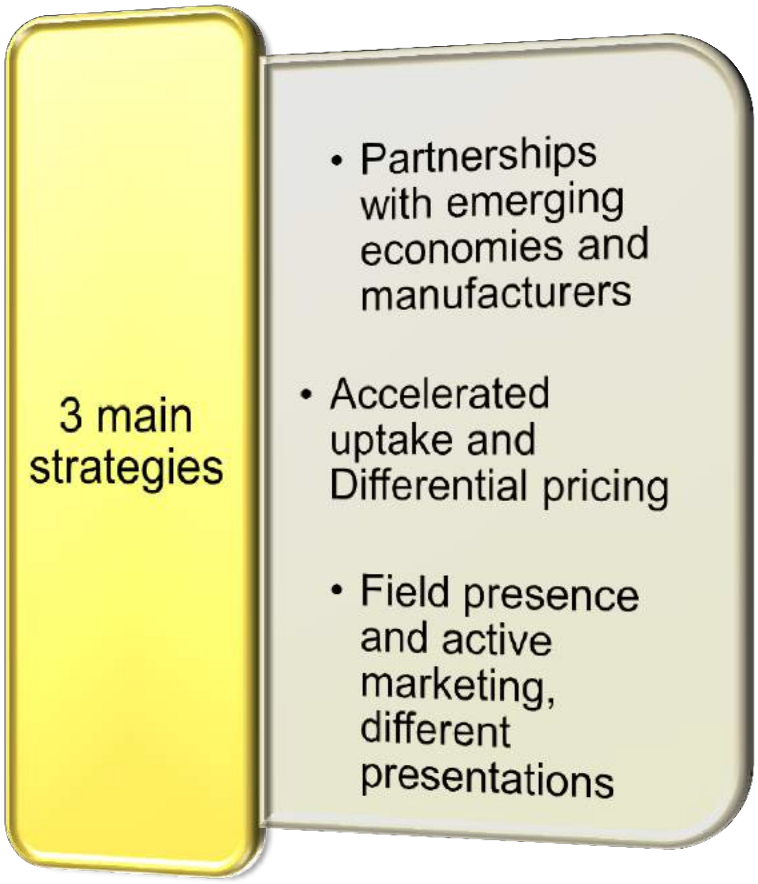
Regular and rapid growth in volume and dollar value

Emerging economies and markets	UN market	Private sector in Low and Middle income countries

MNC : Key strategies for developing countries

3 main targets:

- Emerging economies
- UN markets (UNICEF/GAVI and PAHO)
- Private sector, middle income group markets



World Health Organization

Arrangements with emerging economies and manufacturers

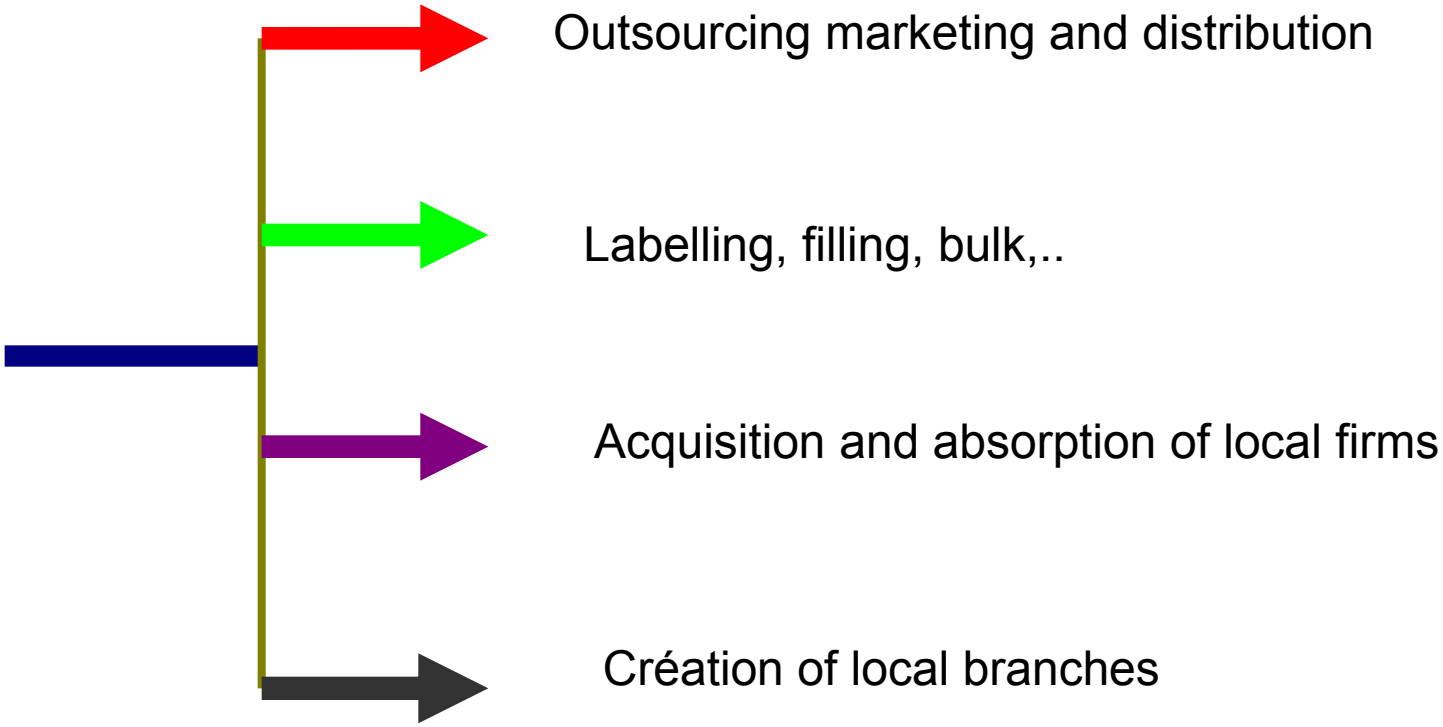
- Various types of arrangments, contracts and partnerships

- Taking into account country potentials and particularities:
  - size of population and potential market,
  - legislation favouring or not domestic production and TT,
  - production costs, scientific and technical capacity, price regulation,
  - NIP, immunization in the private sector,
  - regional influence,..

- Directly with countries and local manufacturers or through PPP or PDP

Various types of arrangements

Objectives:
lower costs, increase production capacity, competitive position
access to large public and private market, …



A new trend: more active vaccine marketing in DC

- Emerging markets such as Mexico, Brazil, Turkey, Indonesia, Russia, China and India are among key priorities for MNC
- Singapour, Malaysia, Vietnam, Philippines, Egypt, GCC and others: second line
- Wide licensing and registration of new and innovative vaccines
- Increased presence of sale forces and MNC representatives : "pharma like model"

MNC = Multinational Corporation

New business MNC model is emerging?

- More mapping, market segmentation and price differentiation
- Outsourcing selected part of R&D, production and commercialization/Access to promising markets and local capacities, low costs
- Risk sharing with countries and funders
- Collaborative networks and active presence at GHIs

UN Market: UNICEF and PAHO

Spectacular increase in the last 10 years

Both UNICEF SD and PAHO

Polio, measles, new vaccines

National, regional and global priority

MDGs, GIVS, GAVI, AMC, IFFim, GPEI, Measles partnership, BMGF, DOV/GVAP

World Health Organization

UN MARKET (in value)

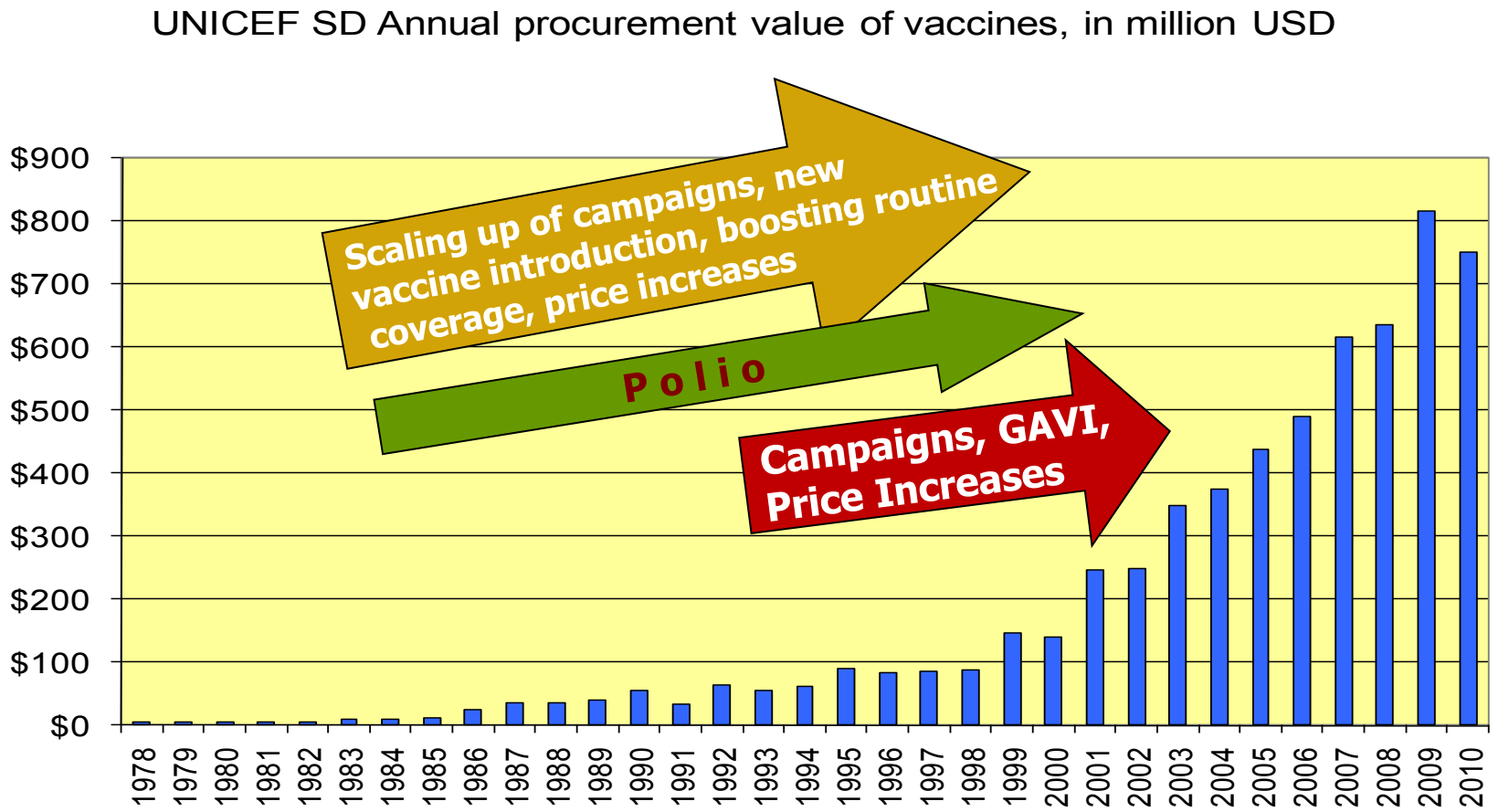
	2002	2011	%
UNICEF SD	$ 220 million	$ 1,03 Billion	+ 468%
PAHO RF	$ 120 million	$ 400 million	+ 333%
Total	$ 340 million	$1,430 billion	+ 420%

Around 7, 5 % of total vaccine sales

Sources: our WHO estimates based on UNICEF SD and PAHO RF data

World Health Organization

UNICEF annual vaccine procurement has increased five fold since 2000 - supporting UNICEF Programmes and on behalf of Partners, Global Programmes Governments and NGO's

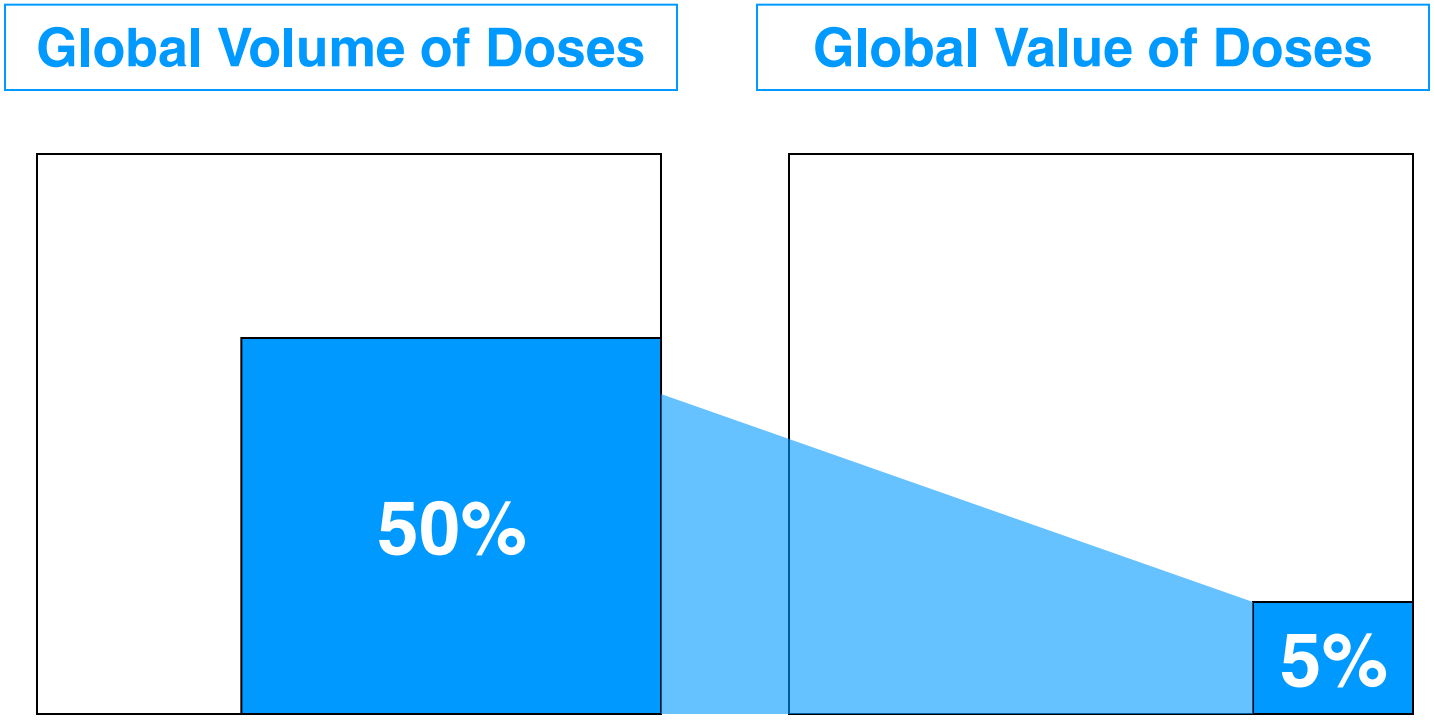


The arrows indicate the main programme drivers for the increased procurement value.

Source UNICEF Supply Division

World Health Organization

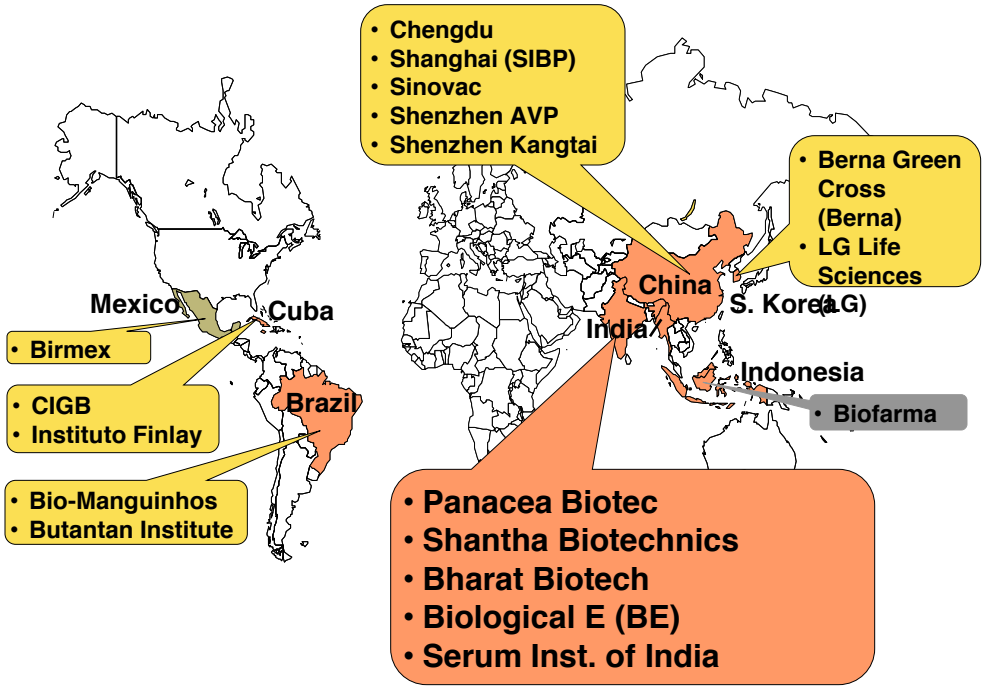
The UNICEF 2012: buying 50% of the global volume of vaccine doses, mainly EPI vaccines, but representing only 5% of total market value



Sources. UNICEF SD

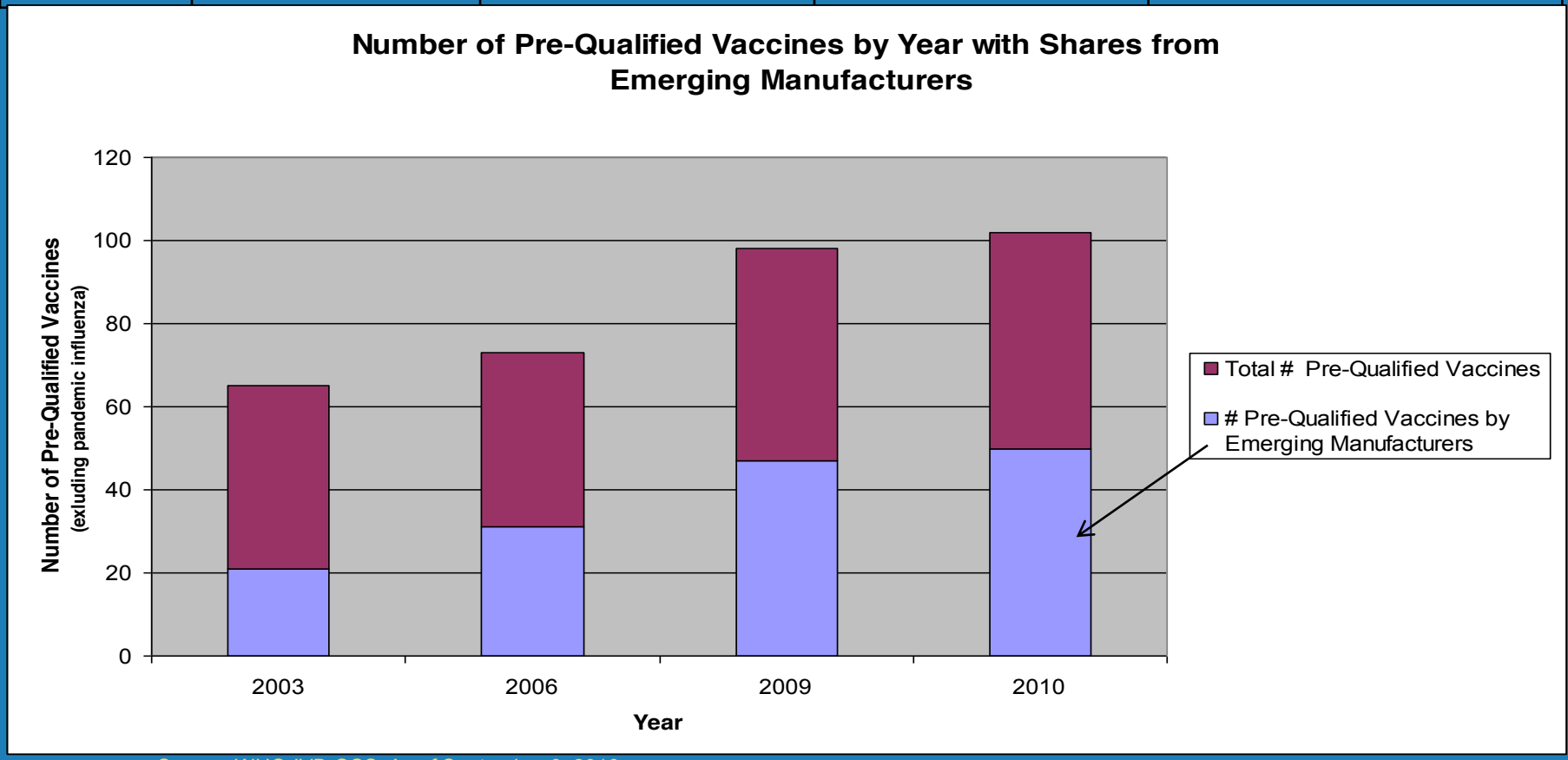
World Health Organization

EMERGING MANUFACTURERS ARE PLAYING AN ACTIVE ROLE



World Health Organization

Year	Total # Pre-Qualified Vaccines (excluding pandemic influenza)	# Pre-Qualified Vaccines by Emerging Manufacturers (excluding pandemic influenza)	% of Pre-Qualified Vaccines by Emerging Manufacturers	# Emerging Manufacturer Countries with Functional NRA's
2003	66	21	32.3%	6
2006	73	31	42.5%	6
2009	98	47	48.0%	6
2010	102	50	49.0%	7

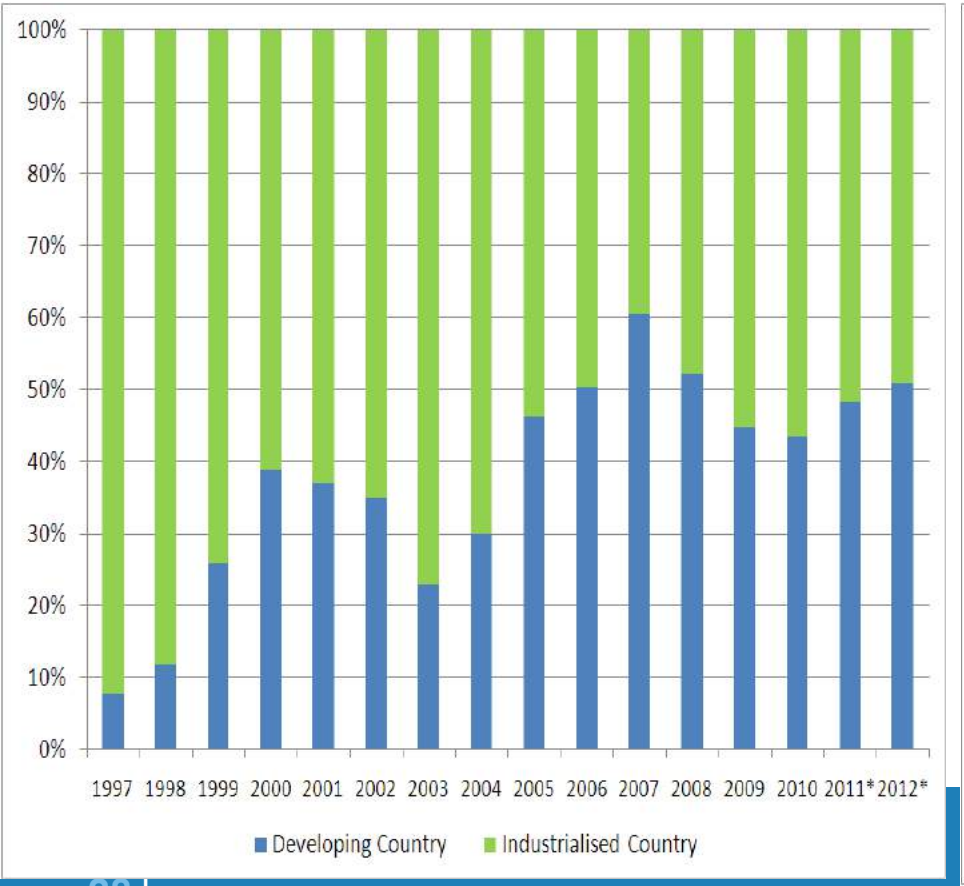


Source: WHO-IVB-QSS. As of September 6, 2010

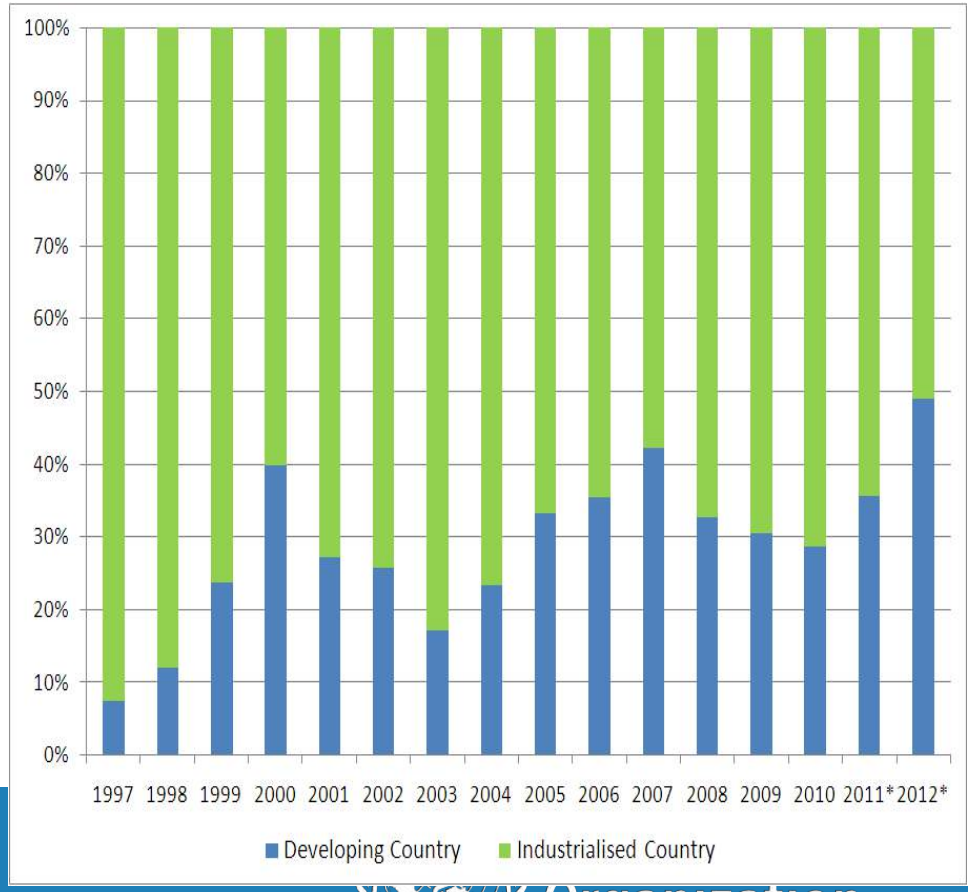
UNICEF SD
Emerging vs. Industrialized manufacturers

Emerging Market Country Manufacturers make up approximately 50% of procurement volumes in 2010 and 30% by value, predominantly due to lower but increasing participation in new vaccine markets and differing cost bases

By Volume

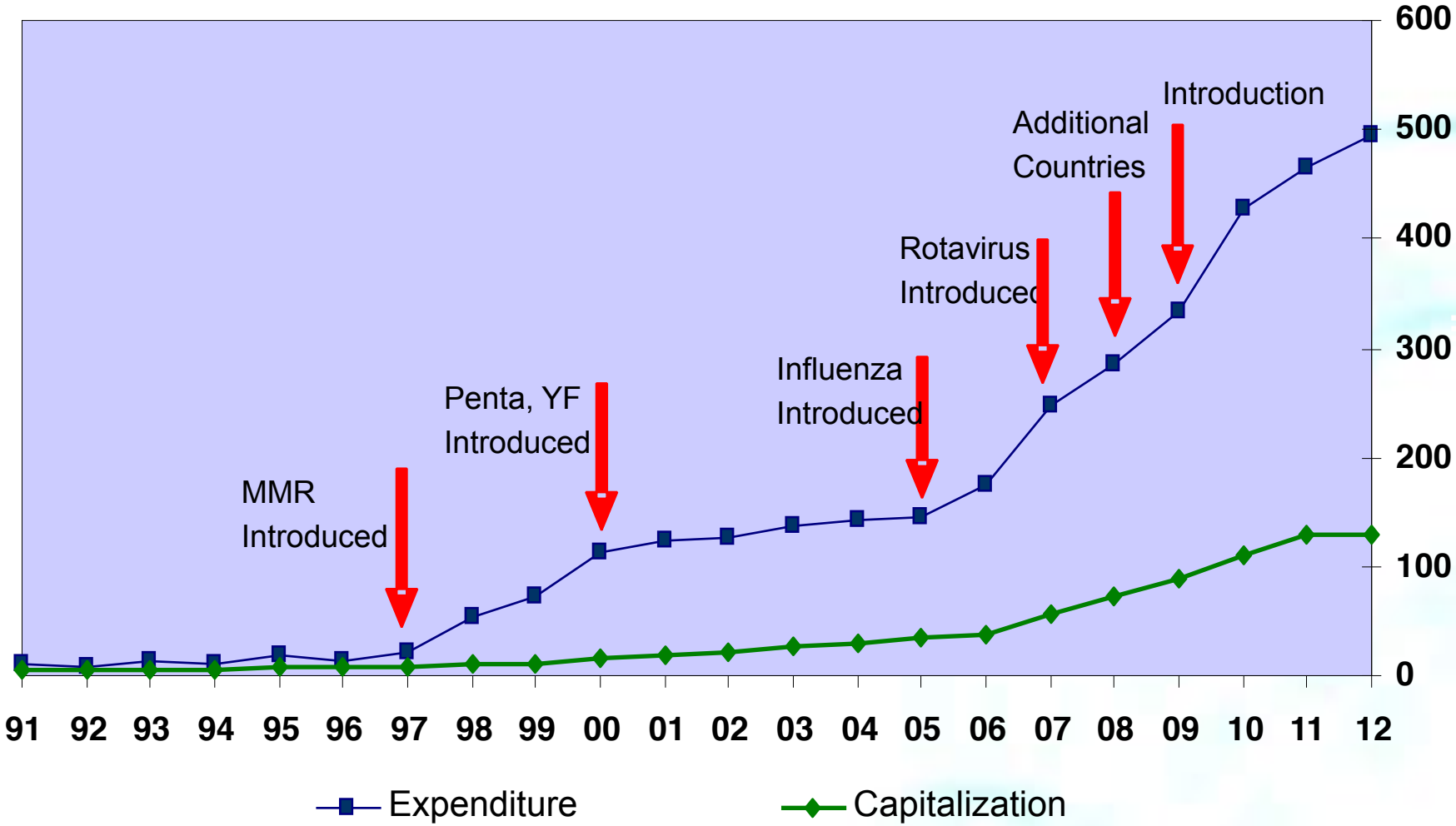


By Value



**2010 – 2012 Data based on awards already made by UNICEF*

Growth of the PAHO Revolving Fund



Source : WHO PAHO

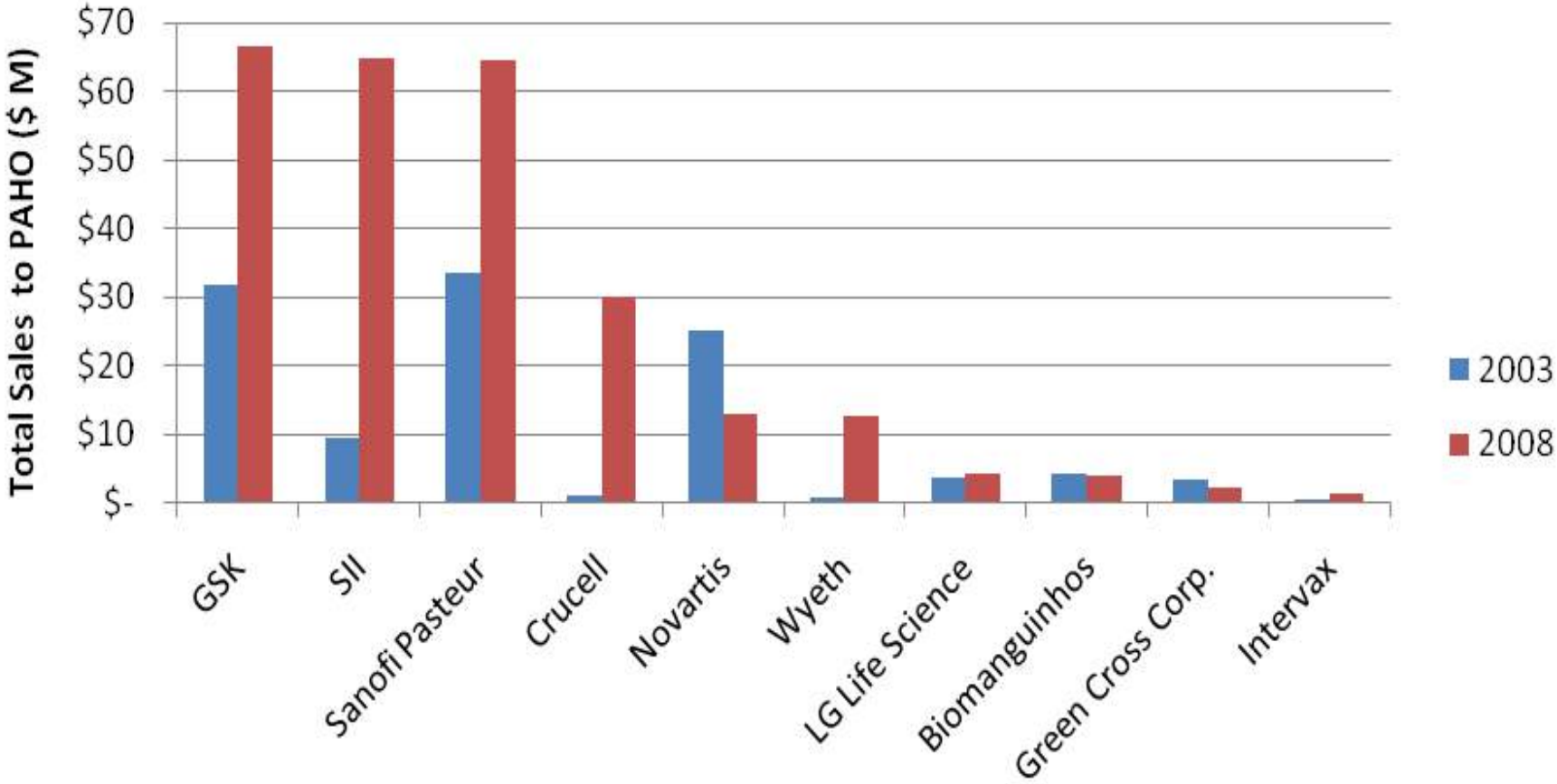
The PAHO Revolving Fund Update: 2012

60 products
28 antigens

39 countries & territories

Expected Purchases:US$ 405 million
Capital Fund: US$ 100 million

Top ten suppliers of PAHO RF 2003-2008



In 2008, no one manufacturer accounted for more than 23% of PAHO purchases

World Health Organization

NEW TRENDS ?

New trends ?

Demand side

- Vaccines and vaccinations : on the top of GoV and UN agenda, unmet needs
- Accelerate uptake and increasing demand in LIC
- Middle Income countries including emerging Countries

Supply

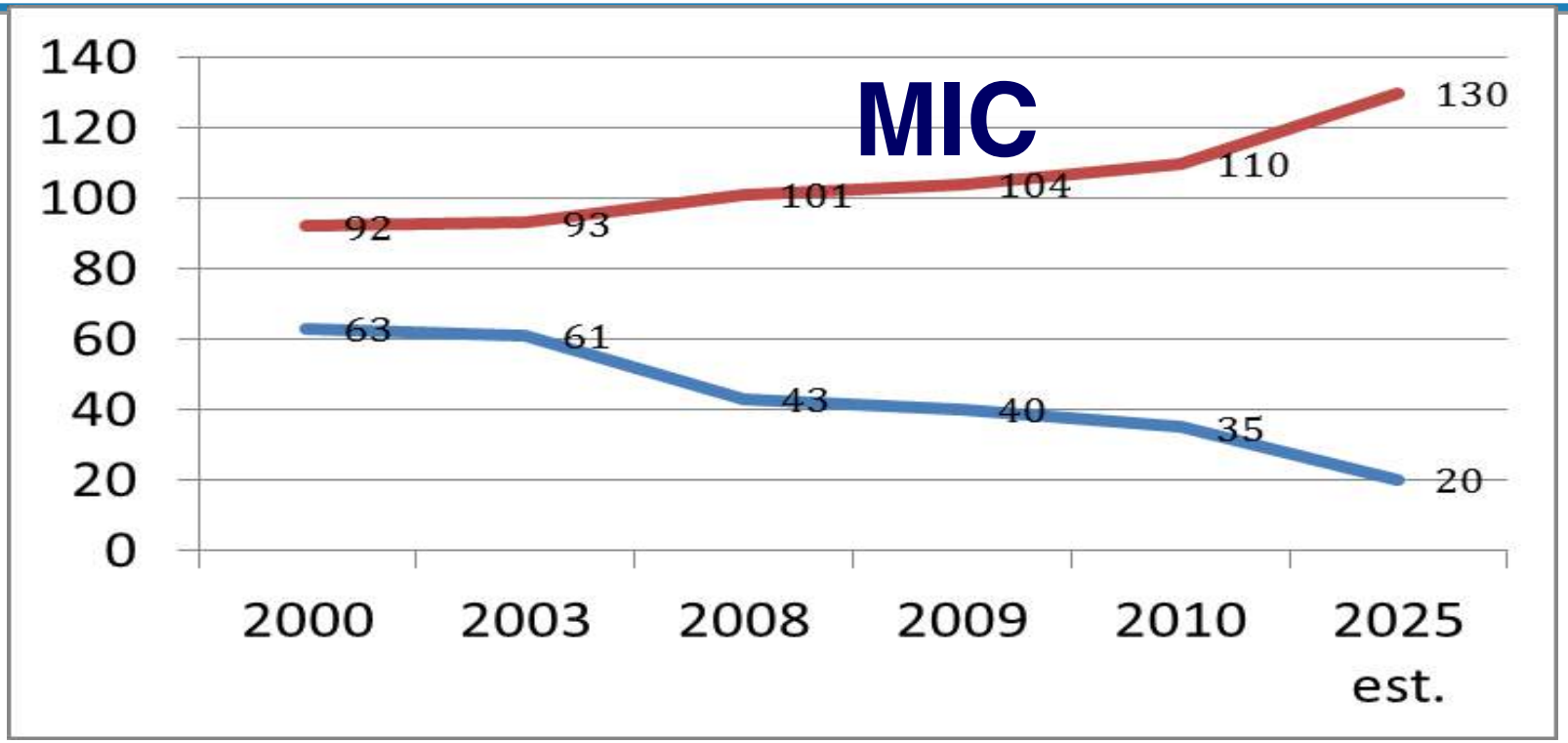
- Increasing capacity
- Remaining tensions on products
- New production and supply strategies

Funding

- GoV resources
- Donors
- Private foundations

More players on demand, supply and financing

By 2025, there will only be 20 LICs



Number of countries by income classification and year
RED = MIC;
BLUE = LIC
Source: Leo and Moss, 2011
CGD A. Glassman

Development of "MIC vaccine market products"

World Health Organization

New trends in the last 5 years and their implications

1) Supply side

- Newcomers: Pfizer, Novartis, Johnson and Johnson,..
- New contractual arrangements between MNF/EM/EE
- Outsourcing of production in developing countries
- New commercial and marketing strategies (high volume/lower price, donation, active marketing,..)
- Product/market segmentation and differential pricing
- MNC: new products and presentations with high return,
- EM: basic and underutilized products high volume/low price
- Persistent supply tensions (basic and new vaccines)

Variety of tools to accelerate new vaccine access and to manage risks

- Innovative procurement approaches as pull mechanisms (AMC)
- Push mechanisms to accelerate vaccine supply (such as Men A)
- Long term commitments may be needed to fund vaccines to stimulate capacity expansion (such as YF)

New supply and procurement strategies

- Reduce risks for both producers and purchasers
- Increase predictability and co-responsabilities

Innovative Finance Achieving Results

Tools Used	Transaction Examples	Goal
Volume Guarantee & Prepayment	Rotavirus Vaccine: • Volume guarantee provided for a portion of the quantities with some volumes paid for in advance • Contract duration of 5-years covering 132M doses • New vaccine launched and sustained at lower price • Financing provided by GAVI, with strategic and technical support from the Gates Foundation ("BMGF")	• $15 per course → €3.76 per course • >$400M in savings over 5 years • Prepayment understood to facilitate expected expansion of manufacturing capacity • Accelerated introduction of Rotavirus vaccine made possible through certainty provided by commitment in new markets
Volume Guarantee	Oral Polio Vaccine (OPV): • Firm contract signed for 2011-2012 with large bulk and fill-finish manufacturer who at the time was considering exit of market • Duration of 2-years originally covering 270M doses per year (540M doses total) • Financing provided by BMGF	• Decrease in price offered to <$0.118 per dose generated significant savings versus current WAP of >$0.13 • Delayed exit of manufacturer by >2 years • Increased visibility for manufacturer and certainty of UNICEF procurement during fragile OPV market
Volume Guarantee & Prepayment	Pentavalent Vaccine (lyophilised): • Contract signed with new entrant to Pentavalent market with volume paid for in advance • Duration for <1 year covering 10M doses • Financing provided by GAVI	• New entrant to market secured volume and able to offer extremely attractive price of $1.80 per dose, • Expanded vaccine security with expanded manufacturing capacity in a fragile market
Volume Guarantee	PCV • Volume guarantees for 20/10/5% of quantities or years 1/2/3 of 10 year contract • Financing provided by GAVI and WB	• Part of overall AMC structure to achieve tail price of max. $3.50 and sufficient production quantities to meet demand

Source: UNICEF SD, DCVMN meeting, Nov 2012

Vaccine Market: Positive trends and Main Issues

- **Positive trends**

  - Immunizations: on the top of the agenda: DOV ands GVAP
  - Promising vaccine pipeline, R&D
  - Growing support: GAVI partners + Gov funding
  - Multiple initiatives, PDPs and PPPs
  - New players on supply and funding
  - More WHO PQ vaccines leading to competition, price decrease
  - Strategic role of UNICEF SD and PAHO and increasing role of funders

- **Concerns :**

  - Oligopoly, limited supply for DC and Shortage risks
  - Upstream factors : Technology transfer and IPRs, R&D for most needed vaccines, DCVM R&D capacity , ..
  - New vaccine costs and prices
  - Financial sustainability ? Govt responsibilities role
  - Future of International initiatives
  - Future of Emerging Manufacturers
  - Impact of the financial crisis?

CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Bernard Lo and Marilyn J. Field, *Editors*

Committee on Conflict of Interest in
Medical Research, Education, and Practice

Board on Health Sciences Policy

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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In preparing this report, the committee and project staff benefited greatly from the assistance and expertise of many individuals and groups. Important information and insights came from four public meetings that the committee organized to collect information and perspectives from a range of academic, professional, consumer, patient, and other organizations and individuals. A number of speakers at these meetings also shared their knowledge at other times during the course of the study. Appendix A includes the agendas of the public meetings and a list of organizations that submitted written statements of views.

The committee appreciates the contributions of the authors of the background papers that appear as Appendix C (Michael Davis at Illinois Institute of Technology and Josephine Johnston at the Hastings Center) and Appendix D (Jason Dana at University of Pennsylvania). Our project officer at the National Institutes of Health, Walter Schaffer, was always helpful in getting our questions answered. We also called on Daniel Wolfson at the American Board of Internal Medicine Foundation for information. In addition, Ariel Winter of the Medicare Payment Advisory Commission helped by answering questions about the commission's work. Mary Nix at the Agency for Healthcare Research and Quality provided data from the National Guidelines Clearinghouse that we could not obtain online. An undoubtedly incomplete list of others who assisted the committee's work includes David Atkins, James Bernat, Carol Blum, David Blumenthal, Deborah Briggs, Laura Brockway-Lunardi, Robert Campbell, Roger Chou, Vivian Coates, Allan Coukel, Bette Crigger, Susan Ehringhaus, Brian Eigel,

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published reports as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Claudia R. Adkison, Emory University School of Medicine
Robert Baron, University of California, San Francisco School of Medicine
Paul Citron, Medtronic, Inc. (Retired)
F. Sessions Cole, Washington University School of Medicine
Peter Densen, University of Iowa Carver College of Medicine
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Harold Sox, Annals of Internal Medicine and American College of Physicians
Jeremy Sugarman, Johns Hopkins Medical Institutions
P. Roy Vagelos, Merck & Co., Inc. (Retired)

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **David Challoner,** University of Florida, and **Judith L. Swain,** National University of Singapore and University of California, San Diego. Appointed by the National Research Council and the Institute of Medicine, these individuals were responsible for making certain that an independent examination of this report was carried out in accordance with the institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Hardly a week goes by without a news story about conflicts of interest in medicine. While this committee met, colleagues and friends sent me many news reports and journal articles on the topic. These reports—even if one expects that initial news reports may not always have the stories quite straight—served as continual reminders that conflicts of interest create deep concerns about the integrity of medicine and medical research and raise questions about the trustworthiness of physicians, researchers, and medical institutions.

As I look back over our deliberations, several themes stand out. First, as with all Institute of Medicine (IOM) reports, the committee was charged with making recommendations that were based on evidence and convincing reasons. Although the committee members were aware of powerful anecdotes and had personal beliefs about the issues, we repeatedly asked whether the evidence supported our conclusions and recommendations. If it did not, we developed a reasoned case on the basis of the committee's experience and the judgment of the committee members about the arguments for the use of different approaches presented in the literature or in statements submitted to the committee. Second, it is a challenge to craft policy recommendations that strike the right balance between addressing egregious cases and creating burdens that stifle relationships that advance the goals of professionalism and generate knowledge to benefit society. The committee tried to consider the possibility that well-intentioned policies may have unintended adverse consequences. Third, regulation alone may have limited effectiveness in the absence of a culture of professionalism

and other incentives that are aligned to promote professional behavior. The committee considered how a variety of organizations—including those that accredit health care institutions and license health care professionals, publish the findings of medical research, use practice guidelines, and pay for medical care—can buttress the conflict of interest policies implemented by institutions that carry out medical research, provide education and patient care, and develop practice guidelines.

This report cannot and did not attempt to resolve all issues related to conflicts of interest in medicine. In view of our expansive charge, we tried to address central questions rather than the many details of this complex topic. For example, we focus on conflicts that involve financial interests because they are at the heart of concerns and debates about conflicts of interest. Furthermore, because relationships with pharmaceutical, medical device, and biotechnology companies have created the greatest concern and were central in the discussions that led the IOM to pursue this study, we focused on those relationships. The committee expects that many of the recommendations and analyses in our report will also apply more generally to professional and institutional relationships with other commercial entities, such as insurers and vendors of nonmedical products.

The committee could not resolve some important issues like harmonizing the different requirements for the disclosure of financial relationships because they would require much more time and additional expertise. Instead, to standardize aspects of disclosure policies and procedures, the committee recommended a focused consensus development process that would involve multiple stakeholders on the issue.

Our committee was diverse, involving members with different professional backgrounds and areas of expertise. These different perspectives led to spirited discussions and debates. Each of us listened to points of view and information that we had not previously considered. We tried to listen to and understand other viewpoints and be open to new perspectives, even if in the end we did not agree on all issues. Appendix F describes the different views on one issue, a proposal by some committee members for broader requirements for public disclosure. In general, the committee hoped that by explaining our reasoning on difficult issues our audiences would better appreciate the multiple considerations that a sound conflict of interest policy should address.

As chair, I want to personally thank the committee members for their hard work and their willingness to engage on difficult topics. I am deeply grateful to them for the time and effort that they took from their busy schedules to devote to this project. This report is truly a collaborative effort and is much the better, I think, for the back-and-forth discussions. I also want to personally thank our IOM staff for their tremendous efforts in making this report possible. Robin Parsell skillfully handled meeting

and other logistics, and Franklin Branch provided research assistance in many areas. Marilyn Field was unstinting in her background research, drafting and revising of the manuscript, and high standards for our work. And I want to thank Lindsay Parham, my research assistant at the University of California at San Francisco, for her expert help with background research.

Bernard Lo, M.D., *Chair*
Committee on Conflict of Interest in
Medical Research, Education, and Practice

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BOXES

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ABSTRACT

Patients and the public benefit when physicians and researchers collaborate with pharmaceutical, medical device, and biotechnology companies to develop products that benefit individual and public health. At the same time, concerns are growing that wide-ranging financial ties to industry may unduly influence professional judgments involving the primary interests and goals of medicine. Such conflicts of interest threaten the integrity of scientific investigations, the objectivity of professional education, the quality of patient care, and the public's trust in medicine.

This Institute of Medicine report examines conflicts of interest in medical research, education, and practice and in the development of clinical practice guidelines. It reviews the available evidence on the extent of industry relationships with physicians and researchers and their consequences, and it describes current policies intended to identify, limit, or manage conflicts of interest. Although this report builds on the analyses and recommendations of other groups, it differs from other reports in its focus on conflicts of interest across the spectrum of medicine and its identification of overarching principles for assessing both conflicts of interest and conflict of interest policies. The report, which offers 16 specific recommendations, has several broad messages.

- *The central goal of conflict of interest policies in medicine is to protect the integrity of professional judgment and to preserve public trust rather than to try to remediate bias or mistrust after it occurs.*
- *The disclosure of individual and institutional financial relationships*

is a critical but limited first step in the process of identifying and responding to conflicts of interest.

- *Conflict of interest policies and procedures can be strengthened by engaging physicians, researchers, and medical institutions in developing policies and consensus standards.*
- *A range of supporting organizations—including accrediting groups and public and private health insurers—can promote the adoption and implementation of conflict of interest policies and promote a culture of accountability that sustains professional norms and public confidence in medicine.*
- *Research on conflicts of interest and conflict of interest policies can provide a stronger evidence base for policy design and implementation.*
- *If medical institutions do not act voluntarily to strengthen their conflict of interest policies and procedures, the pressure for external regulation is likely to increase.*

Physicians and researchers must exercise judgment in complex situations that are fraught with uncertainty. Colleagues, patients, students, and the public need to trust that these judgments are not compromised by physicians' or researchers' financial ties to pharmaceutical, medical device, and biotechnology companies. Ties with industry are common in medicine. Some have produced important benefits, particularly through research collaborations that improve individual and public health. At the same time, widespread relationships with industry have created significant risks that individual and institutional financial interests may unduly influence professionals' judgments about the primary interests or goals of medicine. Such conflicts of interest threaten the integrity of scientific investigations, the objectivity of medical education, and the quality of patient care. They may also jeopardize public trust in medicine.

Surveys show the breadth and diversity of relationships between industry and physicians, researchers, and educators in academic and community settings. For example,

- gifts from drug companies to physicians are ubiquitous;
- visits to physicians' offices by drug and medical device company representatives and the provision of drug samples are widespread;
- many faculty members receive research support from industry, and industry funds the majority of biomedical research in the United States;
- many faculty members and community physicians provide scientific, marketing, and other consulting services to companies; and some serve on company boards of directors or on industry speakers bureaus; and
- commercial sources provide about half of the total funding for accredited continuing medical education programs.

Although certain of these financial relationships may be constructive, recent news reports, legal settlements, research studies, and institutional announcements have documented a variety of disturbing situations that could undermine public confidence in medicine. These situations include

- physicians and researchers failing to disclose substantial payments from drug companies, as required by universities, government agencies, or medical journals;
- settlements with the U.S. Department of Justice by medical device and pharmaceutical companies to avoid prosecution for alleged illegal payments or gifts to physicians;
- companies and academic investigators not publishing negative results from industry-sponsored clinical trials or delaying publication for over a year after the completion of a trial;
- academic researchers putting their names on manuscripts, even though they first became involved after the data were collected and analyzed and after the first drafts were written by individuals paid by industry; and
- professional societies and other groups that develop clinical practice guidelines choosing not to disclose their industry funding and not to reveal the conflicts of interest of the experts who draft the guidelines.

Although the causes of these situations are various and their extent is unclear, they highlight the tension that may exist between financial relationships with industry and the primary missions of medical research, education, and practice. In addition to these examples, research on industry gifts and other financial relationships has generated troublesome findings. For example, systematic reviews of the evidence sponsored by a pharmaceutical company are more likely than other reviews to present conclusions favorable to the company, even when the actual findings of the analysis are not favorable. In addition, articles based on company-sponsored clinical trials are more likely to draw conclusions favorable to the company's product than articles trials not sponsored by industry. Although these findings do not necessarily show that the research is biased and other explanations can be offered (e.g., companies do not fund trials unless they see a reasonable likelihood of success), they do raise legitimate questions about possible undue influence.

To cite another example, the availability of drug samples may be associated with the prescription of new brand name drugs when they are not recommended by evidence-based practice guidelines or when appropriate but less expensive drugs or generic equivalents are available for the same indication. Although one argument for the use of drug samples is that they help low-income patients, research suggests that these individuals are not the

primary recipients of such samples. Also, although small gifts to physicians may seem to be inconsequential, some research suggests that small gifts can contribute to unconscious bias in decision making and advice giving. It also seems unlikely that companies would give such gifts to physicians if they did not believe that they would benefit the company in some way.

In addition to information that raises concern about the scope and consequences of industry financial ties in medicine, surveys and other studies have reported inconsistencies in the adoption and implementation of conflict of interest policies by medical institutions. Relationships and practices that are forbidden by one institution may be allowed and even encouraged by others. Reports also have described shortcomings in the oversight of conflicts of interest in research by federal agencies and medical institutions.

Unfortunately, the empirical evidence relevant to financial relationships and conflicts of interest is limited. On many topics related to conflicts of interest, no systematic studies are available. For other topics, data are suggestive rather than definitive. The studies that have been conducted have primarily been observational rather than interventional, in large part because the issues cannot be investigated using randomized controlled trials of the effects of different kinds of relationships or different approaches to identifying and managing conflicts of interest. A number of academic medical centers, professional associations, and other institutions have taken steps to strengthen their conflict of interest policies, but few data that can be used to assess the consequences—positive or negative—of these changes are available. Some prominent physicians and researchers have argued that concerns about conflicts of interest are far out of proportion to the evidence that they exist or are harmful, and some contend that measures designed to address conflicts of interest have interfered with beneficial collaborations with industry. Critics of conflict of interest policies have also charged that the great majority of individuals who have not acted in an unethical manner may be subjected to onerous regulations and tacit conclusions that they are culpable of misconduct until proven otherwise.

Responding to the situations and concerns outlined above, the Institute of Medicine appointed a committee to investigate and develop a consensus report on conflicts of interest in medical research, education, and practice and in the development of clinical practice guidelines. Consistent with its charge, the committee

- examined conflicts of interest in medical research, education, and practice and in the development of clinical practice guidelines and
- developed analyses and recommendations to inform the design and implementation of policies that identify and manage conflicts of interest in these contexts without damaging constructive collaborations with industry.

Because the evidence on many issues is limited, the committee had to rely on its experience and judgment in evaluating the analyses and arguments presented in the literature and in statements submitted to the committee. During its work, the committee kept in mind the core goals of medical research, education, and practice and practice guideline development, which include serving the best interests of patients and society through the generation of valid scientific knowledge, the independent evaluation of evidence and the application of critical thinking, and the creation and use of evidence-based recommendations for patient care.

Reflecting concerns that were raised during the planning of the project and the central issues in debates and policies on conflicts of interest in medicine, the committee focused on financial relationships involving pharmaceutical, medical device, and biotechnology companies. Although it did not investigate in depth the conflicts of interest associated with different physician payment arrangements or with physician referral of patients to facilities in which they have an ownership interest, the committee recognized the seriousness of those types of conflicts and the difficulties that policy makers have encountered in trying to eliminate or manage them. It also recognized other sources of conflicts of interest, for example, desires for professional advancement and recognition.

After examining a wide array of evidence, analyses, and perspectives on conflicts of interest, the committee reached several overarching conclusions. They are as follows:

- The goals of conflict of interest policies in medicine are primarily to protect the integrity of professional judgment and to preserve public trust rather than to try to remediate bias or mistrust after they occur.
- The disclosure of individual and institutional financial relationships is a critical but limited first step in the process of identifying and responding to conflicts of interest.
- Conflict of interest policies and procedures can be strengthened by engaging physicians, researchers, and medical institutions in developing conflict of interest policies and consensus standards.
- A range of supporting organizations—public and private—can promote the adoption and implementation of conflict of interest policies and help create a culture of accountability that sustains professional norms and public confidence in professional judgments.
- Research on conflicts of interest and conflict of interest policies can provide a stronger evidence base for policy design and implementation.
- If medical institutions do not act voluntarily to strengthen their conflict of interest policies and procedures, the pressure for external regulation is likely to increase.

PRINCIPLES FOR IDENTIFYING AND ASSESSING CONFLICTS OF INTERESTS

Chapter 2 presents the principles and conceptual framework for identifying and assessing conflicts of interest. Conflicts of interest are defined as *circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest*. Primary interests include promoting and protecting the integrity of research, the quality of medical education, and the welfare of patients. Secondary interests include not only financial interests—the focus of this report—but also other interests, such as the pursuit of professional advancement and recognition and the desire to do favors for friends, family, students, or colleagues. Conflict of interest policies typically focus on financial gain because it is relatively more objective, fungible, and quantifiable. Financial gain can therefore be more effectively and fairly regulated than other secondary interests.

The severity of a conflict of interest depends on (1) the likelihood that professional decisions made under the relevant circumstances would be unduly influenced by a secondary interest and (2) the seriousness of the harm or wrong that could result from such an influence. The likelihood of undue influence is affected by the value of the secondary interest, its duration and depth, and the extent of discretion that the individual has in making important decisions.

Conflict of interest policies generally emphasize prevention and management rather than punishment. They do not assume that any particular professional will necessarily let financial gain influence his or her judgment. Likewise, a judgment that someone has a conflict of interest does not imply that the person is unethical. Such judgments assume only that some situations are generally recognized to pose an unacceptable risk that decisions may be unduly influenced by considerations that should be irrelevant. Chapter 2 presents criteria, described in the list that follows, that can be used to evaluate conflict of interest policies.

- Proportionality. Is the policy effective, efficient, and directed at the most important and most common conflicts? Conflict of interest policies and procedures may create harms or burdens as well as benefits. Do the policies and their implementation unnecessarily interfere with the conduct of legitimate research, teaching, and clinical practice?
- Transparency. Is the policy comprehensible and accessible to the individuals and institutions that it may affect? Such transparency is essential to determine if conflict of interest policies are reasonable and are being implemented fairly. Transparency can also help institutions learn

from each other about more and less successful ways of handling particular situations.

- Accountability. Does the conflict of interest policy indicate who is responsible for monitoring, enforcing, and revising it? Leaders of accountable institutions explain institutional policies and monitor and accept responsibility for the consequences, both beneficial and harmful.
- Fairness. Does the policy apply equally to all relevant groups within an institution and in different institutions? In an academic medical center, the relevant groups would include faculty, medical staff, students, residents, fellows, members of institutional committees (e.g., institutional review boards, formulary committees, panels developing practice guidelines, and device purchasing committees), and senior institutional officials.

POLICIES ON CONFLICTS OF INTEREST: OVERVIEW AND EVIDENCE

Concerns about conflicts of interest in medicine have a long history, and responses to these conflicts have evolved as relationships with industry have grown more frequent and more complex and as different responses to such relationships have been tried and found in need of modification. Government regulations and voluntary codes of conduct often follow the discovery of instances of questionable or inappropriate relationships and conduct. Government scrutiny of financial relationships and conflicts of interest may also stimulate private, voluntary efforts by academic and other institutions to deal with problems and avoid regulation.

The conflict of interest policies of academic medical centers, professional societies, medical journals, and other institutions vary on many dimensions. It is not clear that all medical institutions have conflict of interest policies. Those that do have such policies vary in what they ask physicians and researchers to disclose about their financial relationships with industry. Such variations may create additional administrative burdens for physicians and researchers who act in multiple roles and make multiple disclosures of their financial relationships with industry to different institutions for various purposes related to medical research, education, and clinical care and clinical practice guideline development.

Institutions also vary in what relationships they prohibit because they view them as creating unacceptable risks of undue influence on primary interests, and they also differ in how they manage conflicts of interest that are not prohibited. The National Institutes of Health (NIH) has identified variations and deficiencies in how research institutions implement the 1995 U.S. Public Health Service (PHS) regulations on conflict of interest, and it has advised institutions on steps that they can take to strengthen their poli-

cies. Similarly, the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU) have developed recommendations and guidance on conflict of interest policies governing research with human participants, but surveys indicate that research institutions have not fully implemented these recommendations.

Although the disclosure of financial interests or conflicts of interest is a necessary part of conflict of interest policies, it is not sufficient in itself to safeguard the integrity of professional judgment or to maintain public trust. For example, when a relationship or conflict of interest is disclosed to individual patients, students, or research participants, they often lack the knowledge and perspective to assess the relationship and may have no satisfactory options if they have concerns about it. Conflicts that are disclosed but not eliminated or managed can continue to pose risks to judgment and undermine public trust.

The recommendations in Chapter 3 establish the fundamental elements of an effective policy response to conflicts of interest in medical research, education, and practice. Recommendation 3.1 calls on all institutions engaged in these activities to establish conflict of interest policies and create conflict of interest committees to evaluate and manage conflicts. Recommendation 3.2 focuses on the essential policy step of requiring physicians, researchers, and senior officials to disclose to their institutions their financial relationships with industry. Unless institutions are informed of these relationships, they cannot identify conflicts of interest or determine whether additional steps—such as the elimination or management of the conflict—are needed to reduce the risk of bias or a loss of public trust. Recommendations 3.1 and 3.2 are similar to the recommendations made in other reports on conflict of interest; but they extend to all institutions that carry out medical research, medical education, clinical care, and practice guideline development.

The disclosure of financial relationships can be effective only if it provides sufficient information for others to use in assessing a relationship and judging the severity of a conflict. At the same time, disclosure can be burdensome, particularly for physicians who must make multiple disclosures for different activities. Recommendation 3.3 calls for the standardization of disclosures with the goals of providing institutions with the specific information that they need to assess relationships while reducing the reporting burdens on physicians and researchers. Such standardization is best pursued through a consensus development process that involves a broad array of concerned parties (e.g., academic medical centers, professional societies, public interest groups, and NIH and other public agencies). On the basis of the agreements resulting from this process, the next step would be for software developers to produce computer programs that allow an individual to fill out a standard questionnaire and then format the information for differ-

ent institutions and purposes. This should reduce the burden on individuals and increase the consistency of the information disclosed.

Even with further policy development and standardization, institutions will still face questions about the completeness and accuracy of the information disclosed to them. Recommendation 3.4 calls for the U.S. Congress to create a national program that requires pharmaceutical, medical device, and biotechnology companies and their foundations to publicly report payments to physicians, researchers, health care institutions, professional societies, patient advocacy and disease-specific groups, providers of continuing medical education, and foundations created by any of these entities. Although many details will need to be worked out, the information should be readily available on a secure, searchable public website that allows the identification and aggregation of all payments that an individual or institution receives from all companies. Such a program of company reporting will enhance accountability by allowing universities, journals, and others to verify the disclosures that have been made to them. It may also discourage the formation of questionable relationships that individuals or companies would prefer not be widely known.

CONFLICTS OF INTEREST IN BIOMEDICAL RESEARCH

Research partnerships among industry, academia, and government are essential to the discovery and development of new medications and medical devices that improve the prevention, diagnosis, and treatment of health problems. Chapter 4 reports on evidence that relationships between academic researchers and industry are widespread and are associated with benefits, for example, greater research productivity. At the same time, evidence suggests that these relationships have risks, including decreased openness in the sharing of data and findings and the withholding of negative results. These kinds of risks justify additional requirements and incentives, as recommended in this report, for institutions to adopt and implement policies to identify and eliminate or manage conflicts of interest.

Consistent with the recommendations of AAMC and AAU, Recommendation 4.1 calls for a general rule that researchers may not conduct research involving human participants if they have a financial interest in the outcome of the research, for example, if they hold a patent on an intervention being tested in a clinical trial. Exceptions should be allowed only if an individual's participation is judged to be essential for the safe and appropriate conduct of the research. An example might be the inventor of a complex new implanted medical device who has unique expertise and technical skills that are essential for the safe implantation of the device during pilot or early-phase studies. If a conflict of interest committee approves the involvement of such a researcher, it should take advantage of the full range of options

for managing the conflict, including placing restrictions on the researcher's role in the study.

Although Recommendation 4.1 does not cover nonclinical research, financial relationships in this arena may also create risks of undue influence that institutions should assess and manage as appropriate to protect the integrity of the science. Additional studies on financial relationships in nonclinical research, their risks and consequences, and the ways in which institutions identify and respond to these relationships would help establish an evidence base that could be used to guide judgments about policies in this area.

CONFLICTS OF INTEREST IN UNDERGRADUATE, GRADUATE, AND CONTINUING MEDICAL EDUCATION

Chapter 5 presents strong evidence that relationships with industry are pervasive in undergraduate, graduate, and continuing medical education. Most medical students and residents are exposed to lunches, gifts, and other interactions with pharmaceutical company representatives on a frequent basis. Faculty members have extensive relationships with these individuals as well.

In analyzing relationships with industry in the context of medical education, the focus should be on the learning environment, the development of core competencies, and consistency between the formal curriculum and the informal or hidden curriculum. The key goals of medical education include helping learners at all levels develop the ability to think critically and appraise the evidence for clinical decision making. In controlled situations, some interactions with representatives of medical device companies may foster the goals of appropriate training, patient safety, and device evaluation. Otherwise, the committee found no bases for concluding that educational goals are promoted by other relationships involving gifts, most visits by pharmaceutical company representatives, service as a marketing consultant, participation in an industry speakers bureau, or acceptance of credit for a ghostwritten article. Indeed, the evidence suggests that some of these relationships are associated with undue influence and thus undermine the goals of medical education. Overall, the risks of these relationships outweigh any possible benefits.

Recommendation 5.1 therefore calls on academic medical centers to prohibit faculty, students, residents, and fellows from accepting gifts (including meals), making presentations that are controlled by industry, and claiming authorship for ghostwritten publications. This restriction is not intended to exclude the acceptance of scientific materials from industry scientists under appropriate material transfer agreements or the payment of reasonable honoraria to speakers who present their own material. Recom-

mendation 5.1 also calls for restrictions on the acceptance of drug samples and visits by drug and medical device sales representatives.

For academic medical centers and community physicians, drug samples present difficult issues. Caring for indigent patients who cannot afford needed drugs is frustrating for physicians who are trying to act in their patients' best interests. Many physicians believe that drug samples allow some patients access to drugs that they could otherwise not obtain. Nonetheless, research suggests that most samples are not in fact given to patients who lack financial access to needed medications and that physicians who have access to samples may change their prescribing habits, for example, by not prescribing the drugs that they would prefer their patients to use or by prescribing drugs in ways that are not consistent with evidence-based recommendations. The committee concluded that the lack of access to affordable medications is serious and disturbing but that drug samples are not a satisfactory answer to this societal problem. Academic medical centers should, at a minimum, oversee and restrict their use.

Because faculty, students, residents, and fellows may not understand the risks posed by conflicts of interest and the rationale for conflict of interest policies, Recommendation 5.2 calls on academic medical centers and teaching hospitals, as part of their educational mission, to provide education on the avoidance of conflicts of interest and the management of relationships with pharmaceutical and medical device industry representatives. Organizations that accredit medical schools and residency programs should develop standards to reinforce this recommendation.

Questions about conflicts of interest have been particularly visible in continuing medical education. Most physicians are required to participate in accredited continuing medical education as a condition for relicensure, specialty certification, or granting of hospital medical staff privileges. Many commercial and academic providers of accredited continuing medical education receive half or more of their funding from industry, which raises concerns about industry influence over the selection of educational topics, the content of presentations, and the overall scope of educational offerings (e.g., whether they provide sufficient coverage of such issues as prevention and physician-patient communication).

Although individual continuing medical education providers and the accrediting organization for continuing medical education have taken steps to limit industry influence, the dependence of many programs on industry funding raises doubts about how successful these steps can be. Recommendation 5.3 calls for a broad-based consensus development process to propose a new system of funding accredited continuing medical education that is free of industry influence, enhances public trust in the integrity of the system, and provides high-quality education. Some members of the committee supported a total end to industry funding, but others were concerned

about the potential for unintended harm from such a ban. The committee recognized that changes in the current system likely would substantially reduce industry funding for accredited continuing medical education. Even if education providers trim their expenses, the costs of accredited continuing medical education would likely increase for many physicians, which could be an economic burden for some physicians, for example, those in rural areas.

CONFLICTS OF INTEREST AND MEDICAL PRACTICE

As is the case in medical research and education, evidence shows that relationships with industry are widespread among physicians in practice. Physician acceptance of gifts and meals from industry representatives is commonplace, as are visits with company sales representatives. Company marketing strategies are sophisticated. As part of these strategies, physicians may be used as marketing agents, physicians' prescribing habits may be tracked through commercial databases, and companies may sponsor so-called seeding trials that are primarily designed to market products to participating physicians. Published studies of these strategies are limited but suggest the risk of undue industry influence on physician prescribing behavior with little or no benefit to patient care. Many physicians may view drug representatives as useful, but reliance on individuals whose charge is to increase sales is not a satisfactory solution to practitioners' need for valid, reliable, and up-to-date medical information.

Several recent policy changes may affect the relationships between industry and physicians in practice. Several drug and device companies are voluntarily making public information on their payments to physicians by physician name and the purpose and the amount of the payment; other companies have been required to do so as part of legal agreements with federal prosecutors. The Pharmaceutical Research and Manufacturers of America also recently revised its code on interactions with health care professionals to prohibit the use of certain marketing tools and gifts (including well-paid speaking engagements) as inducements or rewards for prescribing or recommending a course of treatment. Compliance is voluntary, but the organization says that it will ask member companies to declare whether they have adopted its provisions and will then post the information on its website. The Advanced Medical Technology Association has included similar provisions in its revised code for medical device companies. In addition, some professional societies have recently revised their conflict of interest policies to restrict or manage certain relationships with industry and to make their policies public.

Taking into account the weight of the evidence and the recommendations and actions of other groups or institutions, the committee rec-

ommended the elimination of some problematic relationships between practicing physicians and industry. In broad terms, Recommendation 6.1 calls on physicians in clinical practice not to accept gifts, including meals, from companies; to enter only into bona fide consultation arrangements with written contracts; to avoid presenting or publishing material whose content is controlled by industry or is ghostwritten; to set restrictions on meetings with company sales representatives; and to use drug samples only for patients who lack financial access to medications. This recommendation is generally parallel to Recommendation 5.1 (for faculty, students, residents, and fellows). Independent assessment of the evidence and the practice of evidence-based medicine are core competencies for physicians in clinical practice as well as academic practice; relationships with industry should not undermine those competencies.

Because recommendations directed to physicians are more likely to be adopted if other incentives are aligned with those recommendations, Recommendation 6.1 also calls on professional societies and institutions that provide health care (and that employ physicians or grant them staff privileges) to take actions to support physician acceptance of changes in their relationships with companies. Recommendation 6.2 calls for further revisions to industry practices to be consistent with those outlined in Recommendation 6.1. It is a separate recommendation to emphasize that relationships between physicians and industry are bilateral and that the expectations for givers and receivers in financial relationships should be parallel.

CONFLICTS OF INTEREST AND DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES

Financial relationships with companies affected by clinical practice guidelines are common both for groups convening expert panels to develop guidelines and for the individuals serving on those panels. Groups often do not make public their conflict of interest policies, their sources of funding for guideline development, or the financial relationships of the panel members. This lack of transparency makes it difficult for the readers and users of guidelines to assess the potential for undue influence and bias.

The committee found examples of alleged undue industry influence on the development of clinical practice guidelines but little systematic research. The risks that result from the acceptance of industry funding and the inclusion of individuals with industry ties on guideline development panels include possible bias in the recommendations made in guidelines and possible harm to patients because guidelines may influence physician practice behavior, quality improvement measures, reimbursement incentives, and insurance coverage decisions.

Recommendation 7.1 calls on groups that develop guidelines not to

accept direct funding for guideline development from industry and generally to exclude individuals with conflicts of interest from guideline development panels. Because it may be impossible in some situations to obtain the needed expertise from individuals who have no conflicts, the recommendation also includes measures to limit the likelihood of undue influence if panels include members with conflicts of interest. These measures include requiring that chairs of guideline development panels have no conflicts of interest, limiting members with conflicts of interest to a small minority of the panel membership, and precluding such members from voting on topics in which they have a financial interest. The committee also calls for groups that develop guidelines to involve the public in attempts to identify experts without conflicts of interest, to make such efforts public, and to disclose publicly any conflicts of interest of those selected for membership on panels.

Recommendation 7.2 calls for organizations that have an interest in the use of evidence-based clinical practice guidelines to establish incentives to encourage the developers of guidelines to adopt the committee's recommendations. For example, the National Guideline Clearinghouse could require that the guidelines that it posts include information about the sources of funding for a guideline, the sponsor's conflict of interest policy, and the financial interests of the expert panel members. Similarly, public and private health plans and accreditation and certification bodies could avoid the use of clinical practice guidelines that lack information that allows users to identify conflicts of interest and assess the risks that they pose.

INSTITUTIONAL CONFLICTS OF INTEREST

Institutional conflicts of interest arise when an institution's own financial interests or the interests of its senior officials pose risks to the integrity of the institution's primary interests and missions. Institutional conflicts typically appear when research conducted within an institution could affect the value of equity that the institution holds in a company or the value of a patent that the institution licenses to a company. Institutional conflicts of interest have not received as much attention as individual conflicts of interest, but their consequences can also be damaging. If they are not properly identified and managed, institutional conflicts can undermine the work and reputation of an entire institution, including employees or members who are themselves strictly avoiding individual conflicts of interest.

Recommendation 8.1 calls for the boards of trustees of institutions to establish a conflict of interest committee to make judgments about institutional relationships with industry, including the relationships of senior officials. In their fiduciary role, members of the board oversee the long-term interests of the institution. They stand at a greater distance from the

day-to-day pressures of decision making, which should help them assess more judiciously the potential risks posed by a particular financial interest to the institution's core missions. This committee of the board of trustees could be supported by staff committees on institutional conflict of interest. Recommendation 8.2 calls for NIH to develop regulations requiring institutions covered by the 1995 PHS regulations to adopt institutional conflict of interest policies.

THE ROLE OF SUPPORTING ORGANIZATIONS

In carrying out medical research and education, providing patient care, and developing practice guidelines, physicians, researchers, and the institutions in which they work are part of complex intersecting systems. These systems can amplify or mitigate the pressures that individuals and institutions may experience to expose their primary professional obligations or social missions to undue influence from secondary interests, such as financial gain. Within these systems, a variety of organizations—public and private—can influence the policies and practices of institutions and support the norms of professional integrity. For example, accreditation and certification organizations set standards for medical schools, residency and fellowship programs, and individual physicians. State agencies license and relicense individual physicians, and specialty boards certify and recertify them. Journals publish medical research. The National Guideline Clearinghouse posts clinical practice guidelines. Public and private health insurers use a variety of financial and other incentives to influence the practices of institutions and individual clinicians. The U.S. Department of Justice and the Office of the Inspector General of the U.S. Department of Health and Human Services enforce laws limiting or prohibiting certain conflicts of interest, and NIH is responsible for overseeing compliance with PHS policies covering its grantees.

In addition to discussing incentives for policy adoption and implementation, the final chapter of the report discusses the roles of collaboration and consensus building in building conflict of interest policies that win acceptance and avoid needless burdens. Although the emphasis should be on preventing problems, policies should also be backed by enforcement and appropriate sanctions as well as assessment of their effectiveness.

Recommendation 9.1 proposes that groups such as accrediting organizations, public and private health insurers, and associations of medical journal editors develop incentives to make institutions more accountable for preventing, identifying, and managing conflicts of interest. The accompanying discussion gives examples of such incentives. The final recommendation, Recommendation 9.2, calls for more research to assess the positive and negative consequences of conflict of interest policies and provide a

stronger evidence base for improving conflict of interest policies and their application.

Society has traditionally granted the medical profession considerable autonomy to regulate itself. Society may be willing to continue do so in the case of conflicts of interest; but concern is growing in the U.S. Congress, state legislatures, federal agencies, and elsewhere that stronger measures are needed. Physicians and researchers can play a vital role in designing responsible and reasonable conflict of interest policies and procedures that reduce the risks of bias and the loss of trust while avoiding undue burdens or even harms. They and the institutions that carry out medical research, education, clinical care, and practice guideline development must recognize public concerns about conflicts of interest and take effective measures soon to maintain public trust.

OVERVIEW AND LIST OF RECOMMENDATIONS

TABLE S-1 Report Recommendations in Overview

Recommendation Number and Topic	Primary Actors
General policy	
3.1 Adopt and implement conflict of interest policies	Institutions that carry out medical research and education, clinical care, and clinical practice guideline development
3.2 Strengthen disclosure policies	Institutions that carry out medical research and education, clinical care, and clinical practice guideline development
3.3 Standardize disclosure content and formats	Institutions that carry out medical research and education, clinical care, and clinical practice guideline development and other interested organizations (e.g., accrediting bodies, health insurers, consumer groups, and government agencies)
3.4 Create a national program for the reporting of company payments	U.S. Congress; pharmaceutical, medical device, and biotechnology companies
Medical research	
4.1 Restrict participation of researchers with conflicts of interest in research with human participants	Academic medical centers and other research institutions; medical researchers

TABLE S-1 Continued

Recommendation Number and Topic	Primary Actors
Medical education	
5.1 Reform relationships with industry in medical education	Academic medical centers and teaching hospitals; faculty, students, residents, and fellows
5.2 Provide education on conflict of interest	Academic medical centers and teaching hospitals; professional societies
5.3 Reform financing system for continuing medical education	Organizations that created the accrediting program for continuing medical education and other organizations interested in high-quality, objective education
Medical practice	
6.1 Reform financial relationships with industry for community physicians	Community physicians; professional societies; hospitals and other health care providers
6.2 Reform industry interactions with physicians	Pharmaceutical, medical device, and biotechnology companies
Clinical practice guidelines	
7.1 Restrict industry funding and conflicts in clinical practice guideline development	Institutions that develop clinical practice guidelines
7.2 Create incentives for reducing conflicts in clinical practice guideline development	Accrediting and certification bodies, formulary committees, health insurers, public agencies, and other organizations with an interest in objective, evidence-based clinical practice guidelines
Institutional conflict of interest policies	
8.1 Create board-level responsibility for institutional conflicts of interest	Institutions that carry out medical research and education, clinical care, and clinical practice guideline development
8.2 Revise PHS regulations to require policies on institutional conflicts of interest	NIH
Supporting organizations	
9.1 Provide additional incentives for institutions to adopt and implement policies	Oversight bodies and other groups that have a strong interest in or reliance on medical research, education, clinical care, and practice guideline development
9.2 Develop research agenda on conflict of interest	NIH, Agency for Healthcare Research and Quality, and other agencies of the U.S. Department of Health and Human Services

RECOMMENDATION 3.1 Institutions that carry out medical research, medical education, clinical care, or practice guideline development should adopt, implement, and make public conflict of interest policies for individuals that are consistent with the other recommendations in this report. To manage identified conflicts of interest and monitor the implementation of management recommendations, institutions should create a conflict of interest committee. That committee should use a full range of management tools, as appropriate, including elimination of the conflicting financial interest, prohibition or restriction of involvement of the individual with a conflict of interest in the activity related to the conflict, and providing additional disclosures of the conflict of interest.

RECOMMENDATION 3.2 As part of their conflict of interest policies, institutions should require individuals covered by their policies, including senior institutional officials, to disclose financial relationships with pharmaceutical, medical device, and biotechnology companies to the institution on an annual basis and when an individual's situation changes significantly. The policies should

- request disclosures that are sufficiently specific and comprehensive (with no minimum dollar threshold) to allow others to assess the severity of the conflicts;
- avoid unnecessary administrative burdens on individuals making disclosures; and
- require further disclosure, as appropriate, for example, to the conflict of interest committee, the institutional review board, and the contracts and grants office.

RECOMMENDATION 3.3 National organizations that represent academic medical centers, other health care providers, and physicians and researchers should convene a broad-based consensus development process to establish a standard content, a standard format, and standard procedures for the disclosure of financial relationships with industry.

RECOMMENDATION 3.4 The U.S. Congress should create a national program that requires pharmaceutical, medical device, and biotechnology companies and their foundations to publicly report payments to physicians and other prescribers, biomedical researchers, health care institutions, professional societies, patient advocacy and disease-specific groups, providers of continuing medical education, and foundations created by any of these entities. Until the Congress acts, companies should voluntarily adopt such reporting.

RECOMMENDATION 4.1 Academic medical centers and other research institutions should establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research. Exceptions to the policy should be made public and should be permitted only if the conflict of interest committee (a) determines that an individual's participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research.

RECOMMENDATION 5.1 For all faculty, students, residents, and fellows and for all associated training sites, academic medical centers and teaching hospitals should adopt and implement policies that prohibit

- the acceptance of items of material value from pharmaceutical, medical device, and biotechnology companies, except in specified situations;
- educational presentations or scientific publications that are controlled by industry or that contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged;
- consulting arrangements that are not based on written contracts for expert services to be paid for at fair market value;
- access by drug and medical device sales representatives, except by faculty invitation, in accordance with institutional policies, in certain specified situations for training, patient safety, or the evaluation of medical devices; and
- the use of drug samples, except in specified situations for patients who lack financial access to medications.

Until their institutions adopt these recommendations, faculty and trainees at academic medical centers and teaching hospitals should voluntarily adopt them as standards for their own conduct.

RECOMMENDATION 5.2 Academic medical centers and teaching hospitals should educate faculty, medical students, and residents on how to avoid or manage conflicts of interest and relationships with pharmaceutical and medical device industry representatives. Accrediting organizations should develop standards that require formal education on these topics.

RECOMMENDATION 5.3 A new system of funding accredited continuing medical education should be developed that is free of industry influence, enhances public trust in the integrity of the system, and provides high-quality education. A consensus development process that includes representatives of the member organizations that created the accrediting body for con-

tinuing medical education, members of the public, and representatives of organizations such as certification boards that rely on continuing medical education should be convened to propose within 24 months of the publication of this report a funding system that will meet these goals.

RECOMMENDATION 6.1 Physicians, wherever their site of clinical practice, should

- not accept of items of material value from pharmaceutical, medical device, and biotechnology companies except when a transaction involves payment at fair market value for a legitimate service;
- not make educational presentations or publish scientific articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged;
- not enter into consulting arrangements unless they are based on written contracts for expert services to be paid for at fair market value;
- not meet with pharmaceutical and medical device sales representatives except by documented appointment and at the physician's express invitation; and
- not accept drug samples except in certain situations for patients who lack financial access to medications.

Professional societies should amend their policies and codes of professional conduct to support these recommendations. Health care providers should establish policies for their employees and medical staff that are consistent with these recommendations.

RECOMMENDATION 6.2 Pharmaceutical, medical device, and biotechnology companies and their company foundations should have policies and practices against providing physicians with gifts, meals, drug samples (except for use by patients who lack financial access to medications), or other similar items of material value and against asking physicians to be authors of ghostwritten materials. Consulting arrangements should be for necessary services, documented in written contracts, and paid for at fair market value. Companies should not involve physicians and patients in marketing projects that are presented as clinical research.

RECOMMENDATION 7.1 Groups that develop clinical practice guidelines should generally exclude as panel members individuals with conflicts of interest and should not accept direct funding for clinical practice guideline development from medical product companies or company foundations. Groups should publicly disclose with each guideline their conflict of

interest policies and procedures and the sources and amounts of indirect or direct funding received for development of the guideline. In the exceptional situation in which avoidance of panel members with conflicts of interest is impossible because of the critical need for their expertise, then groups should

- publicly document that they made a good-faith effort to find experts without conflicts of interest by issuing a public call for members and other recruitment measures;
- appoint a chair without a conflict of interest;
- limit members with conflicting interests to a distinct minority of the panel;
- exclude individuals who have a fiduciary or promotional relationship with a company that makes a product that may be affected by the guidelines;
- exclude panel members with conflicts from deliberating, drafting, or voting on specific recommendations; and
- publicly disclose the relevant conflicts of interest of panel members.

RECOMMENDATION 7.2 Accrediting and certification bodies, health insurers, public agencies, and other similar organizations should encourage institutions that develop clinical practice guidelines to adopt conflict of interest policies consistent with the recommendations in this report. Three desirable steps are for

- journals to require that all clinical practice guidelines accepted for publication describe (or provide an Internet link to) the developer's conflict of interest policies, the sources and amounts of funding for the guideline, and the relevant financial interests of guideline panel members, if any;
- the National Guideline Clearinghouse to require that all clinical practice guidelines accepted for posting describe (or provide an Internet link to) the developer's conflict of interest policies, the sources and amounts of funding for development of the guideline, and the relevant financial interests of guideline panel members, if any; and
- accrediting and certification organizations, public and private health plans, and similar groups to avoid using clinical practice guidelines for performance measures, coverage decisions, and similar purposes if the guideline developers do not follow the practices recommended in this report.

RECOMMENDATION 8.1 The boards of trustees or the equivalent governing bodies of institutions engaged in medical research, medical education, patient care, or practice guideline development should establish their

own standing committees on institutional conflicts of interest. These standing committees should

- have no members who themselves have conflicts of interest relevant to the activities of the institution;
- include at least one member who is not a member of the board or an employee or officer of the institution and who has some relevant expertise;
- create, as needed, administrative arrangements for the day-to-day oversight and management of institutional conflicts of interest, including those involving senior officials; and
- submit an annual report to the full board, which should be made public but in which the necessary modifications have been made to protect confidential information.

RECOMMENDATION 8.2 The National Institutes of Health should develop rules governing institutional conflicts of interest for research institutions covered by current U.S. Public Health Service regulations. The rules should require the reporting of identified institutional conflicts of interest and the steps that have been taken to eliminate or manage such conflicts.

RECOMMENDATION 9.1 Accreditation and certification bodies, private health insurers, government agencies, and similar organizations should develop incentives to promote the adoption and effective implementation of conflict of interest policies by institutions engaged in medical research, medical education, clinical care, or practice guideline development. In developing the incentives, these organizations should involve the individuals and the institutions that would be affected.

RECOMMENDATION 9.2 To strengthen the evidence base for the design and application of conflict of interest policies, the U.S. Department of Health and Human Services should coordinate the development and funding of a research agenda to study the impact of conflicts of interest on the quality of medical research, education, and practice and on practice guideline development and to examine the positive and negative effects of conflict of interest policies on these outcomes.

1

Introduction

Patients and the public benefit from constructive collaboration between academic medicine and pharmaceutical, medical device, and biotechnology companies. At the same time, medical leaders, public officials, public interest groups, and others have raised concerns about the risks associated with the extensive financial ties that link industry with the individuals and institutions that carry out medical research, medical education, patient care, and practice guideline development. The risks are that individual and institutional financial interests may unduly influence professional judgments involving these primary institutional missions. Such conflicts of interest threaten the integrity of scientific investigations, the objectivity of medical education, the quality of patient care, and the public's trust in medicine.

The benefits of collaboration with industry are most evident in biomedical research. New medications and medical devices have significantly improved outcomes for people with a range of serious and common diseases, including—among many others—coronary artery disease, congestive heart failure, hypercholesterolemia, several types of cancers, and peptic ulcer disease. Such successful products result from a long, complex, and often unpredictable process of translating basic science discoveries into new preventive, diagnostic, or therapeutic products and services. The basic discoveries often come from the laboratories of university and government scientists; but their development into actual products available to clinicians and patients usually depends on the technical, production, and financial resources of pharmaceutical, medical device, or biotechnology companies. It is estimated that it takes an average of 15 years and more than $800 million to discover and develop a new drug, and only about 10 percent of the drugs that enter clinical testing are actually approved for marketing (DiMasi et al., 2003, 2004; FDA, 2004a). Chapter 4 and Appendix E

further examine the nature and value of university-industry collaboration in medical research.

With the benefits of research collaboration and the expansion of financial relationships in other areas have also come conflicts of interest and evidence of bias. For example, in clinical research, unfavorable results in some major industry-sponsored trials have been withheld from publication, thus distorting the totality of the findings included in the scientific literature. These trials involved drugs commonly prescribed for arthritis, depression, and elevated cholesterol levels, among other medications (Wright et al., 2001; Gibson, 2004; Whittington et al., 2004; Kastelein et al., 2008). Not publishing negative results undermines evidence-based medicine and puts millions of patients at risk for using ineffective or unsafe drugs. One striking case involves the withholding of negative findings from pediatric clinical trials of the effects of selective serotonin reuptake inhibitors on depression (Healy, 2006; Turner et al., 2008). Findings were withheld so frequently that although one meta-analysis of the published literature (ACN, 2004) concluded that these drugs were safe and effective, another meta-analysis (Whittington et al., 2004) that took into account unpublished as well as published data concluded the opposite: that the risks outweigh the benefits for all but one drug in this class of antidepressants. A recent analysis found that more than half of the trials used to support Food and Drug Administration approval for the marketing of a drug or medical device had not been published within 5 years after approval (Lee et al., 2008). In addition, litigation has revealed documents that link bias in publications to financial relationships with pharmaceutical manufacturers (Steinman et al., 2006; Psaty and Kronmal, 2008; Ross et al., 2008). As discussed in Chapter 4, the statistical associations involving industry sponsorship do not prove causality, but they do raise serious concerns about undue industry influence and have prompted a range of responses, including the creation of publication protections in university-industry research contracts and the issuance of regulations and other requirements that the results of clinical trials be reported in clinical trial registries.

In medical education, it is particularly troublesome when a faculty member is a promotional speaker for a pharmaceutical, medical device, or biotechnology company or agrees to be listed as an author for a ghostwritten publication. This is because faculty members are expected to present unbiased information and objective assessments of the scientific literature and to help medical students, residents, and fellows develop life-long habits of exercising independent judgment and critically evaluating scientific evidence. They are also expected to serve as role models of professionalism. These expectations may be undermined by some financial relationships between faculty and industry and by failures to disclose such relationships.

In clinical care, patients need to trust that their physicians' recommen-

dations are not distorted by commercial interests. Such trust may contribute to the healing process and to patients' sense of well-being. Some financial relationships between physicians and industry raise concerns about the risk of bias in clinical decisions. For example, companies have paid some physicians large but generally undisclosed amounts to give talks to other physicians, whose prescribing practices were then tracked by company sales representatives (Elliott, 2006; Carlat, 2007). Drug samples and other gifts to physicians by company sales representatives are major marketing tools that evidence suggests influence prescribing choices (see Chapter 5). Furthermore, during the last decade, several federal prosecutions alleging that companies made illegal payments to physicians to induce them to use the companies' drugs or medical devices have led to settlements in which the companies agreed to modify various marketing practices and, in some cases, to post publicly their payments to physicians (see Chapter 6). The prevalence of illegal payments is not known.

Another area of concern is clinical practice guidelines. Clinical practice guidelines influence patient care, quality and performance standards, and reimbursement for health care professionals and institutions. If a risk exists that guidelines are biased or may be viewed as biased in favor of the products of the companies that sponsored the guideline development process or companies that have financial relationships with experts involved in the process, then patients may be harmed and users' trust in the guidelines may be undermined. Evaluating the potential for such bias is often difficult, however, because many entities that develop practice guidelines do not have clear conflict of interest policies for this activity, do not disclose their funding sources, and do not reveal the relevant financial relationships or conflicts of interest for the experts responsible for developing a set of guidelines. A review of clinical practice guidelines that do include information on financial relationships of the participants suggests that conflicts of interest are common (for examples, see Chapter 7 and guidelines posted on the website for the National Guideline Clearinghouse).

Conflicting interests are, to some degree, both ubiquitous and difficult to avoid. For example, regardless of how they are paid for their services (e.g., on a fee-for-service or a capitated basis), physicians will face some incentives that may at times conflict with their professional responsibility to provide care that best serves their patients' interests. Medical school faculty may face conflicts in the time and energy that they devote to each element of their academic responsibilities—research, teaching, and clinical care.

Many conflicts are unavoidable features of multifaceted professional roles and obligations. Others are optional, for example, the creation of a consulting or a speaking agreement with a pharmaceutical, medical device, or biotechnology company. These kinds of financial relationships with industry are the focus of this report.

As explained further in Chapter 2, this report specifically defines a conflict of interest as existing when an individual or institution has a secondary interest (e.g., an ownership interest in a start-up biotechnology company) that creates a risk of undue influence on decisions or actions affecting a primary interest (e.g., the conduct of objective and trustworthy medical research). This definition frames a conflict of interest in terms of the risk of such undue influence and not the actual occurrence of bias.

Some argue that concerns about conflicts of interest are overstated and that policy responses have been excessive, inconsistent, and unduly burdensome on physicians and researchers (see, e.g., Stossel [2005, 2007], Duvall [2006], Borgert [2007], and Bailey [2008]). According to that viewpoint, problems related to conflicts of interests are rare. Thus, the vast majority of scientists, educators, and clinicians should not be subject to onerous conflict of interest rules and regulations because of a few miscreants. The argument continues that burdensome rules and regulations stifle valuable collaborations between industry and academia. Moreover, allegations of conflict of interest inappropriately call into question the motives and integrity of individual scientists and clinicians, because a financial relationship related to one's research, teaching, or clinical practice does not prove the actual presence of bias in decisions or judgments. Consequently, it would be better to focus on detecting and minimizing bias rather than on disclosing, limiting, or managing financial relationships with industry. Furthermore, some of the intended beneficiaries of conflict of interest policies—for example, research participants—do not seem to be concerned about the financial interests of the investigators (see, e.g., Hampson et al. [2006] and Weinfurt et al. [2006a] and the further discussions in Chapters 3 and 4). Another criticism is that the focus on conflicts of interest related to financial ties with industry distracts attention from other threats to objectivity and public trust, such as career ambitions, a desire for recognition, intellectual bias, personal ties, and physician payment methods.

As discussed in Chapter 2, many objections to conflict of interest policies are based on misunderstandings of their purpose and nature. If they are correctly explained, the policies should not be seen as impugning anyone's motives. They are, in fact, a way of avoiding intrusive investigations into people's motives. They also protect against bias or distrust when other methods (e.g., assessments of actual bias after the fact) are not feasible or sufficient. Although other secondary interests may inappropriately influence professional decisions and additional safeguards are necessary to protect against bias from such interests, financial interests are more readily identified and regulated.

Opposition to conflict of interest policies often focuses on what might be lost with further restrictions on ties to industry. For example, eliminating industry support for accredited continuing medical education might

result in increases in the fees that physicians must pay for such education, a reduction in the number of accredited courses, and a drop in income for institutions that provide continuing medical education. To cite another example, if universities insist on contract terms that restrict a company's ability to withhold or censor research findings, then companies might move more research contracts elsewhere (e.g., to contract research organizations or overseas research centers that do not have such restrictions). Similarly, some faculty members may leave a university if that university restricts faculty members' financial ties with industry. Such losses (costs) tend to be immediate, easily identifiable, and tangible.

In contrast, the costs of conflicts of interest and the benefits of mitigating or eliminating them tend to be less tangible, less immediate, and more diffuse. Eliminating direct industry funding of continuing medical education, for example, could increase evidence-based physician prescribing practices, which over time could reduce wasteful health care spending and improve the quality of patient care, but demonstrating such causal relationships could be difficult or impossible. Another benefit of dealing with conflicts of interest that is even harder to define and document but that is significant could be the maintenance of public trust in medical professionals and institutions. Indeed, the maintenance of trust is a major objective of conflict of interest policies across a broad range of professions, in addition to medicine (see Appendix C).

Research suggests that people are generally not good at making trade-offs between costs and benefits that are immediate and tangible and those that are less immediate and less tangible (for a review, see Rick and Loewenstein [2008]). People tend to put a disproportionate emphasis on costs and benefits that are immediate and tangible. For example, the impact of a single, free drug company-sponsored lunch on a physician's prescribing practices or on public trust may be small to insignificant, but the cumulative consequences of many lunches to many physicians may be great. The human tendency to overweight the immediate and tangible compared with the delayed and intangible thus complicates efforts to understand and respond to conflicts of interest.

OVERVIEW AND THEMES OF REPORT

This Institute of Medicine (IOM) report examines the extent of financial relationships with industry and conflicts of interest in medical research, education, and practice and in the development of clinical practice guidelines. It reviews policies that have been adopted or proposed to avoid or manage these conflicts and recommends steps that can be taken to improve the design, implementation, and evaluation of these policies. The report builds on the analyses and recommendations of other groups. It is different,

however, in its focus on conflict of interest across the spectrum of medicine and in its identification of overarching issues and strategies that can be used to limit the negative effects of conflicts of interest while preserving the benefits of collaboration with industry, particularly in moving discoveries from basic science into improved patient care. The report has several broad messages.

1. The goal of conflict of interest policies in medicine is to protect the integrity of professional judgment and to preserve public trust rather than to try to remediate problems with bias or mistrust after they occur.

In all aspects of medicine, judgments must inevitably be made, and reasonable people will disagree over some judgments. Both science and medicine depend on public trust that judgments are made in good faith and are not unduly influenced by the financial interests of professionals or the institutions with which they are affiliated. Well-formulated and well-explained conflict of interest policies can help identify individual and institutional relationships that could reasonably be questioned and allow judgments to be made prospectively about whether particular relationships should be eliminated, permitted, or managed.

It is prudent to require physicians and medical researchers to avoid or manage situations that offer a significant possibility of bias rather than to wait to investigate allegations of bias or misconduct until after they occur. Investigations performed to uncover bias after the fact can be difficult, time-consuming, and heavily burdensome for all involved. Furthermore, when bias occurs in clinical research, medical education, or practice guideline development, it can harm research participants or patients, waste scarce resources, and damage individual and institutional reputations, including the reputations of those whose relationships with industry are appropriately structured and disclosed and serve the public good. If trust is eroded by continuing revelations of withheld negative research findings, promotional relationships disguised as consulting services, and similarly troublesome situations, it may be hard to restore.

2. Disclosure of individual and institutional financial relationships is a critical but limited first step in the process of identifying and responding to conflicts of interest.

Institutions that carry out medical research, medical education, patient care, and practice guideline development depend on individuals' disclosure of their financial relationships with industry. Without such disclosure, institutions will lack the information they need to identify and assess conflicts of interest and determine what additional steps—such as eliminating or managing the conflicting interest—may be necessary. Disclosure by institutions is likewise important because institutions may also have financial relationships that create conflicts of interest. The disclosures need to be sufficiently specific and comprehensive to allow an initial assessment of the

risk of undue influence. At the same time, the harmonization of disclosure requirements and procedures can reduce administrative burdens for researchers and physicians who must make multiple disclosures to different institutions for different purposes.

Disclosure does not resolve or eliminate conflicts of interest. Institutions must also evaluate and act upon the disclosed information. Actions might include the elimination of a relationship, further disclosure (e.g., to research participants, patients, or the public), or other types of management (e.g., restricting the participation of a researcher with a conflict of interest in the enrollment of study participants or analysis of study data).

3. Conflict of interest guidelines and policies can be strengthened by engaging physicians, researchers, and medical institutions in developing policies and consensus standards.

For conflict of interest policies to be truly effective, buy-in from physicians and researchers will be important, so that they regard conflict of interest policies as a means to help them fulfill their professional responsibilities and not as externally imposed nuisances. Furthermore, if those who are subject to conflict of interest policies participate in policy development, they may suggest how the policies can be framed to avoid unintended adverse consequences and undue administrative burdens. In several areas in which substantial policy variation or disagreement exists and greater agreement is needed, the report proposes the creation of consensus development panels with a broad range of participants, including consumer representatives. Two areas that are ripe for consensus building involve the standardization of information that physicians and researchers are required to disclose (Chapter 3) and the development of a new system of financing continuing medical education (Chapter 5).

4. A range of organizations—public and private—can promote the adoption and implementation of conflict of interest policies and help create a culture of accountability that sustains professional norms and promotes public confidence in professional judgments.

Institutions that carry out medical research, medical education, clinical care, and practice guideline development have the primary responsibility for addressing conflicts of interests in these activities. These institutions do not, however, act in isolation. Rather, they interact with many other organizations—including academic and trade membership associations, accreditation and certification bodies, patient advocacy groups, health plans, and federal and state agencies—that have a stake in reducing the severity of individual and institutional conflicts of interest. As discussed in Chapter 9, these organizations can create incentives to encourage institutions to adopt and implement policies that are consistent with the recommendations of this committee and other organizations, such as the Association of American Medical Colleges, the Association of American Universities, and the International Committee of Medical Journal Editors. Such incentives would

encourage and reinforce professional responsibility and promote public trust.

5. Research on conflicts of interest and conflict of interest policies can provide a stronger evidence base for policy design and implementation.

The current evidence base for conflict of interest policies is not strong. A program of research on conflicts of interest and conflict of interest policies could provide policy makers with a better evidence base and a basis for understanding the nature and consequences of conflicts of interest in different situations. It could likewise guide policy makers as they revise policies and procedures to make them more effective and less burdensome.

6. If medical institutions do not act voluntarily to strengthen their conflict of interest policies and procedures, the pressure for external regulation is likely to increase.

The continuing publicity about conflicts of interest in medicine and the failure of individuals and institutions to adhere to conflict of interest policies has prompted calls for government regulation. Indeed, this report recommends some areas for government action, but it also emphasizes that risks as well as the potential benefits of regulation should be considered.

Origins of the Study

This study grew out of discussions within the IOM about the threats to objectivity and public trust in biomedical research and medicine created by conflicts of interest related to certain types of financial relationships between industry and researchers based in universities and federal agencies. Consideration of the topic was further stimulated by inquiries from groups outside the IOM about whether the IOM would examine conflicts of interest and industry ties as they might affect the publication of research and the development of clinical practice guidelines. In response, the IOM proposed a broad-ranging study that would examine conflicts of interest across medical research, medical education, clinical practice, and practice guideline development.

The IOM appointed a 17-member committee to oversee the study and develop the study report. (See Appendix A for more information about study-related activities.) Consistent with its charge, the committee

- examined financial relationships with industry and conflicts of interest in medical research, education, practice, and practice guideline development and
- developed analyses and recommendations to inform the design and implementation of policies for the identification and management of

conflicts of interest in these contexts without damaging constructive collaborations with industry.

To address this broad charge, the committee consciously adopted a crosscutting perspective and tried to view medicine as a complex system with many interacting components and interested parties. It drafted its report for a diverse audience of academic, scientific, professional, medical institution, industry, consumer, news media, and government leaders. Their understanding of the hazards of conflicts of interest and the elements of effective, balanced policies aimed at preventing conflicts of interest from occurring is essential.

During the course of its work, the committee searched for and assessed empirical evidence relevant to its charge, and it read and heard a wide range of views. The analyses and recommendations in this report reflect the committee's conscientious effort to understand and take these views into account. The committee also examined how conflicts of interest are handled in other professions (see Appendix C).

Focus and Concepts

Given the breadth of its charge, the committee focused on conflicts of interest involving *physicians, biomedical researchers, and senior institutional officials*. These individuals have been at the center of most controversies about conflicts of interest and most proposals for policy change. Many of the conclusions and recommendations presented in this report will, however, be generally relevant to nursing, pharmacy, dentistry, and other health professions and to other health researchers. In some cases, institutional policies may extend beyond researchers, professionals, and senior officials. For example, professional society policies governing members of a panel developing clinical practice guidelines will cover all members, including consumers, patients, and the representatives of health insurers.

This report generally uses the term *institutions* to refer to academic medical centers; professional societies; patient or consumer groups; and other entities that carry out medical research, provide medical education and clinical care, or develop clinical practice guidelines.[1] The report also distinguishes (particularly in Chapter 9) supporting *organizations*, such as accrediting agencies and state licensure boards, that may create incentives

[1] For the purposes of this report, the committee distinguished companies that produce commercial medical products from other mostly noncommercial medical institutions (and their personnel) that these companies seek to influence. (Some providers of continuing medical education are for-profit concerns.) The committee recognized that commercial companies conduct or sponsor research and may undertake activities with educational value.

for institutions to adopt and implement effective and credible conflict of interest policies or codes of conduct and for individuals to follow these policies or codes. Some entities, such as medical journals, cross these definitional boundaries and are covered by recommendations related to both institutions and organizations.

Reflecting the discussions that led to this study and the emphasis of much research, press coverage, and public and professional debate, this report emphasizes *financial interests and relationships* involving *pharmaceutical, medical device, and biotechnology companies* that make—or that are developing—medical products used in patient care. (For convenience, the report sometimes refers to these companies as "industry" or "medical product companies," although some start-up biotechnology and other companies may not yet have products approved for marketing.) Other interests, such as the desire for public recognition, may also threaten objectivity and public trust, but financial interests are the central focus of conflict of interest debates and policies.

Notwithstanding the prominence of medical product companies in discussions of conflicts of interest in medicine, the committee recognized that significant conflicts of interest in medical research, education, and practice can be created by financial relationships involving many other kinds of companies. These include health insurers; prescription drug and other benefit management companies; law firms; investment companies; and suppliers of food, office supplies, and other nonmedical goods and services. Much of the discussion in this report about the adoption of policies and the disclosure of information should be relevant to financial relationships involving these other commercial entities.

The committee also understood that serious conflicts of interest may arise from the way in which physicians are paid for their clinical services and from physician ownership interests in hospitals, diagnostic centers, and facilities. The IOM did not plan this study to investigate these issues, but they are briefly discussed in Chapter 6.

Although the analyses presented in this report build on a series of reports on responsible research and integrity in science issued by the IOM and the National Research Council, those earlier reports did not examine conflict of interest in depth. Nonetheless, they provide useful perspectives. In particular, the reports *Integrity in Scientific Research* (IOM/NRC, 2002) and *Responsible Research* (IOM, 2003) underscore the importance of creating organizational and social environments that support and encourage responsible and ethical behavior by individuals and institutions. This report also builds on recommendations made in other reports that called for the undertaking of more and better comparative effectiveness studies and other steps needed to build and communicate the evidence base for clinical practice (see, e.g., previous IOM studies [1991, 2007]). One recommendation

of this report (Recommendation 9.2) is that the evidence base for conflict of interest policies needs to be strengthened to help policy makers identify effective policies and avoid unwanted consequences.

HISTORICAL AND POLICY CONTEXT

Concerns about conflicts of interest have a long history; and the responses to these conflicts have evolved as relationships with industry in medical research, education, and practice have grown more frequent and more complex. They have also evolved as different responses to such relationships have been tried and found to be in need of modification.

The following brief review indicates, first, that both government regulations and voluntary codes of conduct often follow the discovery of instances of questionable or inappropriate relationships and conduct. This is similar to the pattern in other areas, such as the oversight of research involving human participants.[2] Second, government scrutiny of conflicts of interest may stimulate private, voluntary efforts by academic and other institutions to deal with problems and avoid regulation. Third, when these efforts are found to be wanting and government acts, legislators and administrators may still delegate to regulated institutions many of the details of policy development, implementation, and monitoring.

Expanding Relationships Between Industry and Medicine

Relationships between physicians, medical researchers, and medical schools and companies that produce medical products have a long history, as have efforts to encourage such relationships. For example, in the early 1920s, Eli Lilly worked with researchers at the University of Toronto to manufacture insulin in quantities adequate for research and then clinical use; the university also granted royalty-free patents to other companies to expand the drug's availability worldwide (Thayer, 2005). In 1925, the National Research Council (which the National Academy of Sciences established at the request of President Woodrow Wilson to organize scientific research) created a short-lived National Research Fund that raised money from private companies to support research in academic institutions (Swann, 1988).

The mixing of product marketing and medical information for physicians likewise has a lengthy history (see, e.g., Podolsky and Greene [2008]).

[2] In general, this report follows the practice of recent IOM reports in referring to research participants rather than research subjects (IOM, 2001, 2003, 2004; NBAC, 2001). This report uses the latter terminology when quoting and sometimes when referring to reports that employ that terminology.

More than a century ago, a review in the *Chicago Medical Recorder* of *Merck's Manual of the Materia Medica* (now the *Merck Manual of Diagnosis and Therapy*) observed: "[a]lthough this little book is gotten out by a manufacturing firm and with some view towards its advertising value, it nonetheless is of such merit that it is deserving of mention in this column" (quoted by Lane and Berkow [1999, p. 112]). Then, as now, recognition of the value of industry contributions can coexist with unease about commercial motivations and potential bias.

Professional societies and the medical products industry also have longstanding relationships, for example, industry advertising in journals sponsored by medical societies. As early as the late 1940s and early 1950s, the American Medical Association (AMA) began to market information from its new physician database to pharmaceutical companies and to commission studies of the effectiveness of different marketing techniques, the results of which were sent to pharmaceutical and device companies—along with pamphlets promoting advertising in the *Journal of the American Medical Association* (Greene, 2007). This AMA business has generated some controversy and is discussed further in Chapter 6 (see also Steinbrook [2006]).

Biomedical research saw a marked expansion of government funding after World War II. By 1965, spending by the National Institutes of Health (NIH) and other federal agencies accounted for almost two-thirds of the total funding for biomedical research, whereas it was about 7 percent in 1940 (Ginzberg and Dutka, 1989). Then, in the late 1970s, the balance began to shift toward commercial funding. By the turn of the 21st century, the share of health research and development funding accounted for by industry reached 55 to 60 percent (see Chapter 4). New relationships and collaborations between universities and industry during the late 1970s and 1980s were stimulated by a combination of economic conditions, pressures on the federal budget, scientific discoveries, needs for expertise outside universities, and other factors, including legislative incentives for universities to develop discoveries commercially. A Congressional Research Service report noted that another factor in universities' pursuit of industry funding was a "desire to lessen the regulations associated with the expenditure of Federal dollars" (Johnson, 1982, p. 2).

Industry has also become a major source of funding for medical education, particularly continuing medical education. Between 1998 and 2007, the share of continuing medical education provider income accounted for by commercial sources, excluding advertising and exhibits, grew from 34 to 48 percent, with higher rates for some providers, such as for-profit education and communication companies and medical schools (ACCME, 2008a). Through their support for professional society journals and meetings, pharmaceutical and medical device companies are also important sources of

income for professional societies, often accounting for 30 to 50 percent or more of the total income of professional societies (see Chapter 8).

Growing Concerns About Relationships with Industry

As they have evolved, relationships between industry and medicine have brought many benefits, primarily in biomedical research. They have also raised concerns that such relationships can—if they are not properly managed—threaten the objectivity of medical research, education, and practice and undermine public trust in critical American institutions.

Table 1-1 lists some notable events in the emergence of relationships with industry and conflict of interest as a concern in medicine. They include congressional hearings in the 1980s that posed questions about whether conflicts of interest were reducing openness in universities and biasing the advice given to policy makers. A Congressional Research Service report on the commercialization of academic biotechnology research observed that "the credibility of university scientists associated with industry has fallen into question" (Johnson, 1982, p. 5). An article in *Science* from the same period titled The Academic-Industrial Complex (Culliton, 1982) summarized the ethical concerns that these relationships presented to university administrators and faculty:

> How can universities preserve open communication and independence in the direction of basic research while also meeting obligations to industry? Is it acceptable for one corporation to dominate research in an entire department? Are there adverse consequences in terms of collaboration among faculty in various departments if one group must worry about protecting corporate rights to licenses? Will patent and licensing provisions delay scientific publication? Should corporate sponsorship be subject to peer review? Under what conditions may a faculty member have an equity position in industry? Do such ties compromise loyalty to university teaching and research? Will graduate students be compromised or poorly served? Will extensive corporate ties erode public confidence in university faculty as disinterested seekers of truth? (Culliton, 1982, p. 961)

Concerns about conflict of interest beyond the research context were also growing during the 1970s and 1980s. Some concerns related to questions about commercial bias in scientific publications. Others focused on physician referral of patients to specialty centers in which they had a financial interest and on the prevalence of company-provided gifts, lavish entertainment, marketing activities that were disguised as scientific information, and other relationships in both community and academic medical settings.

TABLE 1-1 Timeline of Selected Events Relevant to the Evolution of Conflict of Interest Principles, Policies, and Practices

Year	Event
1959	Senator Estes Kefauver initiates hearings on pricing practices in the pharmaceutical industry that expand to cover marketing practices
1962	President John F. Kennedy issues a memorandum, Preventing Conflict of Interest on the Part of Advisers and Consultants to the Government (27 FR 1341)
1964	American Association of University Professors and American Council on Education (ACE) issue a statement on conflicts of interest in government-sponsored research
1971	The National Academy of Sciences (NAS) approves a letter (On Potential Sources of Bias) to ask members of its study committees to describe financial and other factors that in their judgment "others may deem prejudicial"
1972	The U.S. Congress passes the first antikickback statute (P.L. 92-603)
1978	The U.S. Congress enacts the Ethics in Government Act (P.L. 95-521) to promote confidence in the integrity of government officials and prevent conflict of interest
1980	Patent and Trademark Amendments of 1980 (P.L. 96-517) (Bayh-Dole Act) and Stevenson-Wydler Technology Innovation Act (P.L. 96-480) encourage the commercial development of federally developed or funded technologies
1981	Economic Recovery Tax Act of 1981 (P.L. 97-34) provides a 25 percent tax credit for 65 percent of private investments in universities for basic research
1982	U.S. House of Representatives holds hearings on university-industry cooperation in biotechnology
	The presidents of five leading universities meet with scientists and industry leaders to discuss conflict of interest and university-industry ties (Pajaro Dunes Conference)
1983	California Fair Political Practices Commission orders an investigation of the University of California's enforcement of rules on disclosure of corporate support of faculty research after finding that more than 50 faculty members had financial interests in companies that were funding their research
1984	Association of American Universities (AAU) conducts a survey of university policies on conflict of interest in privately funded research
	Editorial in the *New England Journal of Medicine* announces policy on conflict of interest
1985	AAU issues the report *University Policies on Conflict of Interest and Delay of Publication*
1986	ACE issues the report *Higher Education and Research Entrepreneurship: Conflicts Among Interests*
1987	U.S. Public Health Services (PHS) issues Grants Policy Statement, which states that grant recipients should have written guidelines on conflict of interest
	Accreditation Council for Continuing Medical Education (ACCME) adopts Guidelines for Commercial Support (revised and issued as standards in 1992)
1988	U.S. House of Representatives holds hearing on scientific misconduct and hears concerns about conflicts of interest. Additional hearings follow (one is titled Is Science for Sale?)

TABLE 1-1 Continued

Year	Event
	International Committee of Medical Journal Editors (ICMJE) develops a statement of requirements for authors that includes a provision for authors to voluntarily disclose relevant financial interests and expands the scope of the policy in 1993 and 1998
1989	The U.S. Congress passes a law (Omnibus Budget Reconciliation Act of 1989) barring self-referral arrangements for clinical laboratory services under Medicare; legislation passed in 1993 and 2004 expands and refines the restrictions
	Ethics Reform Act of 1989 (P.L. 101-94) allows federal advisory committee members (special government employees) to participate, despite a conflict of interest, if an agency determines that the need for the individual to participate outweighs the conflict
	The National Institutes of Health (NIH) issues and then withdraws draft guidelines on policies on conflict of interest for recipients of PHS research grants
1990	A U.S. House Committee on Government Operations report (*Are Scientific Misconduct and Conflicts of Interest Hazardous to Our Health?*) recommends the development of PHS regulations that "clearly restrict financial ties for researchers who conduct evaluations of a product or treatment in which they have a vested interest"
	Association of American Medical Colleges publishes *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research*
	American Medical Association (AMA) adopts statement on inappropriate gifts to physicians from industry
	American College of Physicians issues a position paper on physicians and the pharmaceutical industry
1992	NAS report *Responsible Science* (1992) concludes, "The issues associated with conflict of interest in the academic research environment are sufficiently problematic that they deserve thorough study and analysis by major academic and scientific organizations" (p. 78)
1993	ICMJE approves statement on conflict of interest in peer review and publication
	Minnesota law limits drug company gifts to physicians and requires company disclosure of payments to physicians (excluding drug samples and educational materials)
1994	The National Science Foundation (NSF) issues Investigator Financial Disclosure Policy "to help ensure the appropriate management of actual or potential conflicts" (effective 1995)
1995	PHS (60 FR 35815, 42 CFR 50) publishes regulations on the responsibility of grant applicants for promoting objectivity in research
1998	The Food and Drug Administration publishes regulations requiring disclosure by clinical investigators of certain financial relationships (63 FR 5233)
1999	The death of Jesse Gelsinger in a gene transfer experiment provokes controversy after it is revealed that the principal investigator and his university had ownership interests in the company making the interventional product

See Table 1-2 for reports issued after 1999

Continued

TABLE 1-1 Continued

Year	Event
2001	ICMJE publishes new, more stringent policies on conflict of interest
	Vermont requires pharmaceutical companies to disclose payments to doctors and certain health care organizations related to marketing activities
	To promote adherence to its ethical guidelines, AMA, with funding from industry, initiates the campaign "What you should know about gifts to physicians from industry"
2003	HHS issues Compliance Program Guidance for Pharmaceutical Manufacturers, which observes that gifts "potentially implicate the anti-kickback statute if any one purpose of the arrangement is to generate business for the pharmaceutical company"
2004	The U.S. Congress questions NIH about the apparent failure of dozens of employees to disclose relationships with industry
	NIH issues stringent new policies for employees and later moderates them
	HHS issues final guidance to institutional review boards on financial relationships in clinical trials
	ACCME issues revised Standards for Commercial Support
2007	The U.S. Department of Justice announces deferred prosecution or nonprosecution agreements that allow five orthopedic device companies to avoid criminal prosecution for providing financial inducements for surgeons to use their products
2008	The Pharmaceutical Research and Manufacturers of America releases revised *Code on Interactions with Healthcare Professionals* and recommends an end to some gift-giving practices
	The Advanced Medical Technology Association issues revised *Code of Ethics*
	HHS issues regulations requiring physician-owned hospitals and physician owners of hospitals to disclose physician ownership interest to patients
	Massachusetts limits gifts and payments to physicians from pharmaceutical and device companies and requires companies to publicly disclose certain payments
2009	Federal legislation proposed to require disclosure of company payments to physicians and others and reporting of physician ownership interests in health care facilities

SOURCES: This timeline draws on a variety of materials, including the websites of the organizations cited above. Other resources include Johnson (1982), Budiansky (1983), OTA (1984), Steneck (1984), IOM (1991), Maatz (1992), Frankel (1996), Lemmens and Singer (1998), McCanse (2001), Krimsky (2003), Rapp (2003), Huth and Case (2004), Kassirer (2004), NIH (2004), Brody (2007), Parascandola (2007), Ross et al. (2007), Emanuel and Thompson (2008), ORI (2008), Lopes (2009), MedPAC, (2009), and Carpenter (in press).

Evolving Public and Private Responses to Concerns About Conflict of Interest

In the early 1960s, in recognition of the importance of outside advice on complex scientific and policy questions from objective experts, the fed-

eral government (through a presidential memo) established policies to limit conflicts of interest among special government employees serving as advisory committee members and consultants. In the academic community, the American Association of University Professors (AAUP) and the American Council on Education (ACE) issued a joint statement, On Preventing Conflicts of Interest in Government-Sponsored Research at Universities (AAUP/ACE, 1965). The statement spoke of the importance of university-industry relationships but stressed the need to protect the integrity of educational institutions in the face of ties between these institutions and both government and industry. It called for universities to advise government research agencies about the steps they were taking to avoid problems. According to McNeil and Roberts (1991), this statement forestalled government regulation and led to the adoption of policies by most major research universities of "very general guidelines" on conflict of interest that relied on faculty-initiated disclosure (p. 149). By 1967, a number of universities, including Yale, Harvard, Stanford, Michigan, Chicago, Minnesota, and California, had adopted conflict of interest policies that had been approved by the Federal Office of Science and Technology (Wellman, 1967).

A few years after AAUP and ACE issued their statement and after some incidents that raised concerns about bias and conflict of interest, the National Academy of Sciences approved a letter, On Potential Sources of Bias, which it issued in 1971. The letter asked members of the organization's scientific study committees to describe financial and other factors that in their judgment "others may deem prejudicial" (quoted in Parascandola [2007]). According to Parascandola, "[s]cientists universally opposed the policy, however, for a range of reasons—while some argued that all experienced and knowledgeable experts were inherently conflicted, others were offended at the suggestion that any expert could be biased" (p. 3774).

Such negatives responses to conflict of interest policies continue. Nonetheless, the adoption of policies has expanded as the scope and complexity of relationships with industry have increased and instances of questionable or illegal behavior have accumulated—with the attendant negative publicity.

In 1984, the Association of American Universities declined to propose conflict of interest policies for its members, but it did undertake a survey of university policies (OTA, 1984; McNeil and Roberts, 1991). It found that 19 of the 46 responding institutions relied on faculty members to determine whether they had a possible conflict of interest and then to initiate disclosure; 26 institutions had a university-initiated, annual disclosure process (reported in Maatz [1992]). In addition, 21 schools had policies on faculty equity or managerial ties to industry that required disclosure and approval.

In what appears to be the first policy of its sort, the editor of the *New*

England Journal of Medicine announced in 1984 that the journal would ask authors to disclose their relationships with companies that could be affected by their published findings (Relman, 1984). By 1990, the Association of American Medical Colleges had issued for its members guidelines on dealing with conflicts of interest, and AMA had provided guidance to physicians on accepting gifts from industry.

Congressional concerns about financial relationships between physicians or researchers and commercial entities have led to legislation on several occasions and also to threats of legislation. As early as 1972, the U.S. Congress prohibited companies from offering and physicians and others from accepting overt or covert payments or other rewards in return for the referral of patients or ordering of services paid for by Medicare or Medicaid. Beginning in 1989, the Congress also enacted a series of restrictions (known as the "Stark laws," after their sponsor) on self-referral arrangements, which occur when physicians refer patients to specialty hospitals, imaging centers, or other facilities in which they have a financial interest. Also, in 1989, congressional hearings and other pressures prompted NIH to issue draft guidelines on conflict of interest for its grantees. The agency then withdrew these guidelines after criticism that they were too restrictive and would "devastate productive relationships between university researchers and industry, deny scientists outlets for their discoveries at the bench and interfere with the technology transfer" (Mazzaschi, 1990, p. 137). The U.S. Public Health Service eventually issued regulations in 1995 (see Appendix B).

In recent years, members of Congress have raised questions about industry support for continuing medical education, industry payments to physicians, and faculty member disclosure of such payments. As discussed in later chapters, members of Congress have proposed legislation that addresses some of these questions. Some proposals would require companies to report consulting and other payments to physicians, and other proposals promote alternatives to pharmaceutical company sales representatives as sources of information for physicians about medications.[3] A few states have adopted policies requiring companies to disclose certain payments to physicians, and some states have created alternative education programs for physicians and other prescribers of medications.

In the 1990s, social science research techniques and findings began to influence understandings of the relationships between physicians and

[3] Examples of legislation that was proposed but not enacted by the 110th Congress (2007-2008) include S. 2029 (Physician Payments Sunshine Act of 2007), S. 3343 (Medicare Imaging Disclosure Sunshine Act of 2008), and H.R. 6752 (Independent Drug Education and Outreach Act of 2008). The first proposal has been revised and reintroduced in the 111th Congress (Grassley, 2009).

industry. For example, in an analysis of marketing literature and interactions between physicians and industry representatives, Roughead and colleagues (1998) noted that "[r]eciprocity is one of the norms by which society abides. . . . The provision of gifts by sales personnel encourages an automatic response of indebtedness on the part of the receiver who will then look for ways to make repayment" (p. 307). Other research has documented the importance of unconscious bias (see Appendix D).

Since 2000, a number of private and public groups have issued reports on conflict of interest in aspects of medical research, education, or practice. Table 1-2 lists some of the more prominent reports, several of which are discussed in later chapters of this report. Most reports have focused on research. Most have recognized the value of legitimate and properly designed research, educational, and technical relationships; but several have recommended some restrictions on other types of relationships and the more effective implementation of policies. In addition, the Pharmaceutical Research and Manufacturers of America (PhRMA) revised its voluntary *Code on Interactions with Healthcare Professionals* (effective January 2009) to more strongly discourage noninformational gifts, such as providing tickets to sporting events and token consulting arrangements (PhRMA, 2008). The Advanced Medical Technology Association has also revised its *Code of Ethics* for medical device manufacturers (effective July 2009) to include generally similar provisions (AdvaMed, 2008). (Other countries also have industry codes on relationships between the pharmaceutical industry and physicians [Jost, 2009].)

The recommendations in the reports listed in Table 1-2 are often similar (but not entirely consistent) in calling for more accountability and openness and more effective implementation. The policies of particular institutions vary, and some individuals may be subject to multiple policies that apply to their different roles and activities. To the extent that the adoption and implementation of policy recommendations have been evaluated, the results are mixed, as discussed in Chapter 3.

Evolution of Other Strategies to Limit Bias in Medical Research, Education, and Practice

At the same time that policy makers, universities, professional groups, and others were responding to concerns about conflict of interest, methodologists, statisticians, and scientists were working to develop and refine methods for designing and conducting research and analyzing data in ways that limit bias—whatever the source—during all stages of scientific investigation, from protocol design through the reporting of the results (see Chapter 4). In addition, academic medical centers have instituted education on evidence-based medicine to instruct future physicians on how to evaluate

TABLE 1-2 Selected Reports on Conflict of Interest Released Since 2000

Date	Organization	**Title of Report or Paper**
2001	Association of American Medical Colleges	*Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*
2001	Association of American Universities	*Report on Individual and Institutional Financial Conflict of Interest*
2001	General Accounting Office	*Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest*
2001	National Bioethics Advisory Commission	*Ethical and Policy Issues in Research Involving Human Participants*, Volume 1 (see the subsection on conflict of interest in Chapter 3)
2001	National Human Research Protections Advisory Committee	*Recommendations on HHS's Draft Interim Guidance on Financial Relationships in Clinical Research*
2002	Association of American Medical Colleges	*Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*
2002	Council on Government Relations	*Recognizing and Managing Personal Conflicts of Interest*
2003	Council on Government Relations	*Approaches to Developing an Institutional Conflict of Interest Policy*
2004	American Association of University Professors	*Statement on Corporate Funding of Academic Research*
2004	National Institutes of Health	*Report of the National Institutes of Health Blue Ribbon Panel on Conflict of Interest Policies*
2007	Committee on Finance, U.S. Senate	*Use of Educational Grants by Pharmaceutical Manufacturers*
2007	Federation of American Societies for Experimental Biology	*Call to Action: Managing Financial Relationships Between Academia and Industry in Biomedical Research*
2007	National Institutes of Health	*Targeted Site Reviews on Financial Conflict of Interest: Observations*
2008	American Council on Education	*Working Paper on Conflict of Interest*
2008	Association of American Medical Colleges	*Industry Funding of Medical Education*
2008	Association of American Medical Colleges/ Association of American Universities	*Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research*

NOTE: These reports do not include organizational codes of conduct or institutional policies. Full citations for these reports are included in the References at the end of the main text of the report.

critically the evidence presented in (or absent from) journal articles, practice guidelines, and other sources of clinical information and advice (see, e.g., Bennett et al. [1987] and EBM Working Group [1992]). Others have worked to shift methods for the development of clinical practice guidelines away from unsystematic expert opinion and consensus processes toward formal, objective procedures for identifying and reviewing the relevant evidence and linking the strength and quality of the evidence to recommendations (see Chapter 7). These techniques and strategies work together with conflict of interest policies to reduce the risk of bias and maintain public trust in medical research, education, and practice.

ORGANIZATION OF REPORT

Chapter 2 sets forth a normative and conceptual framework for the report, including definitions and the criteria used to assess the potential benefits and harms created by financial relationships. Chapter 3 presents an overview of conflict of interest policies and what is known about their impact.

Chapters 4 through 7 are devoted to examinations of industry relationships and conflicts of interest in the domains of medical research, medical education, clinical practice, and practice guideline development, respectively. Chapter 8 discusses the importance of policies on conflicts that arise at the level of the institution. Finally, Chapter 9 discusses the role that accrediting and other supporting organizations can play in promoting the adoption and implementation of conflict of interest policies by the institutions that are on the front lines of medical education, research, and practice. Several appendixes provide additional background about the report or topics mentioned in the report.

2

Principles for Identifying and Assessing Conflicts of Interest

Relationships between physicians and biomedical researchers on the one hand and pharmaceutical, medical device, and biotechnology companies on the other hand are widespread and have produced important benefits, particularly in the development of new tests and treatments. At the same time, these relationships have also created significant risks that the financial goals of industry may conflict with the professional goals of medicine. The goals of for-profit medical companies are to produce products that improve health and, at the same time, to ensure a financial return to shareholders. The primary goals of medicine include improving health by providing beneficial care to patients, conducting valid research, and offering excellent medical education. In pursuing those goals, individual professionals, health care institutions, and research organizations have obligations to put patient interests first, carry out unbiased research, critically appraise information, and serve as role models of professional behavior for students. The problem of conflict of interest arises because in some circumstances in modern medicine these goals and obligations are at risk of being compromised by the undue pursuit of financial gain or other secondary interests.

Medicine today faces many difficult challenges, including, among others, high costs of treatment and associated pressures to cut costs, lack of availability of health insurance, and persistent medical errors. In comparison, the problem of conflict of interest may seem less significant. However, none of the other challenges can be adequately met if conflicts of interest are not well managed. For example, patients and the public need to be able to trust that the high costs of health care and health insurance arise from the provision of services that are beneficial, necessary, appropriately priced, and not inappropriately driven by the financial interests of physicians, other health care providers, or medical product companies. Failure to deal

with the problem of conflict of interest can undermine efforts to address the other serious challenges that medical professionals and researchers face today.

This chapter develops a conceptual framework for identifying and assessing conflicts of interests.[1] In addition to defining the concept of conflict of interest and clarifying some common misunderstandings about its applications, the chapter presents principles to guide the formulation and implementation of conflict of interest policies. The principles take the form of (1) statements of the purposes of conflict of interest policies, (2) criteria for assessing the content of these policies, and (3) criteria for evaluating the implementation of policies. The principles do not directly yield decisions in particular cases or even rules that could be directly enforced, nor do they determine in advance the relative importance of all the values involved in making decisions. In applying them to particular policies and individual cases, there is no substitute for judicious practical judgment sensitive to the institutional context. However, the principles provide an essential framework for formulating and implementing any conflict of interest policy. They focus attention on the most important factors that should be considered when professionals and institutions make decisions and policies regarding conflicts of interest, select the agents who should be responsible for implementing and enforcing those policies, and choose the methods that they will use to regulate conflicts of interest.

WHAT IS A CONFLICT OF INTEREST?

Although conflict of interest policies are now widespread in many areas of medicine, the meaning and purposes of these policies are not always clearly understood. The term "conflict of interest" is used in many different and often inconsistent ways. Nonetheless, institutional and public policies on conflicts of interest need to define what the policies cover and what they do not cover.

The definition that the committee adopted is consistent with the core meaning of the concept as it is used in many institutional policies. It is, however, formulated to clarify key elements that are sometimes obscured in discussions of those policies.

[1] The discussion in this chapter draws on work by Thompson (1993) and Emanuel and Thompson (2008). The committee also consulted other definitions and frameworks, including those of Davis (1998), AAMC (2001), Davis and Stark (2001), NIH (2004), Moore et al. (2005), Lurie (2007), Sage (2007), AAMC-AAU (2008), and Beauchamp and Childress (2009).

> *A conflict of interest is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.*

To avoid common misunderstandings of the concept that can lead to misplaced and ultimately ineffective or counterproductive policies, the committee stresses the importance of each of the three main elements of a conflict of interest: the primary interest, the secondary interest, and the conflict itself.

The primary interest that conflict of interest policies seek to protect varies according to the purpose of a professional activity. Primary interests include promoting and protecting the integrity of research, the welfare of patients, and the quality of medical education. Physicians and medical researchers accept the primacy of these interests when they act in their professional roles. Physicians and researchers exercise judgment and discretion in their work. Patients, the public, research participants, medical students, residents, and fellows need to trust physicians and researchers to act and make judgments in ways that are consistent with these primary interests. These primary interests are sometimes stated as ends or goals (e.g., promoting patient welfare), as obligations (e.g., the physician's obligation to promote patient welfare), or as rights (e.g., the patient's right to have the doctor promote his or her welfare). The committee uses the term primary "interests" to encompass all of these values, however they are stated. Whatever the primary interests are, the point of regulating conflicts of interest is to try to ensure that secondary interests do not subvert physicians' and researchers' decisions and actions regarding those primary interests and do not undermine trust in their clinical or scientific judgment. Furthermore, medical institutions—including medical schools, research institutes, professional societies, scientific journals, patient advocacy organizations, or government health agencies—should also keep these primary interests paramount, as discussed further in Chapter 8.

To be sure, identification of the exact primary interest in specific situations may sometimes be challenging, and primary interests sometimes conflict with each other. For example, in public health emergencies or under conditions of dire resource scarcity, physicians may have fundamental obligations to the population as a whole that may compete with their obligations to individual patients. In clinical research, the welfare of the participants in a study and the study's successful completion may be in conflict. Nonetheless, it is almost always clear that a primary interest should take precedence over a secondary interest.

The second main element of a conflict of interest is the secondary interest. Secondary interests may include not only financial gain but also the desire for professional advancement, recognition for personal achievement,

and favors to friends and family or to students and colleagues. Conflict of interest policies typically and reasonably focus on financial gain and financial relationships. The reason is not that financial gains are necessarily more corrupting than the other interests but that they are relatively more objective, fungible, and quantifiable. A financial interest therefore tends to be more effectively and fairly regulated than other secondary interests. Furthermore, for-profit companies exert influence primarily through their financial relationships with physicians and researchers. They cannot bestow professional rewards such as prestigious scientific prizes that may also lead to conflicts of interest.

Most secondary interests, including financial interests, are—within limits—legitimate and even desirable goals. The secondary interests are objectionable only when they have greater weight than the primary interest in professional decision making. For example, for a researcher or a teacher, financial interests should be subordinate to presenting scientific evidence in an unbiased manner in publications and presentations.

A financial interest does not have to be great for the influence to be undue. Indeed, social science research suggests that gifts of small value may influence decisions (see Appendix D). It also suggests that influence may operate without an individual being conscious of it. When a secondary interest has inappropriate weight in a decision and distorts the pursuit of a primary interest, it is exerting undue influence.

The third key element of the definition is the conflict itself. It is not an occurrence in which primary interests are necessarily compromised but, rather, a set of circumstances or relationships that create or increase the risk that the primary interests will be neglected as a result of the pursuit of secondary interests. A conflict of interest exists whether or not a particular individual or institution is actually influenced by the secondary interest. The claim that a conflict of interest exists is based on common experience and social science research. Both experience and research indicate that under certain conditions there is a risk that professional judgment may be influenced more by secondary interests than by primary interests.

Some of these elements of a conflict of interest refer to degrees or quantities (e.g., more or less influence), but they are not directly quantifiable. What counts as undue is a matter of judgment and depends on the context. It is not a numerical probability but a judgment in a particular situation about whether a risk is undue or inappropriate. The standards for making such a judgment should be transparent and clearly specified in actual policies rather than in vague statements that professionals should avoid "undue influence." Subsequent chapters examine what situations or relationships may be considered inappropriate in research, patient care, medical education, and practice guideline development. Appendix C offers perspectives on conflicts of interest in other professions.

Conflicts of interest should be distinguished from other closely related conflicts. Not all conflicts in medicine are conflicts between a primary and a secondary interest. A conflict of obligation arises when an individual or institution has duties that require different actions but only one of these actions can be taken in the given circumstance. Dilemmas in medical ethics often take this form, that is, the need to make hard choices between two values, neither one of which is clearly superior to the other. A common example is maintaining the confidentiality of a patient with a contagious disease, which may conflict with preventing that patient from harming someone else. There is no conflict of interest in this example because both interests have plausible claims to be considered primary. Conflicts of obligation are essentially conflicts among different primary interests. Both obligations or interests are legitimate, often equally so, and it cannot be said in advance which one should take priority.

Conflicts of commitment are closer to conflicts of interest. They often involve a conflict between what institutions view as employees' primary responsibilities to the institution and the employees' outside commitments, such as voluntary community service, participation in a political campaign, or teaching or conducting research for another institution. Like conflicts between primary interests, conflicts of commitment involve two perfectly respectable activities (indeed, in some cases, identical activities, except that they are conducted at different institutions). Also, like conflicts of interest, the institution can legitimately claim in advance that one activity takes priority over the other if they come into conflict in any way. The concern is not usually about the risk of undue influence over specific decisions (e.g., the prescribing of a particular medication or the reporting of research findings). Rather, the concern is about time and effort, for example, whether individuals are devoting sufficient attention to their responsibilities within their own primary institution. Conflicts of interest and conflicts of commitment are sometimes covered in the same institutional policy; but the circumstances, risks, and evaluative frameworks are sufficiently different that they warrant separate consideration. Nevertheless, it makes sense for the policies to be covered in the same documents and information resources and to be administered by the same officials and committees.

WHAT ARE THE PURPOSES OF CONFLICT OF INTEREST POLICIES?

Institutions, professional organizations, and governments establish policies to address the problem of conflict of interest on behalf of the public. Conflict of interest policies are attempts to ensure that professional decisions are made on the basis of primary interests and not secondary interests. (See the discussion of the policies of other professions in Appendix C.)

As discussed further in Chapter 9, such policies work best when they are preventive and corrective rather than punitive. To the extent that they are effective, they serve two overarching purposes: maintaining the integrity of professional judgment and sustaining public confidence in that judgment. That professionals should promote these purposes constitutes the fundamental principle underlying any respectable conflict of interest policy.

First, the most obvious way in which the integrity of professional judgment can be compromised is through bias. Other practices can also undermine that integrity when they violate standards of professional conduct, such as the failure to publish research findings in a timely manner, the failure to treat students and postdoctoral fellows fairly, and a lack of openness with patients. Conflict of interest policies seek to minimize the influence of secondary interests in all these practices. They most significantly guard against the risk that financial interests will have excessive weight in decisions about the conduct of research, teaching, the provision of patient care, and the development of practice guidelines.

Such policies do not assume that any particular professional will necessarily let financial gain influence his or her judgment, nor do they imply that the individual researcher or physician is an unethical person. They assume only that under some conditions a risk exists that the decisions may be unduly influenced by considerations that should be irrelevant. Nonetheless, physicians and researchers are sometimes offended by assertions that they have conflicts of interest, believing that such assertions impugn their ethical integrity.

To avoid what they believe to be the negative connotations of "conflict of interest," some institutions use such phrases as "relationships with industry" or "financial relationships" to describe not only relationships that may be evaluated for the presence of potential conflicts but also relationships that are judged to be conflicts of interest. This less direct language has the effect of obscuring the serious risks that conflicts pose. Such language is not necessary if it is recognized that the determination that an individual or institution has a conflict of interest is a judgment about the situation and not about the professional who happens to be in that situation.

The second purpose of conflict of interest policies—to help sustain public confidence in professional judgment—is less appreciated but no less important. Here the goal is to minimize conditions that would cause reasonable individuals to suspect that professional judgment has been improperly influenced by secondary interests, whether or not it has. The public includes not only patients and research subjects but also editorial writers and journalists, officials at nonprofit foundations, public officials, and other opinion leaders. When or if the public and public officials distrust physicians, researchers, or educators, they are likely to seek greater government

regulation, withhold funding, and take other steps that could jeopardize future programs of patient care, research, or education.

When a physician, researcher, or educator acts in ways that lead to distrust, the consequences may affect colleagues, patients, students, and the institution or profession as a whole. Similarly, institutional practices can be the source of distrust, and the effects of such distrust may be even more widespread and damaging than distrust of an individual. Physicians retain a high standing with the public compared with the standing of many other professional groups; but physicians should be vigilant, because once public confidence is undermined, it may be difficult to restore.

As discussed in Appendix C, other professions—law, accounting, engineering, and architecture—have also recognized the importance of conflict of interest policies and ethical codes to promote objectivity in decision making and sustain public confidence. In some recent cases, most notably, accounting, failure to adhere to these codes has led to increased government regulation.

WHY NOT EXAMINE THE MOTIVES OF THE DECISION MAKER OR THE VALIDITY OF THE DECISION?

Individuals accused of having a conflict of interest often say that they would never let financial interests influence their decisions. This objection to conflict of interest policies misses the point. Because (as noted above) the conflict is a set of circumstances or conditions involving a risk rather than a specific individual decision, the existence of a conflict of interest does not imply that any individual is improperly motivated. Nevertheless, an individual professional might still object that it is not fair to generalize in this way. He or she may want to say: "Look at my actual decisions and consider my distinguished reputation." However, conflict of interest policies are by their nature designed to avoid the need to investigate individual cases in this way. For at least two reasons, such policies do not focus on the motives in a particular case.

First, reliably ascertaining or inferring motives in this context is usually impossible for those assessing whether a relationship constitutes a conflict of interest. Generally, medical research, patient care, and education involve multiple considerations and many small judgments and decisions that are impractical to review; and even if they were reviewed, they would likely not yield a clear picture of the underlying motivation. Thus, readers of journal articles, medical students, patients, and conflict of interest committees are not in a good position to judge whether secondary interests motivated a decision. The motives behind institutional decisions are usually even more opaque.

Second, any thorough effort to determine motivation in a particular case would be improperly intrusive and highly time-consuming. Fair hearings could not be held and reliable conclusions could not be reached without risking violation of the rights of privacy of the many individuals who might be involved and without distracting many people from other important work.

Sometimes another, closely related objection to a claim that an individual has a conflict of interest is raised. This objection accepts that motives should not be considered but denies the relevance of the conditions under which decisions are made: "Judge my decision—the results of the research, the content of the lecture, the prescription of the drug—and not my financial interests." Here again the problem is that many people affected by professional decisions are not in a position to judge the validity of those decisions. In addition, those who are competent to judge may not be able to do so until after the damage has occurred. Furthermore, the argument for judging outcomes ignores one of the two main purposes of conflict of interest policies: the maintenance of public confidence. Even valid decisions and research may not be widely accepted as such if they occur under conditions in which secondary interests are prominent. Moreover, many decisions in research and clinical care are close calls. Plausible reasons can be cited for each of several alternative choices. The decisive factor in whether a judgment or an action is accepted as valid may turn on whether a researcher or a clinician can be trusted to be acting for the sake of scientific truth and the best interests of patients.

Because it is both intrusive and usually impracticable to investigate motives and because the competent and timely appraisal of decisions is often difficult, it may be tempting to conclude that patients, the public, and researchers simply need to trust physicians. Trust is important, but generalized trust and reliance that medical professionals act in accord with primary professional interests may be difficult to maintain in the face of evidence that this trust is sometimes abused. Furthermore, creating trust in medical professionals who conduct research or develop practice guidelines is hard because they have little or no contact with many of the people who are affected by their decisions and who have only limited knowledge with which to evaluate the decisions. Trust is necessary and desirable, but it must be based on reasonable expectations. Those who rely on professionals must have good reason to trust their decisions. In short, they need assurance that the professionals are trustworthy. Policies designed to reduce conflicts of interest and mitigate their impact provide an important foundation for public confidence in medical professionals and institutions.

SHOULD POLICIES ALSO REQUIRE THAT PROFESSIONALS AVOID THE "APPEARANCE OF CONFLICT OF INTEREST"?

Some conflict of interest policies refer to actual or perceived conflicts of interest and state that professionals should avoid "even the appearance of a conflict of interest." That requirement may lead to confusion. All conflicts of interest involve perceptions or appearances because they are specified from the perspective of people who do not have sufficient information with which to assess the actual motives of a decision maker and the effects of those motives on the decisions themselves.

Policies that contrast actual and perceived conflicts of interest give rise to two problems. First, the contrast suggests that there is no conflict (only an appearance of a conflict) unless the decision maker actually favors secondary interests over primary interests. The implication, then, is that conflict of interest policies should treat a perceived conflict as less serious than an actual conflict. However, when a professional's judgment is actually distorted by the acceptance of a gift or the prospect of influencing a stock in which the professional has an interest, the violation is no longer principally a conflict of interest but becomes a different kind of offense, one that may involve malpractice, scientific misconduct, or kickbacks. Those violations call for the use of procedures quite different from those on which conflict of interest policies should concentrate.

Second, the creation of a category of perceived conflicts, as distinct from actual conflicts, opens the door to overly broad and excessively subjective rules. If perceived conflicts are treated as different from the other (so-called actual) conflicts that the policy regulates, conduct that is perfectly proper can be unfairly called into question. With a loose notion of the perception or the appearance of a conflict of interest, circumstances that are suspicious only to uninformed people or predisposed reporters can be the basis of indiscriminate charges of conflicts of interest. Charges of conflicts of interest should be limited to circumstances specified by policies that are objectively grounded in past experience and reasonably interpreted on the basis of relevant and accessible information.

HOW CAN CONFLICTS OF INTEREST BE ASSESSED?

Conflicts are not binary; that is, they are not simply either present or absent. They can be more or less severe. The severity of a conflict depends on (1) the likelihood that professional decisions made under the relevant circumstances would be unduly influenced by a secondary interest and (2) the seriousness of the harm or wrong that could result from such influence. As discussed later in this chapter, the criterion of proportionality in conflict of interest policies provides that the expected benefits of a relationship may

TABLE 2-1 Criteria for Assessing the Severity of Conflicts of Interest

Likelihood of undue influence
- What is the value of the secondary interest?
- What is the scope of the relationship?
- What is the extent of discretion?

Seriousness of possible harm
- What is the value of the primary interest?
- What is the scope of the consequences?
- What is the extent of accountability?

be considered, and conflicts of interest may be allowed to continue if those benefits outweigh the risks and safeguards that are instituted.

Table 2-1 lists the questions that need to be asked when the severity of a conflict of interest is assessed in particular cases. These questions express criteria or principles that identify the most important factors to be considered in formulating policies and making decisions about conflicts of interest. Assessments of the likelihood of undue influence and the seriousness of the consequences usually reflect general judgments about situations—on the basis of experience—rather than evaluations of the character of the individual in question. The individual's behavior in similar situations in the past might, however, be taken into account. The next two sections discuss the criteria in more depth.

Assessing the Likelihood of Undue Influence

In assessing the likelihood of undue influence, it is reasonable to assume that the greater that the value of the secondary interest is (e.g., the greater that the size of the financial gain is), the more probable is its influence. Thus, equity or other ownership interests in a small biotechnology company have great potential for an increase in value on the basis of the results of a clinical trial (as well as the potential for no value). Large fees for serving on a company advisory board are more valuable than occasional small honoraria for talks. Although absolute value is important, the secondary interest should generally be measured in relation to the typical income for the relevant class of professionals or in relation to the value of a research project, institutional budget, or medical practice.

However, the monetary value of a secondary interest is not the only appropriate measure of its potential impact. The economic value of pens, inexpensive meals, and other nominal gifts or relationships is low; but as explained in Appendix D, small gifts may help to create and sustain relationships, for example, between a physician and a pharmaceutical company

and its representatives. The influence of such gifts and relationships may be subtle and the individual receiving such gifts may not even be conscious of their influence. It may therefore be necessary to manage or prohibit conflicts of interest even when the value of the secondary interest, as measured only by monetary value, is low and the likelihood of harm or wrong in a single instance is low.

Other aspects of relationships besides their dollar value may also increase their general value and therefore the risk of a conflict of interest. For example, payments that augment the income of an individual professional may create more concern than those that exclusively support the academic activities of a whole institution. A consulting arrangement that increases a researcher's income will tend to create more concern than one in which payments are made to the institution, department, or research group as a whole and disbursed under institutional oversight. Similarly, a research contract that is reviewed by a university for consistency with policies on data access, sponsor review, and publication rights will generally create less risk of a conflict of interest than a consulting arrangement that does not receive such review or that is reported only in very general terms (e.g., as involving payments over $20,000 when the actual amount is $200,000).

A second factor affecting the likelihood of undue influence is the scope of a relationship, which refers to its duration and depth. Longer and closer associations increase the scope and therefore the risk. Examples of such associations include a multiyear consulting agreement, a continuing leadership position as a member of a company board, or the weekly or monthly provision of free lunches at a physician's office. Likewise, long-term funding of a university or commercial continuing medical education program has more potential for influence than a one-time grant. Similarly, serving on a company's scientific advisory board, which more intimately ties the professional to the company over time, is more likely to affect the professional's judgment than accepting a fee for speaking about a company-sponsored research project.

The extent of discretion, that is, how much latitude a professional enjoys in making important decisions, is also pertinent. Even though some of their judgments are subject to various kinds of review, the principal investigator in a clinical trial exercises considerable discretion over innumerable, wide-ranging, and often hidden decisions, for example, decisions regarding the eligibility of patients to enter the clinical trial, determinations of clinical end points, ascribing of adverse events to the study intervention, the type of statistical analyses to be used, and the reporting of the results. This discretion is often limited by an independent oversight body, for example, a data and safety monitoring board, an independent panel that adjudicates adverse events, a medical monitor of adverse events, or an external auditor for data collection at individual research sites. Such oversight is usually

required for any clinical trials whose results will be presented to the Food and Drug Administration for regulatory approval of a drug or medical device. In assessing such limits on discretion, it is also important to consider the independence of the judgment of the members of any oversight body. Furthermore, the more closely that the research and data analysis methods follow standard methods, the less room there is for improper influence. Similarly, the more conventional the subject matter of educational presentations, the less scope there is for bias that is not easily detected.

Authority and discretion often vary by role. Principal investigators can influence multiple dimensions of a research project, whereas laboratory technicians or research assistants have less scope for influence in most situations. Deans and chancellors, through their power to control appointments, promotions, salaries, and space, wield great power, although they are typically several steps removed from conducting research projects or teaching courses. At the other extreme, most administrative staff members have little power to influence a university's research or teaching mission.

Assessing the Seriousness of Possible Harm

The starting point in assessing the seriousness of possible harm from a conflict of interest is to identify or specify the value of the primary interest. This report concentrates on the primary goals of medicine, particularly patient care, research, and medical education. Assessing the severity of a conflict requires an examination of the specific primary goal or goals at risk in a particular situation.

A second consideration is the scope of the consequences. The greater that the scope is, the more serious is the potential for harm. Conflicts of interest that may affect multiple patient care decisions have a large scope. For example, practice guidelines that set standards of care and criteria for insurance coverage may affect millions of patients. The results of a clinical trial for a common condition can affect how thousands of physicians prescribe a specific medication. Results from a pivotal trial of a novel type of therapy that may dramatically alter patient care are likely to have a larger scope than other trials that will influence care only at the margins. Thus, conflicts of interest in clinical trials deserve special attention because of the potentially large scope of their effects.

A conflict of interest may also have negative effects on an individual's colleagues or institution. Such effects need to be taken into account even if they do not occur frequently. A pharmaceutical or medical device company's sponsorship of a research project could raise questions about the work of other researchers in the institution and weaken their ability to raise funds from other sources. A professor's close connections with a company not only could raise doubts about the objectivity of his class materials and

presentations, but these connections could also have negative effects on the careers of his teaching assistants and the collegial culture of the institution. In view of such possible consequences, the fact that an individual has a right to engage in an activity should not be allowed to obscure the equally important fact that his or her actions may affect the rights of colleagues and students. The claim of an individual right by a professional does not preclude the possibility that this right may be regulated.

Finally, the seriousness of the possible harm depends in part on the extent of accountability. In general, a conflict of interest is more serious when the level of accountability of the physician, researcher, or educator to his or her peers, institution, licensing board, or similar entity is less extensive. If accountability for decisions is bolstered by an independent review of those decisions by colleagues or other authorities, there is generally less potential for harm and less cause for concern. However, the reviewers must be and must be viewed as being effective and independent and must have no conflicts of interest of their own. Accountability is also greater to the extent that sanctions for serious violations of policies are significant and imposed in a timely fashion, and it is further enhanced if the results of the disciplinary proceedings are regularly disclosed.

In summary, an overall assessment of whether a financial relationship constitutes a conflict of interest and, if so, how severe it is and how it should be managed depends on several considerations: the importance of the financial or other relationship for furthering primary medical values, the likelihood and seriousness of possible harm to those primary values, and the availability of measures that can reduce the likelihood or severity of harm. Chapter 3 discusses such measures and also the procedures applied by universities and other institutions to identify, limit, and manage conflicts of interest.

HOW CAN CONFLICT OF INTEREST POLICIES BE EVALUATED?

The discussion above focused on several questions and factors that should be considered in assessing the severity of a conflict of interest in financial relationships. They are intended to provide guidance for the formulation of the content of policies for controlling conflict of interest, for example, the specification of the information needed from individuals that will be sufficient to evaluate financial relationships, assess the severity of conflicts of interest, and guide responses to identified conflicts. Additional criteria are needed to evaluate the implementation or actual operation of the policies (Table 2-2). Even if policies are well formulated, they must also be well administered.

TABLE 2-2 Criteria for Evaluating Conflict of Interest Policies

Criterion	Description
Proportionality	Is the policy most efficiently directed at the most important conflicts?
Transparency	Is the policy comprehensible and accessible to the individuals and institutions that may be affected by the policy?
Accountability	Does the policy indicate who is responsible for enforcing and revising it?
Fairness	Does the policy apply equally to all relevant groups within an institution and in different institutions?

Proportionality

First, the criterion of proportionality calls for policies to be efficient and effective in addressing serious conflicts of interest in a preventive or a corrective way. Complicated rules and elaborate procedures can become merely bureaucratic obstacles unless they are implemented and regularly reviewed with the goals of the policy in mind. Do the policies actually address the most important and common conflicts? Are the policies practical; that is, can they actually be effectively implemented at an acceptable cost? Are the policies administered in a way that appropriately considers the likelihood of bias, the seriousness of the harm, and the potential benefits of the conflicting secondary interest (as noted above)? Do the policies and their application unnecessarily interfere with the conduct of legitimate research, teaching, and clinical practice? Do the anticipated benefits of the policies outweigh their various costs, such as administrative burdens, and any negative consequences? The effectiveness of a specific policy can be judged only after that policy has been in use for a period of time. Insofar as experience and evaluations have raised questions about the effectiveness of similar policies already adopted, however, these questions can guide the design and implementation of new policies. Finally, whether policies can achieve their overall aims will also depend on their congruence with other criteria, such as fairness and transparency, that contribute to effectiveness and that are also important for their own sake.

The criterion of proportionality should also be applied in individual situations when an assessment is made of whether a financial relationship constitutes a conflict of interest and, if there is a conflict, how it should be handled. For example, when a researcher's financial relationship with a company is evaluated, its expected benefits as well as its risks should be considered. As discussed in Chapters 1 and 4, industry support for well-designed and scientifically meritorious research tends to advance a primary

goal of generating valid scientific knowledge. This may sometimes mean that an institution should allow an individual with a conflict of interest to participate in an activity because the expected benefits exceed the risks and because the risks have been lowered to an acceptable level. For example, an academic medical center may allow a scientist who holds the patent on a promising discovery to participate in developing a product and designing an early-stage clinical trial to evaluate an intervention because his or her involvement may be necessary to ensure that the product is safely and correctly administered. (These kinds of situations, which should be exceptional, are discussed further in Chapters 4 and 7.)

Transparency

Just as disclosure is usually necessary—even if it is insufficient—in dealing with conflicts of interest, so too is transparency necessary in administering conflict of interest policies. Transparent policies are readily available in clear and simple language, together with explanations and essential information about their application. They are also available not only to those who are subject to them (e.g., researchers, authors of journal articles, or members of practice guidelines panels) but also to other stakeholders, including the public. Transparency is essential to determine whether conflict of interest policies are reasonable and if they are being implemented fairly.

Conflict of interest policies may require the public disclosure of financial and some other relationships under certain circumstances, as described in Chapter 3. These disclosure policies reflect the institutions' ethical and sometimes legal responsibility to disseminate relevant information to appropriate parties. In addition, the values of transparency are also served when institutions explain their judgments in certain cases, for example, when they allow an investigator with a financial stake in the outcome of a study with human participants to conduct that research (see Chapter 4).

Rights of privacy and protection of confidentiality place some limits on how much information an institution discloses and to whom. For example, physicians have a countervailing privacy interest when it is proposed that their financial relationships (and perhaps those of their family members) be disclosed to the public, as noted in the discussion in Appendix F of public disclosure of personal information reported to academic medical centers and other institutions. Disclosures beyond the institution can be limited to the minimum amount of identifiable personal information that is needed to carry out policy goals. For some purposes, reporting aggregate or deidentified information to the public is sufficient.

Transparency can also help improve conflict of interest policies across institutions. Information about the way that one institution has handled a

particular case or type of case can enable other institutions to learn about more and less effective practices and adjust their own policies and behaviors accordingly.

Accountability

Accountable individuals and institutions explain and take responsibility for their conduct and decisions. Thus, just as a physician explains the rationale for clinical decisions to patients and researchers explain the rationale for research and research procedures, so too will leaders of accountable institutions explain their policies and their application to the individuals who are directly affected and respond to questions and suggestions.

Taking responsibility for the consequences of individual or institutional actions and decisions may involve offering apologies or compensation to those harmed by these actions and acknowledging the appropriateness of penalties when a representative of the institution has acted improperly or illegally. To demonstrate that it is accountable, an institution not only will develop explicit conflict of interest policies and procedures for implementing its policies but also will devise ways to communicate how they are applied in practice. Institutional leaders will be prepared to explain how judgments about conflicts of interest are reasonably consistent across similar cases and why, for example, they determined that it was sufficient to require only the disclosure of a relationship in one case but appropriate to manage or prohibit the relationship in another case. Finally, institutional leaders will be ready to respond to questions about their own interests and impartiality. As discussed in Chapter 8, leaders should establish procedures for dealing with the conflicts that their own institutions may have.

Public engagement is often important for accountability. For example, accountability is generally enhanced if public representatives serve on institutional panels that review individual relationships that may present conflicts of interest. To cite a somewhat parallel situation, federal regulations require institutional review boards to include at least one member not affiliated with the institution. Also, as part of a commitment to openness and accountability, organizations may invite public comment on their conflict of interest policies and may take seriously suggestions for revisions. Public participation can enhance the credibility and trustworthiness of decisions about individual cases as well as more general policies.

A final aspect of accountability is a commitment to improving conflict of interest policies and their implementation. Setting benchmarks for performance and tracking outcomes can stimulate quality improvement activities, as has been demonstrated with other activities in health care organizations.

Fairness

The formal principle of fairness requires similar treatment for those in relevantly similar situations and different treatment for those in relevantly different situations. This principle has at least two implications for the application of conflict of interest policies.

First, these policies should apply to all employees or members of an institution who make significant decisions for the institution or who have substantial influence over these decisions. In academic medical centers, these decisions may involve medical education, medical research, or clinical care. Thus, residents, fellows, faculty, members of institutional committees (e.g., institutional review boards, formulary committees, and device purchasing committees), and senior institutional officials are all subject to conflict of interest policies and procedures. Although medical students do not usually have an influence over decisions that are made, they too should be expected to follow conflict of interest rules, which are among the important professional norms they are learning as they prepare for their future careers. At the same time, to be fair, conflict of interest policies and procedures may reasonably differ for people in different roles. For a medical student or resident, the policy issue might be accepting mugs, pens, and lunches from companies. For a senior leader in the institution, the issue might be serving on the board of directors of a company manufacturing medical products and receiving personal compensation for this position. In some cases, the policy response might be to prohibit a practice overall, whereas in other instances management of the conflict could be an option, depending on the specifics of the situation, as assessed by the standards listed in Table 2-1.

Second, fairness requires that individuals in different institutions who are in situations that are similar in all ethically relevant ways be treated similarly. Otherwise, the ethical basis for policies may be called into question and conflict of interest policies and decisions may be regarded as arbitrary. Although conflict of interest regulations for U.S. Public Health Service grantees and policies recommended by the Association of American Medical Colleges allow institutions discretion in setting and implementing policies to take account of local circumstances, it is important to justify such variation in ways that are understandable by and plausible to affected individuals, oversight agencies, and the public.

CONCLUSION

The purposes of conflict of interest policies are expressed in the principles that hold that professionals should act to protect the primary interests of medical practice, education, and research and to maintain public confidence in the integrity of those activities. The problem of conflict of

interest is more complex than is often appreciated. As a result, both critics and defenders of conflict of interest policies sometimes misunderstand or misapply them.

A conflict of interest is not an actual occurrence of bias or a corrupt decision but, rather, a set of circumstances that past experience and other evidence have shown poses a risk that primary interests may be compromised by secondary interests. The existence of a conflict of interest does not imply that any individual is improperly motivated. To avoid these and similar mistakes and to provide guidance for formulating and applying such policies, a framework for analyzing conflicts of interest is desirable.

This chapter has presented principles for assessing conflicts of interest and evaluating policies designed to deal with such conflicts. Conflicts should be assessed by considering various factors that determine their likelihood and seriousness. Likelihood depends on the value of the secondary interest, the scope of the relationship between the professionals and the commercial interests, and the extent of discretion that the professionals have. Seriousness depends on the value of the primary interest, the scope of the consequences that affect it, and the extent of accountability of the professionals. Conflict of interest policies should be evaluated by considering their effectiveness, transparency, accountability, and fairness.

A better understanding of the nature of conflicts of interest and the clearer and fairer formulation of rules can support greater confidence in the medical profession and thereby enable physicians, educators, and investigators to concentrate on their primary missions of treating patients, teaching students, and conducting research. With robust conflict of interest policies in place, they can continue to carry out their respective activities not in wary confrontation but in beneficial cooperation with the representatives of industry.

3

Policies on Conflict of Interest: Overview and Evidence

Current conflict of interest policies and practices have evolved over more than four decades of increasing relationships with industry in medical education, research, and practice. The increase has been accompanied by intensifying discussions about how the risks and the expected benefits of these relationships should be evaluated and balanced. Since 1995, the U.S. Public Health Service (PHS) has required most research grantees to establish policies and procedures to ensure that the design, conduct, or reporting of research funded by PHS grants not be "biased by any conflicting financial interest of an Investigator" (42 CFR 50.601). The regulations, which are included in Appendix B, allow grantees considerable discretion in formulating policies and procedures. To provide more specific and comprehensive guidance to academic institutions on conflict of interest policies, the Association of American Medical Colleges (AAMC, 2001, 2002, 2008c), the Association of American Universities (AAU, 2001), AAMC and AAU jointly (AAMC-AAU, 2008), and the Council on Government Relations (COGR, 2002) have issued several reports with recommendations. The Federation of American Societies for Experimental Biology (FASEB) created a conflict of interest tool kit that offers extensive online resources and guidance for academic institutions, researchers, academic and professional societies, journal editors, and industry (FASEB, 2008). In 2008, the trade associations representing major pharmaceutical and medical device companies revised their codes on company interactions with health care professionals (AdvaMed, 2008; PhRMA, 2008). In addition, a number of academic medical centers, professional societies, medical journals, and other institutions have revised their policies in recent years.

Criticisms of current policies and their application come from different directions. Some object that policies requiring the disclosure of financial

interests can be carried too far, encouraging "readers to make *ad hominem* judgements" (Rothman, 2001, p. 1275) or shifting "attention away from the merits of the work and toward the biography of its author" (Jansen and Sulmasy, 2003, p. 40). Another critic describes disclosure policies as a kind of "new scientific McCarthyism" that assumes that researchers with industry ties are "tainted and untrustworthy" (Whelan, 2008, p. A19). One researcher has criticized "conflict of interest vigilantes" who "search for evidence that doctors have failed to disclose corporate connections in publications or in presentations" (Stossel, 2007, p. 59). He has also argued that continuing medical education disclosure policies mainly serve to protect bureaucrats rather than students, are based on ideology rather than evidence, and "are deeply disrespectful of physicians and researchers" (Stossel, 2008, p. 476). (See Chapter 1 for additional criticisms.)

Others, however, argue that conflict of interest policies—when they exist—are often weak, inconsistent, and inadequately administered and enforced. For example, the American Medical Student Association (AMSA) assessed the conflict of interest policies of medical schools and concluded that the policies of the majority of the schools that responded either lacked important elements or were unlikely to influence behavior (AMSA, 2008b).[1] Whether or not one agrees with how AMSA rated the policies, the actual texts of the policies (available at or through the AMSA website) reveal considerable variability, which is consistent with the findings of this report. Members of the U.S. Congress have strongly criticized physicians and researchers who have failed to report substantial financial relationships with industry, as they were required to do, and have proposed that pharmaceutical and medical device companies be required to report publicly their payments to physicians (see, e.g., Grassley [2008b, 2009]). Also in response to concerns about the nature of financial ties between physicians and industry and the lack of disclosure of such ties, Massachusetts enacted legislation in 2008 that requires companies to report payments to physicians, researchers, and medical societies and further provides for a marketing code of conduct

[1] In AMSA's assessment, 9 medical schools received a rating of A and 19 received a rating of B for their policies; 44 schools received a rating of F (18 for the contents of the policies that they submitted, 9 for their refusal to submit policies, and 17 for their lack of a response after repeated requests). Another 46 schools had policies under revision. (The numbers of schools are based on the ratings listed as of February 13, 2009, at http://www.amsascorecard.org/.) The project's methodology, included the rating system, is available at http://amsascorecard.org/methodology and states that "[e]ach policy was graded by two independent assessors, blinded to the institution of origin. Any differences in scoring between the two assessors were resolved by a consensus process. The assessors received formal training in the use of the scoring system, independently evaluating and coming to a consensus on five training policies before beginning to evaluate the medical school policies."

that will prohibit or limit certain of these payments (Wallack, 2008; Lopes, 2009).

This chapter outlines the basic elements of conflict of interest policies, reviews empirical data about the characteristics and consequences of those policies, and concludes with recommendations. Much of the research and descriptive information located by the committee examined the policies of academic institutions and medical journals; but the recommendations apply broadly to all institutions engaged in medical research, medical education, clinical care, or practice guideline development. The specific elements of the policies may vary according to the size, complexity, and other characteristics of different types of institutions (e.g., academic medical centers, professional societies, patient advocacy groups, and nursing homes).

The focus in this chapter is on policies affecting individuals, primarily physicians and biomedical researchers (as explained in Chapter 1). Chapter 8 examines and makes recommendations about policies that govern institutional conflict of interest, which is defined to include the interests of senior institutional officials.

OVERVIEW OF CONFLICT OF INTEREST POLICIES

Most conflict of interest policies include the basic elements of the disclosure of financial relationships, the prohibition of certain relationships, and the management of conflicts of interest that have been identified. All of these elements are sometimes described under the general rubric of managing conflicts of interest.[2] Other common elements of conflict of interest policies include definitions, specification of who is subject to the policies, enforcement provisions, and identification of which officials or units within an organization are responsible for administering and monitoring conflict of interest policies and procedures. Depending on the circumstances and the type of institution, the person responsible for reviewing initial disclosures may be a department chair, the chair of a professional society committee developing practice guidelines, the editor or deputy editor of a journal, or the chair of a continuing medical education program. When an initial review identifies a possible conflict of interest, the case may be referred to a conflict of interest committee or a more senior official for further evaluation and response.

Building on Chapter 2, Box 3-1 outlines a conceptual model of the

[2] PHS rules refer to procedures to "identify and manage, reduce, or eliminate conflicting interests." Federal government policies for its employees are sometimes described in terms of the "'three-D' method of conflict of interest regulation, that is: disclosure, disqualification and divestiture" (Maskell, 2007, p. 3). Disqualification includes recusal from participation in a specific decision.

BOX 3-1
Model of Steps Used to Identify and Respond to a Conflict of Interest

Step 1 Obtain the disclosure of information about financial and other relationships that could constitute a conflict of interest.

No relationships reported: stop. Relationships disclosed: go to Step 2.

Step 2 Evaluate the disclosures—in light of the individual's responsibilities or specific activities (e.g., research, teaching, and patient care)—to determine whether a conflict of interest exists. If necessary, collect additional information to assess the likelihood of undue influence and the seriousness of possible harms.

No conflict exists: stop. Conflict exists: go to Step 3.

Step 3 Determine whether the relationship is one prohibited under institutional or other policies or whether the risks of the relationship are so serious that the individual should either eliminate it or forgo participation in the activity put at risk by the relationship.

Conflict elimination necessary: go to Step 5.
Elimination not necessary: go to Step 4.

Step 4 If management is appropriate, devise and implement a plan to manage the conflict. Go to Step 5.

Step 5 Monitor conflict elimination or management plan and assess adherence.

Plan followed. Plan not followed: go to Step 6.

Step 6 Determine the nature of the noncompliance and the appropriate response (e.g., education, penalty, or revision of the plan) and implement the response.

steps that institutions with a comprehensive conflict of interest policy and implementation strategy might follow when determining whether an individual has a conflict of interest and, if so, how to respond. It shows the elimination of an identified conflict of interest as an early step, although the committee's experience suggests that the elimination of a conflicting relationship is often considered a last option.

A given individual may be covered by several conflict of interest policies. For example, a medical school faculty member may have to understand and follow the policies not only of the medical school but also those of

several other institutions. Depending on his or her activities, these other policies might include those of a medical journal, a provider of continuing medical education, a professional society, or a federal advisory committee. If a faculty member is engaged in research to support an application for marketing approval of a medical product by the Food and Drug Administration (FDA), the researcher can expect the study's sponsor to ask for the disclosure of his or her financial interests related to the company and the investigational product so that the sponsor can submit the required information to the FDA (FDA, 2001). (A recent report by the Office of the Inspector General [OIG] of the U.S. Department of Health and Human Services criticized the administration of these policies and indicated that they were deficient in several respects [OIG, 2009].) Private organizations that fund research, such as the Howard Hughes Medical Institute, also may have conflict of interest policies, which they may oversee directly rather than following the practice of the National Institutes of Health (NIH) of delegating most administrative responsibility to the research institution (Cech and Leonard, 2001). In addition, the faculty of public institutions will likely be covered by state conflict of interest policies.[3]

The committee found few reviews or studies documenting and comparing the conflict of interest policies of institutions engaged in medical research, medical education, or clinical care. It found even less information about the implementation and effects of these policies. Most studies examine the policies of academic institutions, medical and scientific journals, or government agencies. Journal articles or news stories sometime report on individual professional societies and patient or consumer groups.

In addition, through its literature review, public meetings, and other information-collecting activities, the committee identified various examples of institutional policies.[4] Although these examples are not necessarily representative, they helped the committee better understand the nature of policy variability and, in some cases, the rationale for policy differences. Institutions differ considerably in the conflict of interest policy information that they make public on their websites; and even if they are available, online information is not necessarily comprehensive, clear, or current. Since the committee began work, a number of medical schools, professional societies, and other groups have announced changes in their conflict of interest

[3] The state of Washington recently changed its policies on the use of certain university resources for outside work for faculty and some other university employees to "encourage the ethical transfer of technology for the economic benefit" of the state (University of Washington, 2008).

[4] During the study, the committee benefited from initiatives by AMSA and the Institute on Medicine as a Profession to make medical center policies available online. These databases have been useful, although they are not complete, and many schools have indicated that they are updating their policies.

policies and practices. Thus, even relatively recent overviews of conflict of interest policies may be somewhat out of date.

DISCLOSURE: AN ESSENTIAL BUT INSUFFICIENT ELEMENT OF POLICY

Disclosure—that is, revealing to others information that may otherwise be private or confidential—is a frequent response to concerns about conflicts of interest in various sectors of society. Disclosure by physicians and researchers to their academic or other institution is essential because institutional officials cannot evaluate and respond to individuals' relationships with industry if they are not aware of them. Consistent with the conceptual framework outlined in Chapter 2, disclosures should provide sufficient information about the nature, scope, duration, and monetary value of relationships to allow institutions to assess the risk that secondary interests might unduly influence judgments about research, clinical care, education, or other primary interests.

The committee distinguished disclosure to the physician's or researcher's institution from disclosure beyond the institution, for example, to patients, research participants, or the public.[5] One rationale for disclosure—especially public disclosure—is the deterrence of questionable or inappropriate relationships. As Supreme Court Justice Louis Brandeis (1914) famously expressed it, "sunshine is said to be the best of disinfectants." In a similar vein, the code of ethics of the American College of Physicians suggests that physicians considering the acceptance of gifts or other relationships with companies should ask themselves what their patients, the public, or their colleagues would think about the arrangement (Snyder and Leffler, 2005; see also Chapter 6). The *Nature* publishing group urges authors to avoid "any undeclared competing financial interests that could embarrass you were they to become publicly known after your work was published" (NPG, 2008).

Disclosure should have beneficial consequences if it leads physicians to avoid gifts, the use of industry-controlled presentations, and other relationships that create a risk of compromising their decisions and their professional independence. It could also have harmful consequences if physicians or researchers react by avoiding relationships that promote im-

[5] Some analyses refer to the provision of information to institutional officials as "reporting" and reserve the term "disclosure" for the revelation of information to members of the public (e.g., journal readers or patients) (see, e.g., AAMC [2001]). In contrast, some policies refer to reporting of information to external groups. This report follows the common usage (including in federal policies and guidance) and applies the term "disclosure" to the provision of information to internal parties as well as to external parties.

portant societal goals and that are accompanied by adequate measures to protect objective judgment.

What Is Known About Disclosure Policies, Practices, and Consequences

This section first reviews information about the characteristics of disclosure policies and practices. It then turns to evidence about the effectiveness of disclosure.

Presence and Scope of Disclosure Requirements

Medical schools The most recent comprehensive study of medical school conflict of interest policies reports on a 2003 AAMC survey of member schools (response rate of 82 percent) that was designed to characterize their policies and assess the extent to which they were consistent with the association's 2001 recommendations on conflict of interest in clinical research (Ehringhaus and Korn, 2004).[6] It found considerable variation. Almost all (95 percent) of the respondents reported that their policies covered all research involving human participants regardless of the funding source.[7] Sixty-eight percent of the schools used the PHS threshold ($10,000)[8] for individuals to disclose certain financial interests to the institution, whereas 27 percent reported a lower threshold. For elements not required by the PHS regulations, more than 60 percent of the respondents requested disclosure to the institution of equity in nonpublicly traded companies, regardless of the percent share (61 percent) or the estimated valuation (64 percent). The majority requested the disclosure of royalty income either above a certain threshold (38 percent) or regardless of the amount (33 percent).

In addition to requiring disclosure to the institution, policies may also require that financial relationships or conflicts of interest be disclosed to individuals who might be affected by the relationship. These might include research colleagues, research participants, journal readers, students, or

[6] The committee also reviewed several earlier studies for additional context and understanding of policy evolution (see, e.g., Cho et al. [2000], Lo et al. [2000], and McCrary et al. [2000]).

[7] In 2004, the Government Accountability Office reported that 79 percent of universities responding to their survey said that they had a single conflict of interest policy that covered all research. This is consistent with the recommendation of the AAU Task Force on Research Accountability that "all research projects at an institution, whether federally funded, funded by a non-federal entity, or funded by the institution itself, should be managed by the same conflict of interest process and treated the same" (AAU, 2001, p. 5).

[8] The PHS regulations state that individuals do not need to report "salary, royalties or other payments that *when aggregated for the Investigator and the Investigator's spouse and dependent children* over the next twelve months, are not expected to exceed $10,000" (NIH, 2008a, question C6, emphasis added). A similar rule applies to the disclosure of equity interests.

TABLE 3-1 Percentage of Medical Schools Requiring Further Disclosures for Researchers with a Significant Financial Interest in Their Research

Further Disclosure Required	Percentage of Medical Schools
To research participant in informed consent forms	74
To sponsors or funders of the research	65
To editors of journals to which papers or reports of research are submitted	64
In oral presentations of research results	60
In multicenter trials, to investigators, sponsors, and other institutional review boards participating in the trial	42
Other	23

SOURCE: Adapted from Ehringhaus and Korn, 2004.

patients. Again, the AAMC survey showed variation in medical school policies (Table 3-1).

A study by Weinfurt and colleagues (2006b) also reported on variations in disclosure policies. Forty-eight percent of medical schools had policies that mentioned the disclosure of researchers' financial conflicts of interest to research participants. The policies varied in what information was to be disclosed.

Medical and scientific journals The International Committee of Medical Journal Editors (ICMJE) has proposed Uniform Requirements for Manuscripts Submitted to Biomedical Journals that include explanations and provisions about conflicts of interest (ICMJE, 2008). The ICMJE website lists several hundred journals that follow these requirements, but the group does not verify the extent to which a journal does so. The World Association of Medical Journal Editors (WAME) has also made recommendations on conflict of interest policies (WAME, 2008).

Even journals that adopt conflict of interest policies may not apply them equally to industry-funded journal supplements that present papers from a conference or collections of papers on a particular topic. These supplements are generally not peer reviewed and have been criticized for including articles of lower quality (Bero et al., 1992; Rochon et al., 1994). The National Library of Medicine will not cite and index articles from certain types of sponsored supplements unless they include specific disclosures about "any financial relationship the guest editors and authors have with the sponsoring organization and any interests that organization represents, as well as with any for-profit product discussed or implied in the supplement and/or individual articles" (NLM, 2007, unpaged).

Journals may also vary their policies for review articles and editorials

or may not apply their policies to review articles and editorials, which arguably offer more room for bias than original research articles. For example, a 2004 editorial in the *Journal of the American College of Cardiology* stated that the editors generally decline publication of review articles disclosing industry input out of concern for external influence and subtle bias (DeMaria, 2004). Editors of another journal initially declared that they would not accept review articles written by authors with conflicts of interest and then decided that it would accept such articles if the conflicts were not significant (e.g., they involved payments that were less than $10,000) (Drazen and Curfman, 2002).

Two recent analyses found considerable variability in the conflict of interest policies of medical and scientific journals. Cooper and colleagues (2006b) found that 93 percent of biomedical journals reported that they had conflict of interest policies applicable to authors, 46 percent reported that they had policies applicable to reviewers, and 40 percent reported that they had policies applicable to editors. Fifty-seven percent reported that they published disclosures for all articles. Earlier studies reported that the percentage of biomedical journals with disclosure policies was lower (see, e.g., McCrary et al. [2000] and Krimsky and Rothenberg [2001]). Ancker and Flanagin (2007) were able to locate online conflict of interest policies for only 33 percent of 84 "high-impact, peer-reviewed" journals in 12 scientific disciplines, but a subsequent survey found that 80 percent of the 49 responding journals reported that they had policies in place.

Journals vary in whether they give specific guidance to authors regarding what financial relationships or conflicts of interest must be disclosed. Ancker and Flanagin (2007) found that 68 percent of journals provided examples of conflicts of interest and 46 percent defined the term. The committee's review of a convenience sample of journal policies revealed differences in the specificities of the policies. One journal advises simply, "[a]uthors are required to disclose any sponsorship or funding arrangements relating to their research and all authors should disclose any possible conflicts of interest" (AJN, 2008). In contrast, the *New England Journal of Medicine* states that disclosures are to include "all of the authors' relationships with companies that make products studied or discussed in the article, companies that make related products, and other pertinent entities with an interest in the topic" (NEJM, 2008). Some journals ask authors about several specific types of relationships and also ask them to indicate explicitly if they have no relationships. One journal's manuscript agreement form asks authors to certify that their manuscript has not been sponsored by a commercial entity and that if their manuscript includes no acknowledgments, it means that nonauthors have made no substantial contribution to it (AFMI, 2008).

Professional societies and patient advocacy groups The committee found no published reviews of the disclosure policies of professional societies. It examined a convenience sample of professional society documents and websites and found considerable variation in the content and accessibility of those policies. (Unlike professional society codes of ethics or codes of conduct, disclosure policies do not apply to members generally but are limited to individuals holding positions of responsibility, for example, officers or members of policy-making committees.) Some societies had disclosure forms with a simple, open-ended question about relevant relationships, whereas other forms included specific categories of relationships and required that respondents either report such a relationship or check a box stating that they had none. The policies of some professional societies that develop clinical practice guidelines are discussed further in Chapter 7.

The committee did not attempt to conduct a systematic review of the policies of patient advocacy and disease-specific groups. It found little information on such policies in its initial search of organizational websites and other resources. To the extent that these groups engage in activities such as the development of clinical practice guidelines or the provision of accredited continuing medical education, many of the recommendations in Chapter 7, in this chapter, and elsewhere in this report will apply.

Disclosure by Companies of Payments to Physicians

District of Columbia, Maine, Massachusetts, Minnesota, Vermont, and West Virginia require pharmaceutical manufacturers to report their financial relationships with physicians; and a number of other states are considering such requirements (Wallack, 2008; Lopes, 2009; MedPAC, 2009). Minnesota and Massachusetts make the information public. Vermont requires the state's attorney general to make an annual public report based on the information that the pharmaceutical manufacturers have disclosed. Two states also require the reporting of payments by pharmaceutical manufacturers to hospitals and nursing homes. One state requires medical device companies as well as pharmaceutical companies to report payments to physicians. In general, state policies are relatively new, and their implementation and effectiveness have not been formally assessed.

Some pharmaceutical and device companies have voluntarily acted to disclose publicly certain of their payments to physicians (see Chapter 6). The specific details of company plans vary and appear to be evolving as the discussion of public reporting of payments continues. Several companies have been required to make such public disclosures as a condition of settlements with the U.S. Department of Justice (Demske, 2008; see Chapter 6 for additional discussion). In 2007, bills were introduced in the U.S. Congress to establish a requirement for companies to report publicly

their payments to physicians (S. 2029 and H.R. 5605, 110th Congress). As discussed in the final section of this chapter, the Medicare Payment Advisory Commission (MedPAC), which advises the Congress on a range of Medicare policy issues, has recommended a more comprehensive policy for company reporting of payments (MedPAC, 2009).

Time Frame for Disclosure

For employees and others who are involved with an institution for an extended period, disclosure policies generally require an initial disclosure and then periodic (e.g., yearly) disclosures as well as interim disclosures when new relationships arise or when specific events occur (e.g., the submission of a new grant proposal or an application to license intellectual property). For researchers, policies may require the disclosure of financial ties before a study begins (e.g., to university administrators and institutional review board members), during a study, (e.g., to the research team, students, or research subjects), and after the study is completed (e.g., to journal editors when papers are submitted for publication in peer-reviewed journals).

The conflict of interest policies that the committee reviewed varied considerably in the time periods for which disclosure is required. Typically, policies require the disclosure of relationships that are current or that occurred during the previous year. Some policies ask about relationships that are pending, in negotiation, or expected in the next 12 months. The PHS regulations for grantees do not specify a reporting period, except that in determining whether financial relationships exceed the $10,000 threshold for reporting, researchers must consider individual and family financial relationships projected for the next 12 months.

Some organizations require disclosure for periods longer than the previous year (e.g., the American Thoracic Society requires disclosure for the previous 3 years [ATS, 2008] and the *Journal of the American Medical Association* requires disclosure for the previous 5 years [Flanagin et al., 2006]). The requirements may vary by type of relationship. For example, the policy of the American Society of Clinical Oncology specifies disclosure within 2 years for certain relationships (e.g., honoraria and consulting arrangements) but not for others (e.g., research funding) (ASCO, 2007).

Administrative Burden of Disclosure Policies

Disclosure to multiple organizations with various policies can clearly be burdensome for individuals who have received multiple grants, write many papers, serve on various committees and advisory panels, and make many continuing medical education presentations. The committee found little em-

pirical information on the administrative burden of disclosure or other elements of conflict of interest policies for either individuals or institutions.

A 2007 faculty burden survey undertaken for the Federal Demonstration Partnership reported that respondents assigned conflict of interest monitoring an average burden rating of about 1.8 (with a rating of 1 being no burden and 5 indicating a great deal of burden), whereas grants progress reporting received a rating of 3.4 (with a rating of 3 being some burden) (Decker et al., 2007).[9] Some other government-led initiatives to streamline regulatory policies and practices mention conflict of interest policies and practices but generally do not identify them as a critical issue or problem.[10]

The committee found examples of efforts to make it easier for individuals to comply with disclosure policies. For example, to assist their employees in determining whether they have a relationship with a "substantially affected organization" (as described in NIH intramural conflict of interest policies), NIH has developed a searchable list of such organizations (http://ethics.od.nih.gov/topics/sao/sao-list.aspx). Similarly, to help committee members identify and report pertinent relationships, some federal advisory committees and at least one professional society (the American Society of Clinical Oncology) have developed lists of for-profit companies that make products that might be affected by committee decisions on a particular issue (ASCO, 2008).

[9] The response rate for the survey, which was directed to faculty at major research institutions, was less than 40 percent. The Federal Demonstration Partnership, which involves 10 federal agencies and approximately 100 institutional recipients of federal funds, is a cooperative initiative whose goal is to reduce the administrative burdens associated with research grants and contracts (http://thefdp.org/). An earlier partnership survey found that conflict of interest monitoring was cited among the tasks for which respondents received the least institutional assistance (Wimsatt et al., 2005).

[10] For example, the Research Business Models subcommittee, which is under the Committee on Science of the National Science and Technology Council, has, among other priorities, the development of "specific guidance or regulations concerning institutional financial conflicts of interest, and to resolve differences in conflict of interest interpretations and terms and conditions of Federal grant awards" (http://rbm.nih.gov/priorities/sa3.htm). At NIH, the Clinical and Translational Science Awards (CTSA) program has established a research ethics oversight committee, which has in turn created a work group on conflict of interest policies to survey CTSA sites and gather information on policies. The NIH initiative to "reengineer the clinical research enterprise" does not feature conflict of interest policies as part of its assessment of clinical research policies (http://nihroadmap.nih.gov/clinicalresearch/overview-policy.asp). Nonetheless, the presentation to the IOM committee by NIH Director Elias Zerhouni stated that improving conflict of interest administration for grantees was important to NIH (Zerhouni, 2007).

Accuracy and Completeness of Disclosures

Although most organizations are reluctant to publicize violations of their policies, instances of incomplete and inaccurate disclosure periodically make news. For example, in 2008, investigations by U.S. Senate Finance Committee staff led to a front-page story in the *New York Times* on the failure of three Harvard faculty members to disclose in full—even after they were asked to file amended disclosure forms—the substantial payments that they had received from pharmaceutical companies over the period from 2000 to 2007 (Harris and Carey, 2008; see also Grassley, 2008b). (The Senate committee staff obtained the data through separate inquiries to companies and medical schools and then compared the responses.) In some cases, it appeared that the disclosures that had been omitted involved companies whose products the researchers were investigating. The present Institute of Medicine (IOM) committee understands that one of the questions about these cases is whether the institution's disclosure policy actually requested all the information specified in the PHS regulations, but further details of investigations into the matter had not been released as this report was being completed.

Although the IOM committee did not examine the issue, it notes that journalists often fail to report the sources of funding for research that they publicize (see, e.g., Cook et al. [2007]). In addition, journalists themselves may report stories involving pharmaceutical, medical device, or biotechnology companies with which they have conflicts of interest, for example, the acceptance of company-sponsored travel or prizes for reporting or the reliance on opinion leaders suggested and paid by companies (see, e.g., Schwartz et al. [2008]).

Newspapers have also publicized examples of failures by NIH intramural scientists to disclose relationships with industry as required by agency rules and examples of scientists who have maintained relationships that would likely not have been approved under the rules. For example, journalists reported the apparent failure of dozens of NIH scientists to disclose relationships with industry, although only 20 or so actual cases were confirmed in a subsequent investigation performed by NIH (see, e.g., Weiss [2005]). Another story reported on a researcher who was found by an internal investigation to have "actively" chosen in "at least 38 separate instances . . . not to adhere to policies because it was inconvenient or time-consuming; he knew it was likely his participation [with the pharmaceutical companies] would have been disapproved" (Willman, 2006). A report from the OIG of the U.S. Department of Health and Human Services criticized the agency for not obtaining adequate documentation for the outside financial relationships that it explicitly approved (OIG, 2005).

Although cases of nondisclosure may receive considerable publicity,

the frequency and extent of deliberate or unintentional underreporting is unknown, and alternative methods for improving the accuracy of disclosure have not been tested.[11] Weinfurt and colleagues (2008c) reported incomplete and inconsistent disclosure in articles on coronary stents published in 2006. They found that 75 authors disclosed at least one relationship with a pharmaceutical company or other organization, but for only 2 of those authors was that relationship disclosed in all of the authors' articles. Weinfurt and colleagues did not, however, take into account whether some journals either did not require certain relationships to be disclosed or chose not to publish the disclosures with an article. If a national system of public disclosure of payments by pharmaceutical, medical device, and biotechnology companies is enacted, institutions could verify the disclosures that they receive.

Monitoring and Enforcement

The committee found no peer-reviewed studies on the monitoring or enforcement of disclosure requirements specifically or conflict of interest policies generally. One study of journal policies reported that of the 28 journals that had a disclosure policy for authors, 13 had policies that were silent on procedures for responding to an author's failure to make a disclosure (Ancker and Flanagin, 2007). As a means of informing readers and also of promoting adherence to their policies, journals from time to time report on cases in which authors did not disclose pertinent relationships with industry (see, e.g., Petersen [2003], Armstrong [2006], Chabner [2008], DeAngelis and Fontanarosa [2008], and Ross et al. [2008]). They sometimes require these authors to write a letter to the editor acknowledging the error (see, e.g., Kurth et al. [2006], Matteson and Bongartz [2006], and Henschke and Yankelevitz [2008]).

A few journals have more stringent penalties. For example, after problems with authors' failures to disclose, the journal *Environmental Health Perspectives* adopted a policy that (1) imposes a 3-year ban on the publication of articles by authors who have "willfully failed to disclose a competing financial interest" and (2) provides for the publication of a retraction if the editors conclude that they would have rejected the article initially had they known of the undisclosed relationships (EHP, 2009). In general, however, journals decline "to become the COI [conflict of interest] investigative

[11] Although the committee did not locate assessments of different disclosure forms, two studies have assessed procedures for obtaining information about the contributions of the listed authors to a submitted manuscript (e.g., analysis of data and drafting of the manuscript) (Marusič et al., 2006; Ivanis et al., 2008). One found that open-ended forms yielded significantly less information than forms with explicit response categories (Marusič et al., 2006). Those studies were also replicated using different disclosure formats.

squad" and "count on . . . authors to be forthright with us" (Goldsmith, 2006, p. 2148). In addition to exposing offenders to negative publicity, journal reports about failures to make the necessary disclosures may have other consequences for authors. In one case, the Mayo Clinic required investigators found to have made incomplete disclosures to a journal to undergo an internal investigation and to participate in remedial activities (Matteson and Bongartz, 2006).

AAMC has recommended that academic medical centers specify the possible sanctions for noncompliance with policies governing conflicts of interest in research involving human subjects and then regularly assess compliance (e.g., through internal audit mechanisms and other self-evaluation strategies) (AAMC, 2001). A 2003 AAMC survey, which did not review actual policies but which relied on responses to survey questions, found that 80 percent of respondents reported that their policies had sanctions for violations (Ehringhaus and Korn, 2004).

The AMSA assessment cited earlier suggests variability in the oversight and enforcement of conflict of interest policies. On the basis of a review of medical school policies, the report categorized institutions as either having or not having provisions for oversight and enforcement (AMSA, 2008b).[12] Of the 58 schools that initially responded to the survey and supplied written policies for review, 55 percent were characterized as having oversight policies, 45 percent were characterized as having enforcement policies, and 34 percent were characterized as having both.[13]

A report by the Council on Government Relations (COGR; an association of research universities) also suggested inadequacies in the procedures used to promote compliance with conflict of interest policies. It concluded:

> While virtually all research universities and organizations have written policies governing individual financial conflicts of interest in research-related areas, most institutions are still developing formal and informal education programs to assure that the policies are well understood and that compliance by affected faculty and researchers is fully in place. (COGR, 2002, unpaged)

[12] As described in footnote 1, two independent, trained reviewers read the policies that the medical schools submitted (without identifying information) and then rated them according to specified criteria. For the administration and oversight categories, the reviewers gave yes or no answers to these two questions: Is it clear that there is a party responsible for general oversight to ensure compliance? Is it clear that there are sanctions for noncompliance?

[13] Some schools that at first failed to provide relevant policies have since supplied or indicated that they will supply additional information (personal communication, Gabriel Silverman, AMSA Scorecard Director, AMSA, June 6, 2008).

Effectiveness of Disclosure Policies

A physician's or researcher's disclosure of financial relationships, either to the institution or to a broad audience, is a necessary step for identifying and avoiding or managing conflicts of interest, but it also has important limitations. First, disclosure alone does not resolve conflicts of interests or prevent the harms that may result from a conflict. Second, some evidence suggests that the disclosure of a conflict of interest may have little effect or may even be counterproductive in some circumstances.

Experimental studies in psychology Several experimental studies in psychology raise general questions about the effectiveness of disclosure of a conflict of interest and even suggest the potential for unintended adverse consequences. For example, in two sets of experimental studies of disclosure by individuals in an advice-giving role, researchers concluded that the disclosure of conflicts of interest significantly benefited the advice givers but hurt the interests of those to whom the disclosure was made (Cain et al., 2005). Although the authors of those studies noted that the findings should be treated as no more than evidence that disclosure can potentially have unintended consequences, they caution that most of the mechanisms that produce the effects found are likely to exist except when the recipients of the advice are savvy and experienced.

The disclosure of financial relationships can also be ineffective for reasons unrelated to those discussed in the studies just cited. For example, when a large amount of information is disclosed (e.g., on prescription inserts or in certain informed-consent forms), critical points can get lost among less important details. That is, the disclosure of more information may, in some situations, be counterproductive. (Appendix D provides an additional review of the relevant psychological research.)

Journal readers Two randomized studies suggested that the disclosure of an author's financial interests can reduce journal readers' perceptions of the believability and importance of research reports. One study found that journal readers found an article to be less "interesting, important, relevant, valid, and believable" when the authors were disclosed to be employees of a (fictitious) pharmaceutical company instead of employees of an ambulatory care center (Chaudhry et al., 2002, p. 1392). The other study found that readers rated "importance, relevance, validity, and believability" lower if it was disclosed that the authors had stock holdings rather than nothing to disclose and if it was disclosed that the authors had received a research grant from a company rather than nothing to disclose (Schroter et al., 2004).

Research participants Several studies have suggested that disclosures to prospective research participants of investigators' financial relationships have little impact on decisions to participate in research (see, e.g., Kim et al. [2004], Hampson et al. [2006], Weinfurt et al. [2006a, 2008a,b]), and Gray et al. [2007]. In a survey of participants in clinical trials for the treatment of cancer, more than 70 percent of the respondents would still have enrolled in the clinical trial even if the researcher had financial ties to the pharmaceutical company sponsoring the trial or had received royalty payments (Hampson et al., 2006). Only 31 percent wanted the researcher's financial interests to be disclosed.

Other studies have described hypothetical clinical trials to individuals with chronic diseases and varied the kind of information presented about the researchers' financial relationships with the sponsors of the trial (Weinfurt et al., 2008a,b). The respondents' willingness to participate in a hypothetical clinical trial varied substantially, depending on the type of financial relationships. The respondents were more concerned when the researchers held equity in the sponsoring company than when the researchers received a payment to cover the cost for each participant in the study. Trust in the researchers decreased somewhat after the disclosure of equity interests. Other factors, such as the benefits and the risks of the clinical trial, had more of an impact on the respondents' decision to participate in the trial.

These studies of research participation can be criticized on methodological grounds for not explaining the risks of conflicts of interest (e.g., bias in the conduct of research and the failure to publish negative findings) or not linking the responses to actual decisions about research participation. It is not known whether the respondents might have been more concerned about researchers' financial relationships with sponsors if they had been given background information about the risks.

Patients Several surveys in the 1990s suggested that many patients were not aware of industry gifts to physicians but were relatively tolerant of most gifts. One study suggested that, overall, patients were considerably more likely than physicians to believe that gifts from pharmaceutical companies influenced physician practice, but only 54 percent of patients were aware of such gifts (Gibbons et al., 1998; see also Blake and Early [1995] and Mainous et al. [1995]). On a different but related issue, one study of the disclosure of information about physician payment mechanisms in managed care plans found that disclosure did not reduce patients' trust in their physicians and might even have "a mild positive impact" on trust (Hall et al., 2002, p. 197; see also Pearson et al. [2006]). Other studies have suggested that patients are interested in information about how their physicians were paid or, more generally, what financial incentives the patients'

health plan imposes on participating physicians (Kao et al., 2001; Levinson et al., 2005). (Chapter 6 briefly discusses conflicts of interests created by physician payment methods.)

PROHIBITING OR ELIMINATING CONFLICTS OF INTEREST

Prohibition as a Preventive Strategy

Some institutions have conflict of interest policies that prohibit certain financial relationships outright because their risks are considered to greatly outweigh any potential benefits. As described further in Chapter 5, a 2008 report by AAMC recommended that academic medical centers prohibit a wide range of financial relationships with industry. Several medical schools (e.g., the University of Pittsburgh, the University of Texas Medical Branch at Galveston, and the University of California system) have policies prohibiting gifts, and some prohibit participation in company speakers bureaus (e.g., the University of Massachusetts, the Mayo Clinic, and the University of Louisville).[14]

Also in 2008, the Pharmaceutical Research and Manufacturers of America revised its *Code on Interactions with Healthcare Professionals* to state that companies should not offer pens, notepads, and other non-educational items to health care professionals. In Massachusetts, recent legislation gives these guidelines legal force by requiring the public health department to establish "regulations for a marketing code of conduct . . . that shall be no less restrictive than the most recent version" of the codes on interactions with health care providers of the Pharmaceutical Research and Manufacturers of America and the Advanced Medical Technology Association (see Chapter 111N, section 2, Massachusetts Senate No. 2863). Thus, policies may forbid both the giving and the receiving of certain gifts. (Implementing regulations were published in March 2009 [see Lopes, 2009; see also Chapter 6].)

Some conflict of interest policies prohibit certain relationships but allow exceptions. For example, federal policies covering NIH and other employees of the U.S. Department of Health and Human Services state that its employees may not have an "employment relationship" with drug, medical device, or biotechnology companies; grantees; health care providers; or health insurers. They also may not be paid to teach, speak, write, or edit for such organizations. The policies allow for prior approval of certain

[14] Except for the information for the University of California system (University of California, 2008), this information comes from policies summarized by AMSA (2008b) and then checked by reference to documents on the AMSA website or through links to those documents.

exceptions if prohibition of a relationship is not "necessary to ensure public confidence in the impartiality or objectivity with which HHS programs are administered" (HHS, 2005, p. 51572).

To cite another example, AAMC recommends that medical schools set a "rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research . . . [except when] the circumstances are compelling" (AAMC, 2001, p. 7). (The "rebuttable presumption" concept is taken from the law and refers to assumptions that are taken to be true unless they are explicitly and successfully challenged in a particular case.) A compelling circumstance would exist, for example, if a researcher with a conflict of interest has unique expertise or skill with implanting and adjusting a complex new medical device and this expertise is needed to carry out an early-stage clinical trial safely and competently. Generally, some kind of management plan would then be devised. This approach is discussed further in Chapter 4.

Prohibition or Elimination as a Management Strategy

The options for managing conflicts of interest discussed in the next section all permit the continuation of a relationship in some situations in which a conflict exists. In certain cases, however, continuation of the relationship is not acceptable because of the severity of the threat that it poses to the primary interest. In that case, an individual with a conflict of interest may agree to end the relationship that creates the conflict, for example, by selling company stock, resigning from a company governing or advisory board, or ceasing to consult for a company. Alternatively, an individual with a conflict of interest may decide to forgo participation in such an activity rather than eliminate the financial relationship in question. Some relationships with conflicts of interest may be difficult to eliminate, for example, the relationship with a spouse because of a conflict of interest involving the spouse's employment.

The committee found no systematic assessment of the adoption, implementation, or effectiveness of policies prohibiting certain financial relationships with industry. Somewhat more information is available on the management of conflicts of interest.

EVALUATING AND MANAGING CONFLICTS OF INTEREST

The management of a conflict of interest is necessary when an assessment of an individual's financial relationships identifies a conflict of interest and when disclosure alone is inadequate but elimination of the conflict is a requirement that is too severe. AAMC has recommended that medical schools create conflict of interest committees to make these assessments and

propose management strategies, when appropriate. Professional societies may rely on senior staff or members (e.g., chairs of guideline development panels) for assessments of relationships and responses.

The management options will vary depending on the nature of the conflict and the activity under consideration. Examples of management options follow:

- asking an individual with a conflict of interest to reduce the value of a financial relationship so that it falls below a threshold amount;
- requiring that an individual forgo participation in committee votes, deliberations, or decisions about a topic related to that individual's conflict of interest;
- modifying the design of a research project or having a researcher with no conflict of interest serve as the principal investigator; or
- providing an observer to monitor and evaluate the content of a continuing education course conducted by an individual with a conflict of interest for bias.

What Is Known About Management Policies, Practices, and Consequences

The available data suggest that institutions vary considerably in how they oversee and manage conflicts of interest. Ehringhaus and Korn (2004) reported that 76 percent of medical schools responding to the 2003 AAMC survey had established, as recommended by AAMC, a standing committee to evaluate conflict of interest disclosures, and 21 percent included at least one committee member from outside the institution, also as recommended by AAMC. Eighty-one percent of the medical schools responding to the AAMC survey allowed investigators with a significant financial interest to conduct research involving human participants when compelling circumstances exist. Only 61 percent of the respondents indicated that they had adopted the rebuttable presumption or a similar strategy, and only 26 percent indicated that they had a definition of the compelling circumstances or similar conditions that would allow rebuttal of the presumption.

Even within a single university system, conflict of interest practices may vary (see, e.g., several studies of the University of California system reported by Boyd et al. [2004], Lipton et al. [2004], and Boyd and Bero [2007]). For example, within the University of California system, some campuses have standing committees that meet at least monthly, whereas others convene committees on an ad hoc basis (Boyd et al., 2004). Some but not all campuses include committee members from outside the campus community. Some committees are structurally linked through centralized computer systems to other oversight bodies, such as the campus institu-

tional review board, whereas others do not share financial information within the university unless they are asked to do so.

Assessing Risks of Disclosed Relationships

If an organization's policy requires more than just disclosure, the next step is a review to assess whether a disclosed relationship constitutes a conflict of interest and what risks or potential benefits the relationship presents. As described earlier, a department chair or similar individual may review disclosures and identify conflicts of interest or may refer potential conflicts of interest for further review by a conflict of interest committee or other group or official.

The IOM committee found little systematic investigation of the institutional practices and or criteria used to assess financial relationships and conflicts of interest. One small qualitative study of a university system found that individual conflict of interest committees made decisions on a case-by-case basis, taking into account multiple considerations (e.g., the extent and the nature of the financial relationship and the type of research and research design) and following no rigid formula (Boyd and Bero, 2007). The committees rarely made a direct assessment of the likelihood that an investigator would act improperly.

Some specific advice on assessing the severity of conflicts of interest is available. The AAMC-AAU report on conflict of interest in research involving human subjects describes several considerations that should be taken into account when the risks and possible benefits of allowing an investigator with a conflict of interest to participate in such research are assessed (AAMC-AAU, 2008) (Box 3-2).[15] It also discussed the application of these questions to 10 illustrative cases.[16]

The FDA has developed guidance on whether an individual with a conflict of interest should be allowed to serve on one of its advisory committees (FDA, 2008b). Some of the questions roughly correspond to the considerations identified in Chapter 2. For example, one question is whether a "particular matter" under consideration by a committee

> will have a direct and predictable effect on the financial interests of any organization? . . . A "predictable" effect . . . is a real, as opposed to a

[15] In general, this report follows the practice of recent IOM reports in referring to research participants rather than research subjects (see, e.g., IOM [2001, 2003, 2004]; see also NBAC [2001]). When quoting and sometimes when referring to AAMC and other reports that employ the latter usage, the report follows their practice.

[16] The 2002 report by COGR also included an analysis of cases, and some university educational materials likewise feature analyses of case studies as a means of providing an understanding of the risks presented by financial relationships (see, e.g., Columbia University [undated]).

BOX 3-2
Risks and Potential Benefits to Consider in Assessing the Severity of a Researcher's Conflict of Interest

- Risks to human subjects: to what extent could the conflict of interest increase the risk (considering the role specified for the researcher with the conflict of interest in recruiting or treating research participants)?
- Risks of bias in data collection, analysis, and reporting: to what extent could the researcher with the conflict of interest compromise the integrity of the data?
- Risks to reputation: to what extent could the reputation of the researcher with the conflict of interest or the researcher's institution be damaged, even if the institution establishes a plan to manage the conflict?
- Expected benefits to medicine, science, and public health: how do the expected benefits of allowing the research to proceed compare with the risks?

SOURCE: Adapted from AAMC-AAU, 2008.

> speculative, possibility that the matter will affect the financial interest. It is not necessary, however, that the magnitude of the gain or loss be known, and the dollar amount of the gain or loss is immaterial. . . . [M]ost potential advisory committee recommendations pertaining to marketing status, labeling, post-marketing requirements, and device classification or reclassification would ordinarily have a "direct and predictable effect" on financial interests. . . . Financial interests that ordinarily will not be affected in a direct and predictable manner include a grant or contract between an organization and the employee's university to conduct research on a product that is not the subject of the particular matter before the advisory committee or a competitor product. (FDA, 2008b, pp. 10–14)

FDA rules involving clinical investigators also take into consideration aspects of the study design—for example, the use of objective end points, blinding, or the participation of multiple investigators—that might reduce the potential of an investigator's interests to bias the study results (21 CFR 54.5). (The rules cover financial disclosures and the management of the relationships of clinical investigators in studies that companies plan to use to support FDA approval of the marketing of a medical product.)

Management Strategies

Survey data indicate that medical schools employ various strategies to manage conflicts of interest in research (Table 3-2). Disclosure to some outside party seems to be a common and preferred response to an identi-

TABLE 3-2 Percentage of Medical Schools Citing Different Management Policy Options When Researchers Have a Significant Financial Interest in Their Research

Policies Suggested or Required by Organizations Permitting Participation After a Conflict of Interest Is Identified	Percentage of Medical Schools
Monitoring the research project	87
Eliminating the investigator's significant financial interest	83
Disclosing significant financial interests to human subjects on the consent form	86
Using either internal or external data safety monitoring boards	54
Regularly auditing the informed consent and research subject enrollment process	51
Involving a patient representative during the consent and enrollment process	26
Involving a patient representative during recruitment of research subjects	22

SOURCE: Adapted from Ehringhaus and Korn, 2004.

fied conflict of interest (see, e.g., Boyd and Bero [2000] and Ehringhaus and Korn [2004]).

One analysis of cases in which researchers disclosed their financial relationships found that university conflict of interest committees determined that 26 percent of the cases reviewed involved conflicts of interest that needed management (Boyd et al., 2004).[17] The three most commonly applied management strategies were requiring disclosure in publications and presentations (40 percent of the managed cases), appointing an oversight committee to protect the interests of students involved in the project (21 percent of the managed cases), and eliminating the relationship during the period of the project (22 percent of managed cases). The least common management approach was eliminating the conflict of interest or prohibiting the research.

The IOM committee is not familiar with any evaluations of the implementation or the consequences of different management strategies. This is a significant deficit. At one of the committee's public meetings, an experi-

[17] Financial ties were most often with pharmaceutical companies or biotechnology companies. Across the seven campuses involved in the analysis, payment for consulting activities accounted for 54 percent of the financial disclosures, equity holdings accounted for 38 percent of the disclosures, payment for talks accounted for 14 percent, scientific advisory board membership accounted for 13 percent, membership on a company's board of directors accounted for 12 percent, and being a company founder accounted for 7 percent. Over this period, investigators became more likely to have multiple financial ties with a single company, such as financial ties through the receipt of consulting income, honoraria, and stock.

enced clinical researcher questioned the strategy of appointing an oversight committee to monitor research involving an investigator with a conflict of interest (Benet, 2008). In that scientist's view, so many decisions need to be made in the course of a research project that it is not realistic to expect a faculty member to want to or have time to participate in the close and effective monitoring of another faculty member's research. In addition, monitoring imposes costs that might be judged in some cases to exceed the potential benefits.

In Chapter 9, the committee recommends the development and funding of a program of research on conflict of interest. The outcomes of conflict of interest policies, both positive and negative, would be a key issue for consideration in such a program of research.

Knowledge and Attitudes Regarding Conflict of Interest Policies

A few studies suggest that many investigators do not understand their institution's conflict of interest policies and may be skeptical about them. In one in-depth qualitative study of clinical investigators, less than half of the respondents could accurately describe their institution's policies (Boyd et al., 2003). In addition, many respondents believed that the individual investigator, the professional society, and the public at large—not the university—were the appropriate monitors of conflicts of interest. Although many respondents recognized the general risks associated with conflicts of interest, they believed that they were personally not at risk for bias resulting from financial relationships, a common finding in the research reviewed for this report.

In another, web-based survey of researchers at a single medical center (response rate of less than 40 percent), 17 percent of the respondents were not aware of the institution's conflict of interest policies and 60 percent could correctly describe at least one (but not all) of the policies (Lipton et al., 2004). With respect to consequences, 43 percent of the respondents believed that the policies discouraged a faculty member's ability to start new companies, 31 percent believed that the policies discouraged consultation with companies, and 21 percent believed that the policies discouraged sponsored research but another 21 percent thought that they encouraged such research. Although 14 percent believed that the school's policies hindered their own research agenda, 82 percent believed that it had no effect. Among the respondents who actually had a financial relationship that was subject to committee review, 91 percent said that they were satisfied with how the review was handled, but some of the remaining 9 percent who were not satisfied had very negative attitudes toward the process.

Policy Dissemination and Education Strategies

AAMC has advised academic medical centers to provide education and training about their conflict of interest policies to all faculty, staff, students, and trainees (AAMC, 2001). In 2002, NIH reported that the policies of some research institutions were difficult to locate and were sometimes interspersed in various other institutional policies on issues such as ethics, purchasing, and consulting. It recommended that institutions present their conflict of interest policy "as a complete, self-contained document with citations and web links to supporting policies, procedures, and Federal and state regulations, as appropriate" (NIH, 2002, unpaged). The Office of Extramural Research at NIH recently created an online tutorial on conflict of interest and other materials intended to help investigators understand and comply with NIH policies (the tutorial is available at http://grants.nih.gov/grants/policy/coi/).

The IOM committee's review of the policies and other information on conflict of interest from academic medical centers and universities showed that they vary considerably in the informational resources that they make available to their faculty and staff. Some schools provide online resources that are intended to help people easily find relevant institutional policies and resources (including individuals who can answer questions about the policies). Examples include the University of Minnesota, which has a web-based training module on conflict of interest (University of Minnesota, 2008), and Stanford University, which has frequently asked question units on conflict of interest and related university policies, as well as a quiz and other resources (Stanford University, undated).

A professional society may publicize its policies by publishing them in the society's journal(s). It may also make the policies accessible to the public on its website.

Compliance and Enforcement

The earlier discussion of compliance with and the enforcement of disclosure policies reviewed information about compliance with and the enforcement of policies as they apply to individuals. The discussion in this section focuses on the extent to which research institutions follow applicable PHS rules.

A 2002 review of a sample of grantee policies undertaken by the NIH Office of Extramural Research found that institutional policies often did not reflect the requirements of the PHS regulations (NIH, 2002). In 2007, NIH reported on 18 targeted site reviews regarding grantee compliance with PHS conflict of interest policies. It found no instances of intentional noncompliance and concluded that the institutions that it visited generally

had "implemented the Federal regulation thoughtfully and with diligence" (NIH, 2007). It did, however, report some problems with timely and consistent reporting and suggested the need for improvements in several areas, including educational and enforcement procedures, the clarity of the forms used to report conflicts of interest, and definitions.

A 2008 report by the OIG of the U.S. Department of Health and Human Services criticized NIH's oversight of grantee institutions (OIG, 2008). Although NIH accepted some of the report's suggestions, it rejected taking a more active oversight role, particularly requiring and reviewing detailed conflict of interest reports from institutions. Doing so would "effectively, if not legally, transfer the locus of responsibility for managing [financial conflicts of interest] from the grantee institution to the Federal Government" (Zerhouni [2008] in OIG [2008, pp. 20–21]). The OIG disagreed that collection of the information would usurp grantee responsibilities, and it argued that without some details about the nature (and not just the existence) of the conflicts that were identified, NIH lacks important information that it needs to oversee and enforce PHS regulations.

Also in 2008, NIH announced the development of and began testing an electronic reporting and tracking tool that that would allow grantee institutions to prepare and submit required conflict of interest reports and search past reports. Consistent with one of the OIG report's recommendations, the tool would also provide a central web-based location for grantee conflict of interest reports received across NIH (Bravo, 2008; see also NIH [2008b]). In addition, NIH has initiated procedures and training to ensure proper NIH staff oversight of conflict of interest issues involving grantees.

The IOM committee identified some publicly reported instances of NIH enforcement of PHS policies. For example, in October 2008, after congressional inquiries and reports of apparent major inaccuracies in a researcher's financial disclosures to Emory University, NIH suspended a $9 million grant for a study led by the researcher and instituted special conditions for the institution's other studies conducted with the support of NIH grants (Harris, 2008; Kaiser, 2008). Subsequently, the university removed the individual from his post as department chair and significantly restricted his outside activities (Shelton, 2008).

RECOMMENDATIONS

Empirical data on conflict of interest policies are limited, have methodological shortcomings, and tend to focus on academic institutions. Some institutions do not make their policies easily accessible. Institutions also revise their policies, which limits the usefulness of older studies. Nonetheless, the available evidence points to substantial variations in institutional requirements for the disclosure of financial relationships or conflicts of interest.

Variations exist in who is required to report on a conflict of interest, when reporting is required, and what relationships and what details about these relationships are to be reported (e.g., the exact amounts of payments rather than payments above a threshold or within dollar categories). Variations also exist in what relationships are prohibited, what criteria are considered in evaluating financial relationships, what strategies are employed when a conflict of interest is identified, and what is done to monitor and promote adherence to policies. These extensive variations raise concerns that some institutions may not have sufficient data to make determinations about the extent and the nature of an individual's financial relationships or to judge the severity of a conflict of interest. Some institutions may also lack adequate procedures for evaluating and eliminating or managing identified conflicts.

The committee expects that there are many explanations for the variations in policies, including the press of other issues demanding attention, a reluctance to propose changes that may spark controversy and dissension, and cultural traditions that vary in how restrictions on the pursuit of personal gain are viewed. Absent outside pressures and oversight, variation in conflict of interest policies may encourage an unhealthy competition among institutions to adopt weak policies and shirk enforcement. It may also aid investigators who want to avoid restrictions on their pursuit of secondary financial interests.

The recommendations presented in this chapter and in this report are intended to discourage such undesirable institutional and individual behavior but not to damage beneficial collaborations. If institutions do not act voluntarily to strengthen their conflict of interest policies, such inaction may prompt government regulation. (The recommendations below focus on individual conflicts of interest. Chapter 8 presents recommendations on conflicts of interest at the institutional level.)

Adopting Conflict of Interest Policies

The committee's first recommendation deals with institutional basics: the adoption of a policy and the creation of a conflict of interest committee. The details of the policies may vary, depending on an institution's mission and other characteristics, but certain features are fundamental to credible and meaningful conflict of interest policies.

RECOMMENDATION 3.1 Institutions that carry out medical research, medical education, clinical care, or practice guideline development should adopt, implement, and make public conflict of interest policies for individuals that are consistent with the other recommendations in this report. To manage identified conflicts of interest and to

monitor the implementation of management recommendations, institutions should create a conflict of interest committee. That committee should use a full range of management tools, as appropriate, including elimination of the conflicting financial interest, prohibition or restriction of involvement of the individual with a conflict of interest in the activity related to the conflict, and providing additional disclosures of the conflict of interest.

Recommendation 3.1 calls on all institutions that conduct medical research, offer medical education, provide clinical care, or develop practice guidelines to adopt comprehensive conflict of interest policies for their employees. These policies should cover all those whose decisions and judgments affect their institution's missions and primary interests. Consistent with the committee's charge, the recommendation refers only to relationships with pharmaceutical, medical device, and biotechnology companies. In practice, individual institutions will design their policies to cover other relevant relationships. These might include consulting or speaking arrangements with health insurance companies, leadership positions with professional organizations, teaching at other institutions, and service on government advisory committees. (As described in Chapter 2, some of these relationships may present conflicts of commitment.)

So that those who rely on academic medical centers, medical journals, professional societies, patient advocacy groups, and other institutions may assess an institution's conflict of interest policies, the policies should be publicly available, for example, on the institution's website. Although the details will vary, it is also important for institutions to disseminate and explain their policies to those who are subject to them. Strategies might include the provision of an education module and the inclusion of a set of frequently asked questions.

Recommendation 3.1 also calls on academic medical centers and other institutions to create conflict of interest committees to manage conflicts of interest involving individuals. This reiterates a recommendation of AAMC, which found in its 2003 survey that not all medical schools reported that they had such committees. Professional societies and other institutions would also benefit from conflict of interest committees that would implement their policies. For example, a conflict of interest committee for a professional society would review conflicts that arise in different aspects of the society's work, including the development of clinical practice guidelines and the conduct of society meetings and educational programs. (For some very small institutions, the formation of a formal committee may not be necessary if the relevant responsibilities are clearly defined and assigned to appropriate staff or, possibly, volunteers.) A conflict of interest committee should bring experience and consistency to evaluations of financial relation-

ships with industry and decisions about those relationships, although the specific details (e.g., how risks and potential benefits are assessed and what management options are considered) may vary, depending on the activity in question. The recommendation mentions monitoring as an activity of the conflict of interest committee, but in practice, the details of monitoring may best be handled by an administrative unit, with the conflict of interest committee providing more general oversight.

Improving Information for Identifying and Evaluating Conflicts of Interest

Disclosure as an Element of Policy

The disclosure of financial relationships with industry is only one part of a comprehensive conflict of interest policy, but it is nonetheless an essential step. Unless institutions know about these relationships, they cannot assess them and determine whether additional steps—such as the elimination or management of a relationship—are necessary. Recommendation 3.2 identifies key features of policies on disclosure. Recommendations in Chapters 4, 5, 6, and 7 provide guidance about the elimination or management of conflicts of interest in the contexts of medical research and education, patient care, and practice guideline development, respectively.

RECOMMENDATION 3.2 As part of their conflict of interest policies, institutions should require individuals covered by their policies, including senior institutional officials, to disclose financial relationships with pharmaceutical, medical device, and biotechnology companies to the institution on an annual basis and when an individual's situation changes significantly. The policies should

- **request disclosures that are sufficiently specific and comprehensive (with no minimum dollar threshold) to allow others to assess the severity of the conflicts;**
- **avoid unnecessary administrative burdens on individuals making disclosures; and**
- **require further disclosure, as appropriate, for example, to the conflict of interest committee, the institutional review board, and the contracts and grants office.**

Conflict of interest policies should cover individuals who have discretion in the conduct of research and educational activities, the provision of clinical care, and the development of clinical practice guidelines. (Senior officials are also covered by Recommendation 8.1 in Chapter 8, which examines institutional conflicts of interest.) Disclosures should be made

at least annually and more often if an individual's situation changes. They should also be updated during the year if an individual's situation changes significantly, for example, because an existing relationship expands (e.g., a faculty member who is a company consultant is also appointed to the company's governing board) or because a new relationship (e.g., a new consulting arrangement) is created that is relevant to a specific activity (e.g., participation in a panel developing a clinical practice guideline). In addition to requiring disclosure of conflicts of interest to the institutional review board and the other entities listed in the recommendation, policies may also cover additional disclosures, for example, to entities responsible for continuing medical education program oversight.

Elements of a disclosure policy may vary depending on the institution, but the disclosures should be sufficiently specific to support the identification of conflicts of interest and an evaluation of their severity. For example, if information on the dollar value of relationships is reported in categories rather than specific amounts, the highest categories should reach into the hundreds of thousands of dollars. The committee recommends the elimination of minimum thresholds for individual reporting of financial relationships. As discussed earlier in this chapter, the 1995 PHS regulations specify a $10,000 threshold, which applies to the individual and his or her spouse and dependent children. Most PHS grantees have adopted this threshold, although approximately one-quarter require reporting regardless of the dollar value of the relationship. The committee recognizes that elimination of the minimum threshold would add to the burden both for those reporting and for those reviewing relationships but believes that it is important to increase the accuracy of reporting and provide institutions with a more complete picture of an individual's financial relationships across different reporting categories (e.g., consulting, advisory committee service, and speaking). The committee also notes research that suggests that even small payments may put an individual at risk of unconscious bias. In their joint report on conflict of interest in human subjects research, AAMC and AAU also recommended removing minimum (de minimis) thresholds (AAMC-AAU, 2008). NIH should seek revisions in the PHS regulations to eliminate the threshold, but NIH grantees should act without waiting for such revisions.

Greater Consistency in Disclosure Policies

The committee recognizes that the objective of achieving sufficient specificity in disclosures may sometimes be in tension with the objective of minimizing the administrative burdens of disclosure. To the extent that the consensus process proposed in Recommendation 3.3 is successful, it may help resolve these tensions by promoting greater consistency across institutions. Greater consistency should simplify the demands on those who

must understand and comply with the disclosure requirements of multiple institutions.

RECOMMENDATION 3.3 National organizations that represent academic medical centers, other health care providers, and physicians and researchers should convene a broad-based consensus development process to establish a standard content, a standard format, and standard procedures for the disclosure of financial relationships with industry.

To achieve greater consistency in institutional disclosure requirements, Recommendation 3.1 calls for a broad-based national consensus development process. This undertaking would be convened by national organizations representing academic medical centers, other health care providers, physicians, and researchers and would also include representatives of professional societies; consumer and patient advocacy groups; accreditation, certification, and licensing agencies; medical journals and organizations of medical journal editors; health plans and insurers; government agencies, including NIH and the FDA; and organizations with expertise in database development and management. The process used by AAMC to develop its recent recommendations on relationships with industry in medical education offers one model for the process, although the task would be narrower and more detailed in its focus on definitions of the financial relationships to be disclosed, reporting formats, and similar matters.

The committee appreciates that different disclosures may be required for different purposes. For example, the information that a medical journal needs from the authors of a manuscript differs from the information that a government agency may require for members of an advisory panel. For similar institutions (e.g., for medical journals as a category and for similar government advisory panels as a category), the objective would be to develop a consensus on a common format.

A major task for the consensus development process would be to agree on the categories of relationships that need to be disclosed and the type of information about each relationship that is needed to evaluate it. Consulting is an example of a category that needs further specification. That term can cover relationships that range from the provision of promotional or marketing support to a company to the offering of objective technical advice on scientific advances, products in development, or research study design. The institution of standard categories, definitions, and similar agreements should reduce confusion, misunderstandings, and misinterpretations.

In technical terms, the task for the consensus group would be to specify the elements for a relational database, including the definitions and attributes of these elements. Once the elements are specified, the expectation is that software developers would create programs that physicians and

TABLE 3-3 Candidate List of Categories of Financial Relationships with Industry to Be Disclosed

Research grants and contracts
Consulting agreements
Participation in speakers bureaus
Honoraria
Intellectual property, including patents, royalties, licensing fees
Stock, options, warrants, and other ownership (excepting general mutual funds)
Position with a company
Company governing boards
Technical advisory committees, scientific advisory boards, and marketing panels
Company employee or officer, full or part time
Authorship of publications prepared by others
Expert witness for a plaintiff or a defendant
Other payments or financial relationships

researchers could use on their computers to enter, store, and update information on their financial relationships. The software would then format the information as needed for disclosures for various purposes (e.g., submission to an academic medical center or a medical journal). It would be similar to reference software that allows authors to format references to meet the specifications of different journals.

As a starting point, Table 3-3 presents a candidate list of basic categories of the relationships to be disclosed. Each requires further definitions, and some might require subcategories. The committee did not propose a specific format for the provision of information about these relationships. It is important, however, that any format promote completeness and specificity, for example, by requiring individuals to check one box if they have a particular relationship, to check another box to declare explicitly that they do not have the relationship, and to provide certain details about an indicated relationship (e.g., its value, the company involved, and the nature of the work).

In addition to the categories of relationships to be disclosed, the consensus process needs to address several other key questions. For example, what details of relationships need to be reported (e.g., the amount of income and the name of the company)? How should amounts be reported? Would it be preferable to have individuals making disclosures check a box indicating the range of income from a relationship or should they provide specific dollar amounts? Will a single time frame (e.g., the relationships in existence during the previous 12 months) be adequate for all purposes? How should the financial relationships of close family members (e.g., spouses or domestic partners, dependent children, and parents) be considered?

Company Reporting of Payments to Individuals and Institutions

Recommendations 3.2 and 3.3 involve disclosures by individuals to organizations. The next recommendation proposes requirements for companies. Several state laws and proposals for additional state or federal rules reflect concerns about inaccurate and incomplete disclosures. As discussed earlier, these laws and proposals vary, for example, in the types of companies and payments or relationships that they cover and in provisions for public reporting. In response to proposals for additional state and national legislation, several industry groups and individual companies have supported some form of company disclosure while seeking to minimize the administrative burdens of such reporting and to protect information that might reveal business strategies to competitors (Finance Committee, U.S. Senate, 2008). Recommendation 3.4 calls for a broad national reporting program.

RECOMMENDATION 3.4 The U.S. Congress should create a national program that requires pharmaceutical, medical device, and biotechnology companies and their foundations to publicly report payments to physicians and other prescribers, biomedical researchers, health care institutions, professional societies, patient advocacy and disease-specific groups, providers of continuing medical education, and foundations created by any of these entities. Until the Congress acts, companies should voluntarily adopt such reporting.

A national law covering company payments to physicians, researchers, and medical institutions would be a useful supplement to policies that require individual physicians, researchers, and others to disclose financial relationships to institutions. It should provide that company-reported payments be readily available on a searchable public website that allows the aggregation of all payments made to an individual or organization, although some personal identifying information might be restricted to protect individuals against, for example, identity theft. Such a database could help institutions and potentially others to monitor adherence to institutional disclosure policies. It would not substitute for institutional conflict of interest policies. It also would not eliminate conflicts of interest. One objective of drafting and implementing legislation and explaining it to the public and those affected would be to discourage the inference that all reported relationships are bad and to avoid harm to constructive collaborations.

The committee did not investigate program options and administration in detail, but it generally supports the approach to company reporting discussed by MedPAC during several public sessions in 2008 and presented in MedPAC's March 2009 report (MedPAC, 2008a,b,c,d, 2009). Consistent

with the committee's recommendation but in contrast to state policies and some other proposals for federal policy, MedPAC's proposal covers not only payments to physicians but also payments to a range of organizations, including medical schools, professional societies, and providers of continuing medical education. The committee's proposal would add payments to biomedical researchers. The MedPAC recommendation would add payments to pharmacies and pharmacists, health plans, and pharmacy benefit managers as well as payments by medical supply companies. Companies could include clarifying details about the context of a payment (e.g., specifying whether the payment is a research grant that covers all project costs and not just the investigator's salary). The committee considers these to be reasonable provisions for a company reporting program.

Implementing regulations would need to specify clear definitions and exact categories for the reporting of payments. The consensus-building activity proposed in Recommendation 3.3 could contribute to this specification and promote consistency with institutional disclosure policies.

As proposed by MedPAC, the database of company-reported information would be public, but the physician's National Provider Identifier (NPI) would not be given.[18] The entire database would be available to researchers who enter into confidentiality and data use agreements with the secretary of the U.S. Department of Health and Human Services. The database would be searchable by manufacturer; recipient name, location, and specialty (if applicable); type of payment; name of related product (if applicable); and year. The MedPAC report did not include an estimate of the costs to the government of creating and maintaining the systems but notes that the costs would be higher than those of state systems, only one of which makes the data public, but not in a searchable database.

In MedPAC's proposal, company reporting would be required annually, but reporting for a clinical trial could be delayed until the trial was publicly registered or until FDA approval related to the development of a new product was granted (but not later than 2 years after the payments were made). The national policy would preempt state policies, to the extent that they cover the same categories of payments and recipients, and would provide for civil penalties for noncompliance. Legislation introduced in the U.S. Congress in 2009 includes similar provisions on these points (Grassley, 2009).

In addition to the proposal on company reporting, MedPAC has also proposed that the Congress require hospitals and other providers to report (and the government to post on a public website) on physicians' direct

[18] The NPI is a unique number mandated by the U.S. government for most U.S. physicians that is available in a publicly accessible database that links it to the physician's name, practice location, business office location, license numbers, and other identifiers.

or indirect ownership shares in the facility (MedPAC, 2009; see further discussion in Chapter 6). The provision of recommendations on conflicts of interest arising from physician ownership of facilities was outside this committee's charge. The reporting program proposed by MedPAC would make considerable additional information available to researchers, patients, and others.

A discussion of the pros and cons of establishing a broader system of disclosure is presented in Appendix F.

Recommendations in the Following Chapters

The recommendations in this chapter call for institutions to adopt conflict of interest policies consistent with the recommendations in this report and for individual and cooperative institutional efforts and legislative actions to strengthen policies on the disclosure of individual and institutional financial relationships with industry. The next four chapters of this report offer additional recommendations related to policies and practices in the specific areas of medical research, medical education, patient care, and the development of clinical practice guidelines. Chapter 4 calls for institutions to generally bar researchers with a conflict of interest from conducting research with human participants except when the investigator's expertise is essential to the safe and rigorous conduct of the research. Chapters 5 and 6, among other recommendations, call for physicians and researchers to forgo and institutions to prohibit or end certain relationships with industry that present unacceptable risks of undue influence over professional decision making or a loss of public trust.

Chapter 7 includes recommendations for reducing industry influence in the development of clinical practice guidelines and increasing the levels of disclosure of organizational and individual financial relationships. Chapter 8 recommends that institutions establish policies at the board level to identify, limit, and manage institution-level conflicts of interest. The final chapter calls for a range of organizations to develop incentives to promote the institutional adoption and implementation of the policies recommended here. It also calls for the development of a research agenda to evaluate and guide improvements in conflict of interest policies and procedures.

4

Conflicts of Interest in Biomedical Research

Biomedical research provides discoveries that may lead to new or better tests and treatments that improve individual and public health. Patients, patients' families, physicians, other researchers, and policy makers need to trust that the design, conduct, and reporting of such research are unbiased and that the time and effort that they contribute to research will be used to advance science. Participants in clinical trials need to trust that they are not exposed to unnecessary risk. Conflict of interest policies should not only address concerns that financial relationships with industry may lead to bias or a loss of trust but should also consider the potential benefits of such relationships in specific situations.

Research partnerships among industry, academia, and government are essential to the discovery and development of new medications and medical devices that provide improved means for the prevention, diagnosis, and treatment of health problems. Historically, the federal government has taken the lead in supporting discoveries in basic science, whereas commercial firms have focused on the discovery of specific medicines and then their development through clinical trials to the regulatory approval of marketable products. (As discussed below, the development pathway for medical devices often differs from the pathway for pharmaceuticals.) Before 1980, the federal government held the patents resulting from publicly funded basic research, but very few patents were licensed for commercial development. In 1980, the U.S. Congress passed the Patent and Trademark Amendments of 1980 (P.L. 96-517, commonly known as the Bayh-Dole Act, after its sponsors). The law allowed institutions to patent discoveries resulting from federally funded research and to grant licenses for others to develop those discoveries. Universities may retain licensing and royalty fees, which they generally share with their scientists who developed the

patented discovery. Since the law's passage, patent licensing and other financial relationships linking medical researchers and research institutions with industry have expanded substantially (Schacht, 2008). Some scholars, however, have pointed to factors in addition to the legislation that may be associated with the historical increase in the numbers of patents, including a broadening of the criteria that allow materials to be patentable (particularly for life forms) and advances in biomedical research (see, e.g., Mowery et al. [2001, 2004] and Sampat [2006]; see also *Diamond v. Chakrabarty*, 447 U.S. 303 [1980]).

This chapter starts with a brief overview of some dimensions of university-industry collaborations in biomedical research and then summarizes data on the extent of the relationships between pharmaceutical, device, and biotechnology companies and academic research institutions and individual researchers. The next sections review concerns about these relationships and responses to those concerns. (Appendix E provides an additional discussion of the nature and importance of academic-industry collaboration in medical research.) Because many conflicts of interest at the institutional level emerge from research discoveries, the discussion of these conflicts and the responses to them presented in Chapter 8 is also relevant. The final section of this chapter offers recommendations.

COLLABORATION AND DISCOVERY IN BIOMEDICINE

The path from a scientific discovery to the marketing of a new drug, device, or biological product is typically long and complex and involves a diversity of expertise and resources. For example, basic researchers, often at academic medical centers and other research institutions, can identify new potential targets for therapies and new strategies for treatment, suggest additional diseases that may be able to be treated by existing and newly developed compounds, and suggest both how to target therapies to the patients who are the most likely to benefit and how to avoid particular treatments for patients at high risk for adverse events from those treatments. Scientists at the National Institutes of Health (NIH) also contribute to the discovery process, and important clinical research is undertaken at the NIH Clinical Center. In addition, basic scientists at biotechnology and pharmaceutical companies have made fundamental discoveries that have led to new therapies.

Scientists at pharmaceutical companies can help identify or develop drugs that may be active against new biological targets that have been identified by individuals who conduct basic research. These companies also have the critical ability to use good manufacturing practices to produce a candidate drug in sufficient quantities for clinical trials and then for large-scale commercial distribution, if the product is approved for marketing.

Furthermore, they have experience with the Food and Drug Administration (FDA) drug approval process, which includes extensive requirements for preclinical and clinical testing and for manufacturing. Finally, pharmaceutical companies also supply or raise the capital needed to fund the lengthy process of bringing a product to market. Medical device companies and biotechnology companies play analogous roles in translating discoveries made through basic research into products or services for medical and public health practice, although the specific details differ from those involved with the drug approval process. (Appendix E provides a more detailed discussion of the discovery and development process.)

The committee heard testimony that collaboration between academic and industry researchers in the drug discovery process can be mutually beneficial (Benet, 2008; Cassell, 2008). When a new disease mechanism is discovered, academic and industry scientists can work together to identify promising therapeutic targets and treatment approaches. Furthermore, academic researchers can inform industry when they identify potential new targets for chemical intervention. Drug companies can then quickly scan their chemical libraries to search for compounds with potential biological activity and describe what problems they have encountered as they have tried to identify the specific targets of those compounds. This begins the long process of applied chemistry, which is needed to identify a candidate drug.

Many examples illustrate that academic collaboration with pharmaceutical and biotechnology companies can lead to dramatic therapeutic advances that save lives and improve the quality of life. Particularly dramatic are those related to therapies for human immunodeficiency virus (HIV) infection. Collaborations contributed to delineation of the pathophysiology of the disease and the development of successive new classes of drugs, including reverse transcriptase inhibitors, protease inhibitors, and entry inhibitors (Braunwald et al., 2001). These advances have transformed a uniformly fatal illness into a chronic disease that people are now generally able to survive for decades. A few other examples include the following:

- an anticoagulant (abciximab), which is a monoclonal antibody against the platelet glycoprotein IIb/IIIa, that has been shown to prevent thrombotic complications of coronary angioplasty (EPIC Investigators, 1994; Tcheng et al., 2003);
- pulmonary surfactant, which improves survival in neonates with respiratory distress syndrome and which was developed by a number of academic researchers at different universities working in close collaboration with several pharmaceutical companies (personal communication, Jeffrey A. Whitsett, Chief, Section of Neonatology, Perinatal and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, December 9, 2008);

- rituximab, a monoclonal antibody against the CD20 marker on B cells, which is effective in patients with certain types of lymphoma and leukemia, rheumatoid arthritis, and multiple sclerosis and in preventing the rejection of transplanted organs (Maloney et al., 1997; Edwards et al., 2004; Hauser et al., 2008);
- bortezomib, a proteasome inhibitor, which improves survival in patients with multiple myeloma (San Miguel et al., 2008); and
- imatinib, a tyrosine kinase inhibitor, which has greatly prolonged the survival of patients with chronic myelogenous leukemia (Druker et al., 2006).

Compared with the drug development process, the development of complex medical devices tends to be a more continuous process of innovation and refinement that involves frequent alterations in device design, materials, manufacturing processes, or other characteristics. Examples of medical devices that have been developed as a result of close academic-industry collaborations include implanted defibrillators (Jeffrey, 2001), prosthetic heart values (Gott et al., 2003), and mechanical ventilators (Keszler and Durand, 2001). Advances in many technologies, such as pulse oximetry for the monitoring of anesthesia and phototherapy for the treatment of disease, highlight the results that may accrue from a combination of research collaboration and communication with senior clinicians about their experiences (Mike et al., 1996; Dicken et al., 2000; McDonagh, 2001; Severinghaus, 2007; Vreman et al., 2008).

Nevertheless, advances in medical devices may result in conflicts of interest. For example, the process of device refinement (particularly when the refinements are minor or are not associated with well-designed clinical studies) is at the center of controversies over whether some consulting arrangements between orthopedic surgeons and the manufacturers of orthopedic devices represent fair payments for technical services or are inducements for the surgeons to use the device.

To promote further progress in moving discoveries from basic science into successful products, NIH has developed major initiatives to strengthen early translational research, which focuses on transforming specific discoveries into clinically useful products or services (see, e.g., NIH [2008d] and CTSA [2009]). At academic centers, this research may involve populations of individuals with rare diseases or biological agents that do not have obvious commercial potential. Such research may, nonetheless, lay the foundation for companies to develop successful products or at least for company licensing of compounds or agents for which university research has provided proof-of-concept data but for which companies must take the next steps.

INDUSTRY FUNDING AND RELATIONSHIPS IN BIOMEDICAL RESEARCH

Growth and Magnitude of Industry Funding

Industry funding for biomedical research has been growing in recent decades and is now the largest source of funding for such research in the United States. Between 1977 and 1989, the proportion of the total funding for clinical and nonclinical research supplied by industry grew from 29 to 45 percent (Read and Campbell, 1988; Read and Lee, 1994). Between 1995 and 2003, the yearly figures (which are based on sources of information somewhat different from those for 1977 to 1985) ranged from 57 to 61 percent (Moses et al., 2005; see also Hampson et al. [2008]). This funding supports work in the laboratories of pharmaceutical, device, and biotechnology companies; contracts for research conducted by universities and other nonprofit research institutions; and contracts with commercial contract research organizations that carry out clinical trials in academic and private practice settings.

Extent of Academic-Industry Relationships

Industry relationships with academic biomedical researchers are extensive. A 2006 national survey of department chairs in medical schools and large independent teaching hospitals found that 67 percent of academic departments (as administrative units) had relationships with industry (Campbell et al., 2007b). In addition, 27 percent of nonclinical departments and 16 percent of clinical departments received income from intellectual property licensing. Among the department chairs, 60 percent had relationships with industry, including serving as a consultant (27 percent), a member of a scientific advisory board (27 percent), a paid speaker (14 percent), an officer (7 percent), a founder (9 percent), or a board member (11 percent) for a company. In some universities, companies fund individual departments, multidisciplinary research centers, or campuswide research programs (Bero, 2008).

For individual academic researchers, studies from the 1990s show that they have widespread relationships with industry. In a 1996 survey, 28 percent of life sciences faculty who conducted research received support from industry sources (Blumenthal et al., 1996a,b). The prevalence of support was greater for researchers in clinical departments (36 percent) than for those in nonclinical departments (21 percent). In a 1998 study, 43 percent of academic scientists in the 50 most research intensive universities reported receiving research-related gifts (independent of a research grant or contract) during the preceding 3 years (Campbell et al., 1998). The most

widely reported gifts received from industry were biomaterials used in research (24 percent),[1] discretionary funds (15 percent), research equipment (11 percent), and trips to professional meetings (11 percent). Among those receiving gifts, 66 percent viewed them as important to their research.

A study of disclosures at the University of California at San Francisco found that by 1999, approximately 8 percent of principal investigators at the institution reported personal financial ties to the sponsor of a particular research project (Boyd and Bero, 2000). Thirty-four percent of these involved temporary speaking engagements, 33 percent involved consulting relationships, 32 percent involved paid positions on a scientific advisory board or board of directors, and 14 percent involved equity in a firm (more than one type of involvement for a single research project was possible).

Although evidence is limited and not recent, some research suggests that faculty members who have research relationships with industry are more productive in certain respects than faculty who do not have such relationships. One study found that researchers in the former group are significantly more likely than researchers in the latter group to report that they are involved with a start-up company (14 versus 6 percent) or that they have applied for a patent (42 versus 24 percent), have had a patent granted (25 versus 13 percent), have a patent licensed (18 versus 9 percent), have a product under review (27 versus 5 percent), or have a product on the market (26 versus 11 percent) (Blumenthal et al., 1996a). That study also reported that these faculty reported that they had published significantly more articles in peer-reviewed journals in the previous 3 years than faculty without industry funding (15 versus 10 articles) (Blumenthal et al., 1996a). In general, a greater number of biomedical patents should benefit society, since patents are usually a key step in the development of new therapies or diagnostic tests. Likewise, greater publication productivity should, in general, advance scientific knowledge.

The associations reported above do not prove causality. Industry may fund scientists who are more productive or whose research has more commercial potential. Alternatively, industry may provide funding that allows scientists to be more successful commercially and academically, or such support may encourage funded scientists to be more active commercially.

CONCERNS ABOUT RELATIONSHIPS WITH INDUSTRY

Despite their benefits, relationships with industry create conflicts of interest that can undermine the primary goals of medical research. Where

[1] One reviewer of the report observed that companies view the provision of these proprietary materials as a service to the academic community and that they may, in any case, not have a mechanism for charging for them.

there are conflicts, legitimate and serious concerns can be raised about the openness of research and potential bias in the design, conduct, and reporting of research (see, e.g., Gross [2007]). Whether or not the conflicts actually lead to unwarranted secrecy or biased results in particular cases, they have the potential to threaten the reputation of the research enterprise if they are not avoided or identified and managed responsibly.

The review below does not cover marketing activities disguised as research, in particular, so-called seeding trials that companies design to change the prescribing habits of participating physicians rather than to gather scientifically valid information. These studies, which potentially expose study participants to risk without investigating scientifically significant questions, are discussed in Chapter 6.

Industry Funding of Research and Reduced Openness in Science

A fundamental tenet of academic science is that information, data, and materials should be shared. Such sharing could be at risk in academic-industry collaborations. A 2003 National Research Council report identified "the commercial and other interests of authors in their research data and materials" as major obstacles to information sharing (NRC, 2003, p. 1).

A 1995 survey of life sciences faculty in the 50 most research intensive institutions found that 14 percent of those with funding from industry reported that trade secrets had resulted from their research, whereas 5 percent of those without funding from industry did so (Blumenthal et al., 1996a). Trade secrets were defined as information that is kept secret to protect its commercial value. In some cases, this finding may represent the normal and necessary protection of key information prior to the filing of a patent on intellectual property, with the resulting enhanced opportunity for successful commercialization. (Unlike trade secrets, patents require the disclosure of information but protect property interests in a discovery for a defined period.) A 1993 study of academic genetics research found that faculty with research funding from industry were significantly more likely to delay publication of their research results by more than 6 months to allow the commercialization of their research (Blumenthal et al., 1997).

The situation may have changed since the 1993 study cited above because some basic science journals have adopted more stringent policies on data sharing and withholding (see, e.g., NRC [2003], NPG [2007], and Piwowar and Chapman [2008]). In any case, not only journals but also the research institutions themselves could better maintain the integrity of research to the extent that they adopt more stringent policies on data sharing.

A related concern involves access to data. In some industry-supported research, the investigator lacks full access to the study data and depends

almost entirely on company statisticians for analysis (Bombardier et al., 2000; Silverstein et al., 2000; Curfman et al., 2005). The conflict in such situations raises reasonable concerns about the integrity of the data. To address this problem, some journals have recently decided not to publish the results of studies funded by industry unless there is full access to the data and independent repetition of the data analyses by academicians or government employees not affiliated with the sponsor (DeAngelis et al., 2001). In addition, many universities have recently added a requirement for access to study data to the terms of their research contracts with industry.

Research Funding from Industry and Pro-Industry Findings in Published Research

Several systematic reviews and other studies provide substantial evidence that clinical trials with industry ties are more likely to have results that favor industry. One meta-analysis found that clinical trials in which a drug manufacturer sponsors clinical trials or the investigators have financial relationships with manufacturers are 3.6 times more likely to find that the drug tested was effective compared to studies without such ties (Bekelman et al., 2003).[2] Another meta-analysis that included non-English-language studies found that studies that favored a drug were four times more likely to be funded by the maker of the drug than any other sponsor (Lexchin et al., 2003). A more recent literature review found that 17 of 19 studies published since the preceding two meta-analyses reported "an association, typically a strong one, between industry support and published pro-industry results" (Sismondo, 2008, p. 112). Similarly, another review found that industry-funded studies were more likely than other studies to conclude that a drug was safe, even for studies that found a statistically significant increase in adverse events for the experimental drug (Golder and Loke, 2008).

In addition, a study of materials submitted to the FDA in support of successful new drug applications found that clinical trials with statistically favorable results were almost twice as likely to be published as industry-funded studies that did not have favorable results (Lee et al., 2008). Overall, the results of more than half of clinical trials submitted to the FDA in support of a new drug application remained unpublished more than 5 years

[2] "A study was included if it met the following criteria: (1) its stated primary or secondary purpose was to assess the extent, impact, or management of financial relationships among industry, investigators, or academic institutions; (2) it contained a section describing study methods; (3) it was written in English; and (4) it was published following the passage of the Bayh-Dole Act of 1989" (Bekelman et al., 2003, p. 455). "The main outcomes were the prevalence of specific types of industry relationships, the relation between industry sponsorship and study outcome or investigator behavior, and the process for disclosure, review, and management of financial conflicts of interest" (p. 454).

after approval of the drug. Furthermore, comparisons of information submitted to regulatory agencies with information on the same trials published in the medical literature have found changes in the ways that the results of the trials were reported so that the published results appeared to be more favorable than the results reviewed by regulatory agencies. Such selective reporting of trial results includes additions of favorable outcomes, deletions of unfavorable outcomes, and changes in the statistical significance of the outcomes reported (Hemminki, 1980; Melander et al., 2003; Chan et al., 2004a; Rising et al., 2008; Turner et al., 2008). Recent requirements for web-based reporting of clinical trial results are described below.

Other studies have found that research funded by industry was more likely to report conclusions that favored the sponsor's drug, even if the results did not in fact support such conclusions. For example, studies that have examined clinical trials involving specific clinical specialties or particular clinical problems have found an association between industry sponsorship and results that favor industry. Examples include clinical trials of statins for the treatment of elevated cholesterol levels (Bero et al., 2007), breast cancer studies (Peppercorn et al., 2007), clinical trials of new antipsychotic drugs (Heres et al., 2006), and various nutrition-related studies (Lesser et al., 2007; see also Perlis et al. [2005]).

Several possible explanations can be offered for the association between industry support and results that are favorable to the sponsor. First, pharmaceutical and biotechnology companies seek to invest in products that will be shown to be effective and safe; hence, compounds that enter clinical trials have been selected as being likely to succeed. (That is, for-profit companies may be more risk adverse than nonprofit sponsors and fund mostly studies that seem likely to produce favorable results.) Second, investigators might have become persuaded by their own research that a drug is efficacious and, as a result, develop financial relationships with trial sponsors to help promote the future clinical development or use of the drug. Third, industry studies might be less rigorously designed or designed in a way that will bias the findings in favor of a drug, leading to false-positive conclusions that an intervention is effective, or they might be well designed but not actually conducted according to the protocol (Bero and Rennie, 1996; Steinman et al., 2006). Fourth, sponsors may be more likely to fully publish the results of studies with favorable findings (Rising et al., 2008).

The findings of three systematic reviews do not support the suggestion that industry-sponsored trials are poorly designed. They concluded that the quality of industry-sponsored trials is comparable to that of studies funded by other sources (Bekelman et al., 2003; Lexchin et al., 2003; Hampson et al., 2008). The methodologies used in those assessments of the quality of trials did not, however, take into account such issues as the appropriateness of the control intervention, the clinical relevance of the research question,

and whether the findings of the studies were fully published (Lexchin et al., 2003; Hampson et al., 2008).

In addition, it is sometimes suggested that journals prefer to publish articles that report positive findings rather than equivocal or nonexistent relationships. Several studies, based on self-reports from the authors of unpublished studies, suggest instead that authors' decisions to not submit manuscripts with the findings of their studies account for the majority of unpublished studies (Dickersin et al., 1987, 1992; Dickersin, 1990; Easterbrook et al., 1991). Similarly, a more recent study—based on inquiries to investigators about trial results that were not published—suggested that "studies were not published because they were not submitted" (Rising et al., 2008, p. 1568).

Box 4-1 summarizes several incidents that have added to concerns about bias in the reporting of industry-funded studies. Most involve an alleged failure to publish negative findings from industry-sponsored clinical trials or long delays in publication. These incidents involved a number of pharmaceutical companies and different types of drugs. Sometimes the information became known only after legal proceedings led to the disclosure of confidential internal industry documents.

In addition, systematic reviews that look at meta-analyses rather than individual clinical trials as the unit of analysis also find an association between industry funding and conclusions that favor the sponsor's product. One study found that industry-supported reviews had more favorable conclusions, noted fewer reservations about the methodological limitations of the trials included, and were less transparent than reviews conducted by the Cochrane Collaboration.[3] All seven industry-sponsored reviews recommended the experimental drug without reservation, whereas none of the Cochrane Collaboration reviews did (Jorgensen et al., 2006). Another study, a review of meta-analyses of clinical trials of treatments for hypertension, found that meta-analyses conducted by individuals with financial ties to a single drug company were not more likely than meta-analyses conducted by individuals who received funding from other sources to have results that favored the sponsor's drug. Financial ties to a single company were, however, associated with favorable conclusions by the authors of the meta-analyses. Among meta-analyses conducted by individuals with financial ties to one drug company, 27 of 49 (55 percent) reported favorable *results* from the meta-analysis, but 45 of 49 (92 percent) reported favorable

[3] The Cochrane Collaboration describes itself as "an independent, nonprofit, international organization that develops and disseminates systematic reviews of health care interventions and promotes the creation and use of evidence to guide clinical and policy decisions" (see http://www.cochrane.org/docs/descrip.htm). It relies primarily on volunteers who conduct reviews according to specific standards. It has policies intended to limit bias and restrict financial conflicts of interest in its activities.

BOX 4-1
Examples of Biased Reporting in Clinical Research

In a pivotal trial of celecoxib for treatment of arthritis, only data on outcomes at 6 months were presented, even though the original protocol called for the trial to be of a longer duration and the outcomes at 12 months were available when the manuscript was submitted (Hrachovec and Mora, 2001). The outcomes at 6 months showed an advantage for the study drug, but the outcomes at 12 months showed no advantage compared with the use of the control drugs (Wright et al., 2001).

Published clinical trials suggest that selective serotonin reuptake inhibitors have a favorable benefit-risk profile in children with depression. When unpublished data were considered, the evidence indicated that the risks appeared to outweigh the benefits for all but one drug in this class (Whittington et al., 2004).

The results of trials of paroxetine that demonstrated an increased risk of teenage suicide or a lack of efficacy were not published. The data were revealed only after a lawsuit was brought against the manufacturer (Gibson, 2004).

The manufacturer of aprotinin, an antifibrinolytic drug used in cardiac surgery to decrease bleeding, withheld data that use of the drug increased the risk of renal failure, heart attack, and congestive heart failure (Avorn, 2006).

The results of a clinical trial that compared the use of ezetimibe plus a statin with the use of a statin alone in individuals with elevated cholesterol levels were not published until 2 years after the conclusion of the trial. The results showed no difference in carotid artery wall thickness in the two groups (Kastelein et al., 2008).

The results of a pivotal clinical trial of a blood substitute (PolyHeme) in patients undergoing elective vascular surgery were not released for 5 years after the trial was stopped by the sponsor. The trial showed significant increases in the rates of mortality and heart attacks in the group receiving the experimental intervention (Burton, 2006; Northfield Laboratories, 2006).

The manufacturer of an implantable cardioverter-defibrillator allegedly failed to report critical, potentially fatal design defects for more than 3 years (Hauser and Maron, 2005).

The manufacturer of a novel immune modulator for the treatment of HIV infection refused to provide a complete set of data to the investigators in a randomized clinical trial that showed that the investigational agent was ineffective (Kahn et al., 2000).

The manufacturer of a brand-name thyroid hormone attempted to block the publication of an article showing that a generic thyroid replacement therapy had bioavailability similar to that of the brand-name preparation (Rennie, 1997).

conclusions. The authors of the review suggested that there was a "discordance between the data that underlie the results and the interpretation of these data in the conclusions" (Yank et al., 2007, p. 1204).

Thus, although there is little direct evidence that industry sponsorship has led to deliberate skewing of the results or reporting, there are multiple cases in which industry sponsors have withheld important study results and in which the conclusions presented in the reports appear to overstate the study findings. The risk of undue influence in research exists. The risk is particularly relevant in clinical trials, when the prospect of direct harm to patients (as well as research participants) is a more immediate concern than is the case for most nonclinical research. In this case, conflict of interest policies may help prevent an erosion in public confidence beyond that which may result from research that documents bias or the withholding of data.

Ghostwritten research articles also raise concerns about bias as well as the ethics of author attribution. A conflict of interest is inherent in this practice when the industry sponsor has more control over the article than the nominal authors. Chapter 5 discusses ghostwriting and also participation on speakers bureaus and recommends that academic medical centers forbid faculty from accepting the authorship of ghostwritten articles and participation in speakers bureaus.

Terms of Research Contracts

Some academic health centers allow provisions in research contracts that give industry sponsors important control over the reporting of research findings. In a 2004 survey involving academic medical centers, 7 percent of respondents reported that their institution would allow industry sponsors to revise manuscripts or decide whether results should be published, and more than 5 percent reported that they were unsure about the answers to both questions (Mello et al., 2005a). Half allowed the sponsor to draft the manuscript, whereas only 40 percent prohibited that practice. Seventeen percent of the responding institutions reported disputes over control or access to the data from research. Such disputes also figured in some of the incidents cited in Box 4-1 (see, e.g., Rennie [1997] and Kahn et al. [2000]).

Funding arrangements with contract research organizations have also raised concerns about inappropriate control by industry sponsors (Bodenheimer, 2000; Mirowski and Van Horn, 2005; Shuchman, 2007; Lenzer, 2008). For example, the International Committee of Medical Journal Editors (ICMJE) has expressed concern about the role of contract research organizations that conduct the majority of industry-funded trials, often without the protections that many university research contracts require, including rights of access to the source data and rights to publica-

tion (Davidoff et al., 2001). Although the committee found no systematic assessments or comparisons of bias in research conducted by these organizations, any lack of such controls over unilateral industry influence raises concerns.

Issues Involving Research Participants or Students

As Chapter 3 discussed, academic medical centers vary in their policies on disclosure to research participants of investigator's conflicts of interest. It also noted that several surveys suggest that participants in clinical trials currently are not highly concerned about investigators' financial conflicts of interest. Most respondents report that their decision to enroll in a clinical trial would not be greatly affected by learning that the researcher had a financial relationship with the sponsor. Some respondents even believed that "a greater financial interest would make the investigator do a better job" (Weinfurt et al., 2006a, p. 903).

It is not clear, however, whether participants in clinical trials understand how conflicts of interest could potentially compromise study designs and the protection of research subjects or how they could contribute to bias in the reporting of the results—with the possible consequence being harm to future patients. Furthermore, it is not clear that it is reasonable to expect the average participant to understand these issues. In any case, even if research subjects are not worried about conflicts of interest, other important members of the public may be concerned. As noted in earlier chapters, the political and economic support of the research enterprise depends critically on the confidence of the opinion leaders in government, the media, and academia. When they have doubts about the integrity of the enterprise, that essential support may begin to erode.

Concerns have also been raised about how researcher conflicts of interest might affect their advice about or supervision of the research of medical students, residents, fellows, and junior faculty (AAMC, 2008b; AAMC-AAU, 2008). For example, in their recent report on conflict of interest policies in human subjects research, the American Association of Medical Colleges (AAMC) and the Association of American Universities (AAU) noted the potential for the exploitation of these individuals by conflicted senior investigators or advisers. Such exploitation is unethical and also has the potential to bias the design, conduct, and findings of research. Areas that may raise problems with undue influence include decisions about an individual's inclusion or exclusion from a research project; the focus, design, and conduct of a study; the publication of research findings (including the suppression of publication); and the treatment of intellectual property interests.

RESPONSES TO CONCERNS ABOUT CONFLICTS OF INTEREST IN RESEARCH

Limits on Conduct of Research by Investigators with Conflicts of Interest

As discussed in Chapter 1, much of the impetus for conflict of interest policies in universities stems from concerns about industry-funded biomedical research and investigators who have financial stakes in the outcomes of their research. In 1995, the U.S. Public Health Services (PHS) issued regulations that require institutions receiving PHS research funding to develop conflict of interest policies that require the disclosure and management of certain financial relationships between researchers and industry (see Appendix B). Chapter 3 noted reviews by NIH and others that questioned the adequacy of policy adoption and the implementation of the PHS regulations by research institutions, which in turn, raised additional concerns about the adequacy of government oversight of institutional compliance.

Because the PHS regulations were not specific on many issues and because some studies indicated shortfalls in their implementation, AAMC issued a report in 2001 with recommendations to help academic medical centers develop sound conflict of interest policies for research involving human subjects (AAMC, 2001).[4] A key policy recommendation called for institutions to establish a "rebuttable presumption" that researchers may not conduct research involving human participants when they have a financial stake in its outcome. This presumption can be rebutted when compelling circumstances justify the researchers' involvement.[5]

A 2003 AAMC survey indicated that only 61 percent of medical schools had adopted the rebuttable presumption in their policies (Ehringhaus and Korn, 2004). In addition, only a minority of the medical schools with such a policy had defined the compelling circumstances that would support an exception.

To further promote the adoption of conflict of interest policies governing research involving human participants, AAMC joined with AAU to issue a second report that offered additional guidance and support for

[4] As noted in Chapter 1, this report generally follows the practice of recent Institute of Medicine reports in referring to research participants rather than to research subjects.

[5] In the words of the AAMC report, the rebuttable presumption means that an "institution will presume, in order to assure that all potentially problematic circumstances are reviewed, that a financially interested individual may not conduct the human subjects research in question" (AAMC, 2001, p. 12). The report goes on to say that the "rule is not intended to be absolute: a financially interested individual may rebut the presumption by demonstrating facts that, in the opinion of the COI [conflict of interest] committee, constitute compelling circumstances . . . [and] would then be allowed to conduct the research under conditions specified by the COI committee and approved by the responsible IRB [institutional review board]" (p. 12).

policy development and implementation (AAMC-AAU, 2008). The report reemphasized the importance of the rebuttable presumption. It also presented informative case studies and a template for analyzing these cases to illustrate how different situations can be evaluated for the existence of a conflict of interest, the risks presented by the conflict, the options for eliminating or managing a conflict, and the compelling circumstances that might justify the participation of an investigator with a conflict of interest in research with human participants. Among the examples of risks cited in the template is the extent to which the reputation of the researcher with a conflict of interest or his or her institution could be damaged, even if a plan for managing the conflict is created and implemented.

Unlike the PHS regulations that cover both clinical and nonclinical research, the 2008 AAMC-AAU recommendations focused on clinical research. One recommendation did, however, call for medical center conflict of interest committees to review investigator conflicts of interests in certain nonclinical studies. Examples include those that can be "reasonably anticipated . . . to progress to research involving human subjects within the coming 12 months" (p. 9).

The committee found much less information and analysis about conflict of interest policies affecting nonclinical biomedical research than about policies affecting clinical research. Universities and medical schools may have different policies for different kinds of research or may apply different criteria to evaluate conflicts of interest in research that does not involve humans (as reported in Chapter 3). One university, however, recently adopted a conflict of interest policy that explicitly states that "[t]o protect against the risks that may accompany relationships with Interested Businesses, it is not ordinarily allowable for an Individual who has a Significant Financial Interest in an Interested Business to Conduct Research involving that Interested Business" (Columbia University, 2009).

Although an immediate risk to research participants does not exist in basic research, the potential for bias in basic research does exist. The result could be the initiation of clinical trials based on flawed basic science. In general, a weighing of risks against expected benefits should allow conflict of interest committees to apply policies while taking into account differences in clinical and nonclinical research, including differences in what constitutes a reasonable justification for researchers to be involved in research in which they have a financial stake.

Terms for Research Contracts

AAMC has not proposed comprehensive formal recommendations on the terms of research contracts with industry, but it has issued two reports with suggestions and recommendations that respond to concerns about

the integrity of clinical trials (Ehringhaus and Korn, 2004, 2006). The first report provides a checklist of topics, including publication rights and intellectual property, to be covered in research contracts. Among other elements, one or both reports call for contracts to explicitly grant researchers free access to study data, to include no restrictions on publication (except for a slight delay for sponsor review and possible filing of a patent application), and to require a good faith and timely effort to publish the results of research in a peer-reviewed journal.

Requirements to Register and Report on Clinical Trials

Congressional, journal editor, and other requirements for the registration of clinical trials are, in part, a response to concerns about conflict of interest in industry-sponsored research and research reporting. The registration of clinical trials and the provision of key details about the trial protocol and the data analysis plan ensure that basic methods for the conduct and analysis of the findings of a study as well as the primary clinical end points to be assessed and reported are specified before the trial begins and before data are analyzed. The substitution of ad hoc or secondary end points for primary end points and other important departures from the protocol can thus be detected in reports of the findings of a trial. Clinical trials registries also allow others to determine whether the results from a trial have not been presented or reported at all. Researchers carrying out critical literature reviews can then contact the investigators to try to obtain unpublished results. After ICMJE stated that clinical trial registration should be considered a prerequisite for the publication of research articles, the numbers of trials registered increased substantially (Zarin et al., 2005).

In 2007, the U.S. Congress expanded the types of clinical trials of drugs, biologics, and devices—and the kinds of information about these trials—that must be registered (P.L. 110-85). To further address the problem of withholding negative findings, it also required the creation of a link from the ClinicalTrials.gov registry to a database of reports of basic results for applicable trials.[6] The reported results are to include basic demographic and baseline information, findings for primary and secondary outcomes, and a point of contact.

[6] In addition, the Pharmaceutical Research and Manufacturers of America has coordinated the creation of a voluntary online resource to provide information to physicians about the results of clinical trials (see http://www.clinicalstudyresults.org/).

Study Methodology, Data Analysis, and Research Reporting

To the extent that the design of clinical trials is standardized and publicized, the implementation of conflict of interest policies is also assisted. Abuses and patterns of abuses can be more readily detected, which may make more evident the need for changes or reforms in the policies. Efforts to improve the design of clinical trials and other types of research stretch back decades and include a range of techniques, including the random assignment of subjects to intervention and control groups and the blinding of investigators and participants to treatment assignment. In addition, NIH has supported programs to train physician investigators to conduct rigorous clinical research. Experts in research methodology, statistics, and evidence-based medicine have developed techniques to limit bias in research and have codified standards and checklists for reporting research findings. These standards and checklists cover various types of studies, including clinical trials (see, e.g., Moher et al. [2001]), evaluations of clinical tests (Bossuyt et al., 2003), epidemiological studies (see, e.g., von Elm et al. [2007], but see also the comments of the editors of *Epidemiology* [Editors, 2007]), and meta-analyses (see, e.g., Moher et al. [1999] and Stroup et al. [2000]).

ICMJE now specifies a format for the reporting of results and refers authors to the CONSORT checklist for the reporting of the findings of randomized clinical trials (see, e.g., Moher et al. [2001], CONSORT Group [2007], and von Elm et al. [2007]) (Table 4-1). Standards for the reporting of methods and results help editors, reviewers, and readers assess the validity of a research paper. Studies suggest that these standards also improve the design and conduct of the research itself (see, e.g., Plint et al. [2005]).

In addition to these standards for the conduct and reporting of the results of clinical trials, the FDA has suggested that it is desirable for the data-monitoring committees for clinical trials to have statistical reports prepared by statisticians who are independent of the trial sponsors and clinical investigators (FDA, 2001). For industry-funded clinical trials "in which the data analysis is conducted only by statisticians employed by a company sponsoring the research," the *Journal of the American Medical Association* requires that a statistical analysis also be conducted by an independent statistician at an academic institution, such as a medical school, academic medical center, or government research institute, that has oversight over the person conducting the analysis and that is independent of the commercial sponsor (Fontanarosa and DeAngelis, 2008, p. 95; see also a review of opinions about this requirement in Rockhold and Snapinn [2007]).

TABLE 4-1 Checklist for Reporting Clinical Trials from CONSORT 2001 Statement

Item	Description
1	How participants were allocated to interventions (e.g., random allocation, randomized, or randomly assigned)
2	Scientific background and explanation of rationale
3	Eligibility criteria for participants and the settings and locations where the data were collected
4	Precise details of the interventions intended for each group and how and when they were actually administered
5	Specific objectives and hypotheses
6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations and training of assessors)
7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules
8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking or stratification)
9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
10	Who generated the allocation sequence, who enrolled the participants, and who assigned the participants to their groups
11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment; if done, how the success of blinding was evaluated
12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses
13	Flow of participants through each stage (a diagram is strongly recommended); specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe protocol deviations from study as planned, together with reasons
14	Dates defining the periods of recruitment and follow-up
15	Baseline demographic and clinical characteristics of each group
16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by intention to treat; state the results in absolute numbers when feasible (e.g., 10/20, not 50%)
17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval)
18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those that were prespecified and those that were exploratory
19	All important adverse events or side effects in each intervention group

TABLE 4-1 Continued

Item	Description
20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes
21	Generalizability (external validity) of the trial findings
22	General interpretation of the results in the context of current evidence

SOURCE: CONSORT Group, 2001 (see also Moher et al. [2001]).

Peer Review and Journal Policies on Disclosure

Peer review is a key step used to detect and reduce bias in publications and improve the quality of research reporting. Effective review depends on independent reviewers who are not biased by their own financial relationships with industry. As described in Chapter 3, journals vary in the extent to which they apply conflict of interest policies to reviewers. Meaningful peer review is also assisted by the previously described standards for the reporting of methods and data in manuscripts.

In response to concerns about the reporting of research results described earlier in this chapter, medical journals have moved toward increasingly specific requirements for disclosure of authors' financial interests (see ICMJE [2008] and WAME [2008] for the statements of two associations of medical journal editors). Still, as described in Chapter 3, journal policies remain variable. The completeness and accuracy of disclosures are continuing issues for medical journals as well as for academic medical centers and other institutions. These concerns have led to action in some states and recommendations for the federal government to establish a policy that requires companies to report payments to physicians, researchers, and institutions, as outlined in the preceding chapter. Chapter 3 includes a committee recommendation supporting such a program.

Issues Involving Research Participants and Students

As described in Chapter 3, AAMC recommended in 2001 and again in 2008 policies that require some form of disclosure of investigator conflicts of interest to research subjects, and many medical schools have adopted those policies. Chapter 3 also reviewed some of the findings from a set of coordinated research projects and activities to investigate the views of research participants and ways of informing them. This research is itself a major response to concerns about practical and ethical issues in managing conflicts of interest in research, for example, balancing the disclosure of

information with the design of an informed consent form and process that does not overwhelm research participants.

AAMC has also recommended the disclosure of investigator conflicts of interests to other members of the research team. It also advised that schools prohibit "agreements with sponsors or financially interested companies that place restrictions on the activities of students or trainees or that bind students or trainees to non-disclosure provisions" (AAMC, 2001, p. 20). In a later statement about the responsibilities of biomedical graduate students and their advisers, AAMC states that advisers should "recognize the possibility of conflicts between the interests of externally funded research programs and those of the graduate student" and should commit that those conflicts will not be allowed to interfere with the student's thesis or dissertation research (AAMC, 2008b, p. 6). The research adviser also agrees to discuss authorship policies and intellectual property policies related to disclosure, patent rights, and publication. In addition, in a series of questions that should be asked when assessing the risks of allowing an investigator with a conflict of interest to conduct research with human participants and the possibility that a conflict can be appropriately managed, the AAMC-AAU report includes questions about whether the "the roles of students, trainees, and junior faculty and staff [are] appropriate and free from exploitation" and whether special protections are needed for "vulnerable members" of the research team (AAMC-AAU, 2008, pp. 25 and 28, respectively). One protection might be to provide such individuals with access to independent senior faculty members for independent review and guidance when questions and concerns arise.

RECOMMENDATIONS

Relationships between industry and research institutions and researchers are common and are often mutually beneficial. They also serve society by generating valuable preventive, diagnostic, and therapeutic products. At the same time, these individual and institutional relationships have risks that could jeopardize the integrity of scientific research and conflict with the ethical conditions for the conduct of research with humans. Analyses indicate that they are associated with decreased openness in sharing data and findings, and cases in which negative findings are not published in a timely fashion or at all raise concerns. Some studies also suggest that meta-analyses sponsored by a single company tend to present conclusions favorable to industry sponsors even when the actual findings of the analyses are not favorable. Moreover, when investigators themselves have a financial stake in the outcomes of their research, it creates conflicts of interest, which may lead to bias and the erosion of confidence in the research enterprise.

Chapter 2 discussed why conflicts of interest matter even if they do not

actually lead to undue influence or bias in a particular case. Correlations or associations in studies such as those reported here are enough to support concerns over potential conflicts of interest. The purpose of conflict of interest policies is preventive: the policies are intended to remove or reduce relationships that create a risk of undue influence or erosion of confidence in the research enterprise.

As described in this chapter and in Chapter 3, research institutions vary in their conflict of interest policies, including the extent to which they have adopted and implemented PHS conflict of interest regulations and policies recommended by AAMC and AAU. Government and press investigations and payment data reported by companies have revealed failures of individual researchers to fully and accurately disclose their financial relationships with industry, as required by institutional or government policies.

The preceding section of this chapter provided an overview of recommendations for action that should be taken by research institutions, research sponsors, investigators, and medical journals to protect the integrity of biomedical research, safeguard research participants, and preserve public trust. The recommendation below focuses on one specific concern: the conduct of research with human participants by investigators with a financial interest in the outcome of that research. The discussion of the recommendation is followed by a review of standards for nonclinical research and a suggestion that NIH take a lead role in further examination of the involvement of conflicted investigators in this kind of research.

Clinical Research

It is critical that the public trust that research institutions are protecting the integrity of the medical research on which clinical practice and education depend. Such protection is especially important in clinical research because bias in the design, conduct, or reporting of the findings of such research may expose human participants to risks without the prospect of gaining valid, generalizable knowledge and may ultimately expose much larger numbers of patients to ineffective or unsafe clinical care.

Recommendation 4.1 calls for research institutions to allow researchers with a conflict of interest to conduct research involving human participants only when a researcher's participation is truly essential and is also managed to limit risk. This recommendation is similar to the AAMC "rebuttable presumption" described earlier in this chapter.

RECOMMENDATION 4.1 Academic medical centers and other research institutions should establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a

company that could be affected by the outcome of the research. Exceptions to the policy should be made public and should be permitted only if the conflict of interest committee (a) determines that an individual's participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research.

This recommendation covers principal investigators and others who share substantial responsibility for the design, conduct, or reporting of the findings of clinical studies. Relevant financial interests often involve stock or other ownership in a company making a product that could be affected by the results of a study, including not only a product under study but also a product that is an alternative to the intervention under study. (Although AAMC recommended no minimum threshold for the initial disclosure of financial interests, it suggested that "significant interest" should generally be defined as a financial interest of $10,000 or more.)

In exceptional cases, a clinical investigator may be judged to be essential if his or her participation is determined—after careful assessment—to be necessary for the safety, reliability, or validity of the research, circumstances that AAMC described as compelling. Often cited as examples are situations in which inventors of a medical device or investigators responsible for certain kinds of breakthrough scientific discoveries are crucial to research, especially early-phase studies, because of their "insights, knowledge, perseverance, laboratory resources" or access to "special patient populations" (AAMC-AAU, 2008, p. 6; see also Witkin [1997] and Citron [2008]).

A specific example of a compelling situation might involve the participation in a pilot study of the inventor of an implanted medical device that requires a complex, new surgical procedure that has not been mastered by others. The reasons for allowing a researcher with a conflict of interest to participate in a pilot or early-phase study or other investigation in a particular situation should be persuasive to others who are presented with the facts of the case. In most cases of a conflict of interest, no compelling argument that the investigator's participation is essential can be made. Even if the investigator's participation is essential, the elimination of the conflict of interest (e.g., through the sale of stock) is the preferred step. If an exception is granted, it should be made public.

If an exception is made for an investigator with a conflict of interest, the next step is for the conflict of interest committee to establish a strategy for managing the conflict and a plan for monitoring the strategy's implementation during the course of the research. For instance, the plan might specify that the researcher with the conflict of interest not serve as the principal investigator. It might also restrict the researcher recruiting

subjects; obtaining informed consent; assessing the clinical end points; analyzing data; or writing the results, conclusions, and abstracts for publications reporting the findings of the study. The plan might, however, allow the researcher to participate in aspects of study design, fund raising, and manuscript review.

Nonclinical Research

Most of the discussion of conflicts of interest in research has focused on clinical research. This emphasis reflects concerns that research participants might be harmed or that bias might contribute to the making of incorrect decisions about approving new drugs and devices or changing clinical practice. Because conflicts of interest in various kinds of nonclinical research have been little investigated, the committee found it difficult to evaluate arguments about the extent and the consequences (or the lack of consequences) of investigator and institutional conflicts of interest in this sphere of research. It thus did not make a formal recommendation about conflicts of interest in nonclinical research. The committee did, however, hear testimony that new models of academia-industry collaboration are needed to promote basic scientific discoveries and the development of new therapies while also addressing concerns about conflicts of interest (Moses, 2008; see also Moses and Martin [2001]).

No matter the type or stage of research, certain fundamentals still apply. All researchers should be subject to an institution's disclosure policies, as described in Chapter 3, and the institution's conflict of interest committee or its equivalent should be notified when investigators have financial stakes in the outcomes of their research. Similarly, following the conceptual framework presented in Chapter 2, once a financial relationship or interest has been disclosed, it should be evaluated for determination of the likelihood that it will have an undue influence that will lead to bias or a loss of trust. If a risk is judged to exist, a conflict of interest committee might conclude that the implementation of safeguards is necessary. Such safeguards could consist of a management plan that includes the involvement of a researcher without a conflict of interest in certain aspects of the research and disclosure of the conflict to coinvestigators and in presentations and publications.

Additional studies on the extent of financial relationships in nonclinical research and their consequences, as well as the consequences of conflict of interest policies, are needed to establish a sounder base of evidence for future policies. Given its extensive and direct relationships with basic scientists, NIH could play a central role in gathering such evidence. As discussed in Chapter 9, NIH could fund research on conflicts of interest in nonclinical scientific research. Furthermore, NIH could convene working groups and

public meetings to promote a fuller understanding—empirical, conceptual, and practical—of conflicts of interest in nonclinical research and propose responses. Such meetings might identify good practices in developing academia-industry relationships in nonclinical research and suggest how such relationships might be developed in ways that promote constructive collaboration while appropriately addressing concerns about conflicts of interest. The development of illustrative case studies might help institutions better understand and manage conflicts of interest in nonclinical research.

Other Relevant Recommendations in This Report

The adoption of the recommendations made elsewhere in this report would also affect researchers, research institutions, and companies. These recommendations call for standardization of the procedures used to disclose conflicts of interest to harmonize the requirements of different institutions and reduce the disclosure burdens on individuals (Recommendation 3.3), implementation of methods for the easier verification of certain financial disclosures (Recommendation 3.4), limitations on certain relationships with industry (e.g., acceptance of gifts and participation in promotional activities) for academic medical center personnel (Recommendation 5.1), and promotion of reforms in industry policies on consulting and research grants (Recommendation 6.2).

Chapter 8 includes a recommendation that responsibility for the oversight of institutional conflicts of interest be lodged in the governing boards of institutions (Recommendation 8.1). Many conflicts of interest at the institutional level involve research or proposed research in which a university or medical school has a financial stake related to its interests in patents or start-up companies.

In addition, the committee recommends that other public and private organizations create incentives to support the adoption of the recommendations made in this report (Recommendation 9.1). As one example, NIH could expand its recent efforts to provide more guidance and oversight to grantee institutions covered by the PHS regulations, issue regulations directing grantees to adopt institutional conflict of interest policies (Recommendation 8.2), and take a lead role in the development of a research agenda on conflict of interest (Recommendation 9.2). NIH could also consider requiring investigators funded by NIH awards to be trained on conflict of interest principles and policies. (NIH has a new training module on conflict of interest that could be tailored for investigators.) Other public agencies that support academic biomedical research, for example, the U.S. Department of Defense, could also provide guidance compatible with that presented in this report.

Taken together, the changes recommended here should not burden socially valuable collaborations between academic researchers and industry. Rather, they should help justify and maintain public trust in their integrity.

5

Conflicts of Interest in Medical Education

Medical education prepares physicians for a lifetime of professional work. Education that is objective and that teaches students how to critically evaluate the evidence prepares physicians to keep current with scientific advances throughout their professional lives.

This chapter is organized around the concept of the learning environment, which shapes and reinforces the professional attitudes and behavior of physicians throughout the continuum of learning that begins in medical school and extends through residency training and to lifelong learning. Learning environments in medicine are diverse. They include conference rooms and lecture halls, patient care locales (such as inpatient service and outpatient practice locations), laboratories, and the Internet. Some continuing education programs take place at restaurants or resorts.

If the learning environment provides the stage for education, the curriculum provides the script. Reviews of undergraduate and graduate medical education often emphasize the "formal curriculum" (i.e., required courses and explicit educational objectives).[1] That formal curriculum aims to help students develop the core competencies that are defined by accreditation agencies. Each educational activity has learning objectives, and the totality of educational sessions must address all the core competencies.

The learning environment also includes two other elements: the informal curriculum (i.e., ad hoc interactions among teachers and students) and

[1] The committee follows the convention in medical education of referring to the years of medical school as "undergraduate medical education" and the post-M.D. years of residency and fellowship as "graduate medical education." Unless otherwise described (e.g., research fellows), fellows are physicians in subspecialty training programs. This report refers to "residents" and "fellows" rather than "trainees" (a description commonly used by medical educators).

the hidden curriculum (i.e., institutional practices and culture) (see, e.g., Hafferty [1998], Ratanawongsa et al. [2005], Cottingham et al. [2008], and Haidet [2008]). Ideally, these two elements convey messages that are consistent with the formal curriculum, but in practice they may not. For example, the formal curriculum might include course work on medical ethics, research methodology, and appropriate relationships with industry. Concurrently, the informal and hidden curricula might be characterized by disparaging faculty comments on their institution's conflict of interest policies and the failure of institutions to adopt and implement sound policies.

Unfortunately, some aspects of each curriculum may contribute to undesirable attitudes or practices. The Association of American Medical Colleges (AAMC) observed in a 2008 report that the conflicts created by a range of common interactions with industry can "[f]or medicine generally, and for academic medicine in particular . . . have a corrosive effect on three core principles of medical professionalism: autonomy, objectivity, and altruism" (AAMC, 2008c, p. 4). Members of the U.S. Congress have also expressed concern about commercial relationships in medical education, primarily continuing medical education (see, e.g., Finance Committee, U.S. Senate [2007]). In contrast to the requirements for recipients of U.S. Public Health Service research awards, the federal government does not require the recipients of direct or indirect funds for medical education to establish and administer conflict of interest policies.

This chapter next provides a brief background on the current context of medical education. It then examines the literature on conflict of interest issues and responses in the learning environments of undergraduate, graduate, and continuing medical education. The discussion covers access to educational environments by sales representatives of medical product companies (e.g., drug detailing, which is a visit to a doctor by a sales representative for a pharmaceutical company), the provision of drug samples and other gifts to faculty and students, and industry-sponsored scholarships and fellowships. A separate section considers a concern that cuts across all phases of education: intellectual independence in presentations and publications and the risks associated with speakers bureaus and ghostwritten publications. (Chapter 4 discussed concerns about how researcher conflicts of interest might affect their advice or supervision involving the research of medical students, residents, fellows, and junior faculty.)

The committee concluded that, in general, industry financial relationships do not benefit the educational missions of medical institutions in ways that offset the risks created. The chapter thus ends with recommendations that are intended to protect the integrity and limit the potential for undue industry influence in medical education. As explained in Chapter 1, the committee focused on conflicts of interest involving physicians and biomedical researchers; but much of the core rationale for the recommendations

may be relevant to nursing, pharmacy, dentistry, and other professions, even though some of the specifics might differ. Chapter 6 considers many of the same issues in the context of physicians in practice outside academic settings.

BACKGROUND AND CONTEXT

Scale and Oversight of Medical Education

American medical education evolved during the 19th and early 20th centuries from pure apprenticeships to proprietary medical schools of variable quality to a reformed and formal educational system that stresses both science and professionalism. During the middle decades of the 20th century, an increasingly elaborate structure of graduate (post-M.D.) medical education emerged, characterized by multiyear residencies in medical specialties beyond the traditional internship year. The latter half of the century saw the growth of requirements by state licensing boards and specialty certification boards for demonstrated participation in accredited continuing education activities (Caplan, 1996).

Today, the scale of American medical education is impressive. The United States has

- 130 accredited medical schools (AAMC, 2008d),[2] approximately 400 major teaching hospitals (Salsberg, 2008), more than 100,000 faculty members (Salsberg, 2008), and approximately 75,000 medical students (AAMC, 2008e);
- 8,355 accredited residency programs for 126 specialties and subspecialties (2006–2007) and more than 107,000 active full-time and part-time residents (2005–2006) (ACGME, 2007b); and
- 740 national providers of accredited continuing medical education (and 1,600 accredited state providers)[3] that reported more than 7 million physician participants in their programs (ACCME, 2008a, 2009), a number that includes multiple registrations among the nation's more than 800,000 active physicians (a count that includes medical residents) (Salsberg, 2008).

[2] The count includes four schools granted preliminary accreditation in 2008. It does not include accredited Canadian schools or the 20 accredited U.S. schools of osteopathic medicine.

[3] These providers are accredited by state medical societies under the rules of the Accreditation Council on Continuing Medical Education.

The Liaison Commission on Medical Education (LCME) is the oversight agency that is responsible for the accreditation of the nation's medical schools. Its members are appointed by AAMC and the American Medical Association (AMA). The Accreditation Council for Graduate Medical Education (ACGME) accredits residency training programs in the United States. The sponsoring institution for a residency program may be a hospital, medical school, university, or group of hospitals (ACGME, 2008). Accreditation bodies define the core competencies for students, residents, and fellows and ensure that the formal curriculum covers all essential aspects of medical education. ACGME board members are appointed by AAMC, AMA, the American Board of Medical Specialties, the American Hospital Association (AHA), and the Council of Medical Specialty Societies (CMSS). Accredited continuing medical education providers are accredited by the Accreditation Council for Continuing Medical Education (ACCME). Its member organizations are AHA, AMA, AAMC, CMSS, the Association for Hospital Medical Education, and the Federation of State Medical Boards. State medical societies may also accredit providers within a state.[4] In addition, AMA, the American Academy of Family Physicians, and certain other groups set standards and certify credits for specific courses that physicians can take (from accredited providers) to meet state licensure board and other requirements for accredited continuing medical education (see, e.g., AMA [2006, 2008b]).[5] Accredited providers usually issue certificates to document that a physician has completed a certified course. Consistent with common usage, this report uses the phrase accredited continuing medical education to refer to education that is (1) presented by accredited providers and (2) certified for course credits.

Changing Environment and Fiscal Challenges

Academic medical centers dominate the provision of undergraduate and graduate medical education. The institutions consist of two related enterprises: a medical school that trains physicians and conducts research and a system that provides health care services. The latter system may include teaching hospitals, satellite clinics, and physician office practices. Academic health centers include other health professions schools, such as a school of dentistry, nursing, or pharmacy (Wartman, 2007).

[4] As described by ACCME, "ACCME has two major functions: the accreditation of providers whose CME [continuing medical education] activities attract a national audience and the recognition of state or territorial medical societies to accredit providers whose audiences for its CME activities are primarily from that state/territory and contiguous states/territories" (ACCME, 2005).

[5] AMA also authorizes credits for other activities, such as publishing an article in a peer-reviewed journal or achieving and maintaining specialty board certification.

In recent years, academic medical centers have struggled financially because of low levels of payment for poor and uninsured patients, reductions in the Medicare indirect medical education adjustment for hospital payment rates, and lower profit margins for the provision of hospital services to Medicare patients. (In the late 1990s, medical schools also faced declining admissions, but admissions increased from 2003 to 2007 [AAMC, 2008a].) At the same time, teaching hospitals have faced rising costs because of the incorporation of new medical informatics systems and expensive medical technologies and restrictions on the numbers of hours that residents may work. The Medicare Policy Advisory Commission has characterized 53 percent of major teaching hospitals as being under high financial pressure—compared to 28 percent of hospitals overall (MedPAC, 2009). Given these circumstances, financial support from industry may seem attractive.

Physicians in training also face financial challenges. In 2006, the median levels of debt of medical students graduating from public and private medical schools were $120,000 and $160,000, respectively (Jolly, 2007). Medical school graduates can expect to pay approximately 9 to 12 percent of their after-tax income after graduation for educational debt service (Jolly, 2007). This level of indebtedness and the delayed gratification of a profession that requires years of training before independent practice is permitted can contribute to a sense of entitlement, which, in turn, may position medical students, residents, and fellows to be strongly influenced by gifts and attention from representatives of pharmaceutical and medical device companies (see, e.g., Levine [2008]). Sierles and colleagues (2005) found that 80 percent of the medical students that they surveyed believed that they were entitled to gifts. In addition, as discussed in Chapter 6, once they are in practice, limits on reimbursements for physician services make debt repayment more of a burden than in the past and may make gifts and other financial relationships with industry more appealing.

Industry Funding of Medical Education

During most of the 20th century, medical product companies were not major participants in medical education. The exception was sales representatives, who provided information to residents and faculty as well as to nonacademic physicians. In the latter decades of the century, however, medical product companies became increasingly involved in sponsoring continuing medical education, including grand rounds and other academic-based programs. In a 2008 report on industry funding of medical education, a task force of AAMC observed generally that

> Over recent decades, medical schools and teaching hospitals have become increasingly dependent on industry support of their core educational mis-

> sions. This reliance raises concerns because such support, including gifts, can influence the objectivity and integrity of academic teaching, learning, and practice, thereby calling into question the commitment of academia and industry together to promote the public's interest by fostering the most cost-effective, evidence-based medical care possible. (AAMC, 2008c, p. iii)

The committee found no data on the amount or proportion of undergraduate or graduate medical education supported by industry. It also found little systematic information on specific categories of financial support, for example, grants for residencies or fellowships, direct or indirect financial support for grand rounds, or donations for buildings or other capital items. The most extensive information on academic institutions' ties with industry comes from a 2006 survey of department chairs at medical schools and the 15 largest independent teaching hospitals (67 percent response rate). The responses indicated that 65 percent of clinical departments received industry support for continuing medical education, 37 percent received industry support for residency or fellowship training, 17 percent received industry support for research equipment, and 19 percent received unrestricted funds from industry for department operations (Campbell et al., 2007b). The committee did not categorize industry payments for meals, gifts, and visits by sales representatives as support for medical education because these activities do not fit the learning objectives in the formal curriculum.

Information on industry funding for accredited continuing medical education comes from yearly surveys by ACCME. Figure 5-1 shows that commercial sources (excluding advertising and exhibits at programs organized by accredited providers) provide a substantially larger share of income for education providers today than they did in 1998. By 2003, about half of all funding for accredited continuing medical education programs came from commercial sources. The fees paid by program attendees once provided the majority of provider income, but today industry-supported programs are often provided free or at reduced cost to physicians (Steinbrook, 2008a).

LEARNING ENVIRONMENTS IN MEDICAL SCHOOLS AND RESIDENCY PROGRAMS

The ultimate mission of medical education is to prepare physicians to provide effective, safe, high-quality, efficient, timely, affordable, and patient-centered care to patients. In revising the standards that provide the framework for essential aspects of medical education, both LCME and ACGME have recently emphasized how the learning environment can affect the development of core professional values and core competencies, includ-

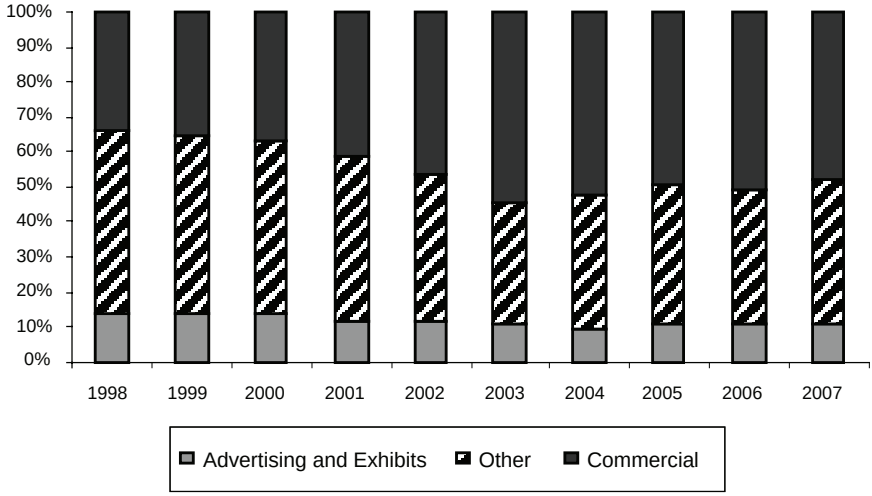

FIGURE 5-1 Sources of income reported by respondents (accredited providers of continuing medical education) to ACCME annual survey, 1998 to 2007. SOURCE: Compiled from ACCME, 2008a.

ing how to critically review the evidence and to commit to lifelong learning about scientific advances.

Both LCME and ACGME recognize the power of the local learning environment to shape the knowledge, skills, behaviors, and attitudes of the next generation of physicians. To achieve accreditation, institutions providing undergraduate or graduate medical education must have curricula and resources that, among other requirements, (1) promote the development of appropriate professional attributes; (2) help learners at all levels think critically and appraise the evidence base for research reports, practice guidelines, and marketing materials; and (3) provide appropriate role models and mentoring. In addition, a standard on the creation of the appropriate learning environment must be implemented (LCME Standard MS-31-A). Recently, ACGME has required institutions to have a statement or institutional policy that addresses interactions between vendor representatives or corporations and residents and their programs (Requirement III. B.13 [ACGME, 2007a]).

The Learning Environment in Undergraduate and Graduate Medical Education as a Target of Industry Influence

Scope of Relationships Between Industry and Students, Medical Schools, and Teaching Hospitals

Interactions between medical students and industry are common. Table 5-1 summarizes the results from a survey of third-year medical students at eight major medical schools. Almost all students had received an industry-provided lunch or other gift. More than one-third had attended a social event hosted by a drug company.

Information from two surveys of residency directors similarly documents frequent interactions with pharmaceutical companies. For example, a 2002 survey of emergency medicine residency program directors found that approximately 40 percent allowed industry to fund social activities, and a similar percentage allowed pharmaceutical representatives to teach residents (Keim et al., 2004). Twenty-nine percent said that industry travel support could be made contingent on residents attending an industry event. Only 50 percent said that they always or very frequently followed ACGME recommendations for industry funding of core lectures, and 10 percent said that they always or very frequently allowed pharmaceutical representatives unrestricted access to residents. In a 2002 survey of psychiatric residency program directors, 88 percent reported that they allowed industry to provide lunches for their residents, and among this group, the mean was about five lunches per week (Varley et al., 2005). Approximately a third of the programs solicited travel funds from industry (31 percent) or allowed residents to seek such funding from industry on their own (34 percent).

Value of Relationships

Some interactions with industry can have educational value, for example, when an industry scientist participates in a seminar on drug development strategies or when a device company representative provides supervised training on a complex and innovative medical device that has recently been approved for marketing. Other examples may include unrestricted grants to academic medical centers that support student or resident research stipends or participation in scientific conferences. On a much larger scale, universities have benefited from company gifts for buildings, research programs, and auditoriums.

Pharmaceutical companies argue that their representatives provide information on new drugs. Yet, medical students, residents, and fellows have ready access to the latest scientific information through faculty members, information technologies that allow them to search the medical literature,

TABLE 5-1 Third-Year Medical Students' Interactions with Drug Companies

Type of Event	No. of Students. (N = 826)	No. (%) of Students Who Received a Gift or Participated in at Least One Event	Exposure Frequency per Month[a]	
			Mean (SD)	Range
A lunch provided by a drug company	793	768 (96.8)	1.08 (0.76)	0–4.2
A small, noneducational gift (e.g., pen or coffee mug)	801	754 (94.1)	0.87 (0.69)	0–3.5
A journal reprint or a glossy brochure from a pharmaceutical representative	800	716 (89.5)	0.53 (0.52)	0–3.5
A snack (e.g., donut, candy, coffee) provided by a pharmaceutical representative	800	713 (89.1)	0.75 (0.72)	0–8.5
A grand rounds sponsored by a drug company	798	690 (86.5)	0.54 (0.57)	0–2.4
A dinner provided by a drug company	801	405 (50.6)	0.13 (0.21)	0–2.4
A drug sample from a pharmaceutical representative	799	435 (54.4)	0.10 (0.20)	0–2.1
Another social event (e.g., party) sponsored by a drug company	799	272 (34.0)	0.06 (0.11)	0–0.8
A book donated by a drug company[b]	826	421 (51.0)		
Attendance at a workshop sponsored by a drug company[b]	826	214 (25.9)		
Registration fee for a conference paid for by a drug company[b]	826	37 (4.5)		
Participation in a market survey sponsored by a drug company[b]	826	29 (3.5)		
Participation in a research project sponsored by a drug company[b]	826	22 (2.7)		
Travel expenses for a conference paid for by a drug company[b]	826	15 (1.8)		
Nominated for an award sponsored by a drug company[b]	826	5 (0.6)		
Obtained a fellowship sponsored by a drug company[b]	826	4 (0.5)		

[a]For each student, an exposure index was calculated as the sum of the monthly frequencies for the first eight items.
[b]Monthly frequency data were not requested.
SOURCE: Sierles et al. Medical students' exposure to and attitudes about drug company interactions: a national survey. *Journal of the American Medical Association* 294(9):1034–1042 (September 7, 2005).

and open-access sources of evidence-based literature reviews and summaries. The committee recognizes that some medical students and residents who have become accustomed to interactions with representatives may value the meals that they receive as a respite and may view the gifts that they bring as either inconsequential or as an appropriate reward for their demanding schedules and economic sacrifices.

The discussion below focuses on several different types of academic-industry relationships and the literature about their consequences. Each section includes a discussion of private- and public-sector responses to concerns about the extent and consequences of these relationships. In addition to consulting reports by AAMC and other groups, the committee examined the policies of a number of medical schools. It found many of these policies at or available through links from the websites of the American Medical Student Association (AMSA) and the Institute on Medicine as a Profession (IMAP). The AMSA website also includes the organization's scorecard, which presents school-by-school ratings of various policy elements (e.g., the policy on the acceptance of gifts) and which has received considerable attention from the media.[6]

The committee notes that the recommendations in the 2008 AAMC report on medical education apply off campus as well as on campus. The report calls for academic medical centers to "communicate to off-site training facilities their expectation that the off-site venues will adhere to the standards of the academic center regarding interactions with industry" (AAMC, 2008c, p. 10).

Site Access by Drug and Device Company Representatives

Issues and Evidence

Drug detailing, that is, a visit to a doctor by a sales representative for a pharmaceutical company, is a common way that companies promote their products and establish relationships with physicians in academic and community settings. In 2004, an estimated 36 percent of the $57.5 billion that pharmaceutical companies spent on product promotion went for detailing (Gagnon and Lexchin, 2008).

Medical device companies also employ sales representatives to promote their products to physicians and hospitals, although the responsibilities of

[6] The AMSA ratings, the methodology, and other information can be found at http://amsascorecard.org/. The IMAP information can be found at http://www.imapny.org/coi_database/. Both groups use information and policies received in response to a survey conducted under the auspices of the Prescription Project with funding from the Pew Charitable Trust. Some schools did not respond initially, and others refused to supply their policies.

some of these representatives may be more complex. They may provide training, equipment calibration, and additional services or advice related to implants and other sophisticated technologies used in the operating room and elsewhere (see, e.g., ECRI Institute [2007]). In one instance, the Food and Drug Administration (FDA) has required physicians to be trained by company representatives as a condition for the approval of a device (see, e.g., FDA [2004b] and Dawson [2006]).

The committee did not locate any information about how drug or device detailing activity differs between academic and nonacademic settings or how specific tactics of detailing and their effects may vary by setting or type of physician (e.g., resident versus faculty member versus community physician). Interactions with drug company representatives are common in academic settings. Medical students average about one interaction with drug company representatives a week, and 80 to 100 percent of students report interactions (see, e.g., Bellin et al. [2004], Sierles et al. [2005], and Fitz et al. [2007]). As described by one faculty member,

> [d]rug company representatives are a major presence. They sponsor Journal Club (where trainees learn to review new data and research), they pay for many of our weekly speakers and regularly offer free dinners for the residents and faculty. They enjoy free access to our mailboxes and regularly detail our trainees in their offices, hallways and in our little kitchen. (Shapiro, 2004, p. F5)

Medical students and residents reported that they received insufficient training in interacting with drug representatives. Studies also indicate that students and residents believe that their own prescribing behavior is not affected by drug company gifts, although they believe that the prescribing behavior of their colleagues is (Sierles et al., 2005; Zipkin and Steinman, 2005). Limited evidence suggests that educational interventions "show some promise" in affecting the attitudes and behaviors related to relationships with industry (Carroll et al., 2007).

Overall, research suggests that drug company representatives may influence prescribing patterns and requests for additions to hospital formularies. The effects appear to be modest but consistent across various kinds of research and disciplines. One review concluded that the "pharmaceutical industry has a significant presence during residency training, has gained the overall acceptance of trainees, and appears to influence prescribing behavior" (Zipkin and Steinman, 2005, p. 777). Another review (which was not limited to educational settings) concluded that detailing "affects physician prescription behavior in a positive [i.e., the more detailing that there is, the more of an effect that it has] and significant manner" (Manchanda and Honka, 2005, p. 787).

Taken together with the information reviewed below on the role of drug samples and gifts (which typically accompany sales visits), the literature suggests that academic medicine and the public have reason to be concerned about the easy access of sales representatives to medical students, residents, and faculty. In addition, the committee could find no evidence that the exposure of students and residents to drug and device sales representatives—without additional training and supervision—contributes to the achievement of learning objectives or the development of core competencies, for example, increasing an individual's ability to critically evaluate presentations or promoting adherence to evidence-based clinical practice guidelines.

Responses

AAMC has recommended tight limits on site access by sales representatives from medical product companies, particularly uninvited and unscheduled visits and unsupervised access to individual students and residents (see Box 5-1) (see, e.g., AMSA [2008a] and AAMC [2008c]). The recommended rules for device representatives are somewhat less stringent than those for drug representatives and allow limited exceptions for training on the use of complex new devices and the other activities mentioned above. A number of medical schools and teaching hospitals have adopted policies consistent with the AAMC recommendations.

A quality assurance and risk management document prepared by the ECRI Institute (2007) recommends several additional safety and administrative provisions for device representatives who are allowed access to the operating room.[7] The recommendations include training requirements for device representatives as well as procedures to ensure patient safety, privacy, and informed consent and to prevent kickbacks (ECRI Institute, 2007). In addition, the ECRI Institute document suggests that medical schools have not provided adequate training in the use of devices. It emphasizes that hospitals and physicians are responsible for seeing that personnel have the appropriate training on the use of the devices that they regularly use, so that reliance on device representatives is limited and appropriately supervised.

[7] ECRI Institute is a technology assessment organization that has a long history of providing advice to health care institutions and government on medical device safety. It is one of the Evidence-Based Practice Centers designated by the Agency for Healthcare Research and Quality and is a Collaborating Center of the World Health Organization.

BOX 5-1
AAMC Recommendations on Site Access by Sales Representatives

Site Access by Pharmaceutical Representatives

- To protect patients, patient care areas, and work schedules, access by pharmaceutical representatives to individual physicians should be restricted to non-patient care areas and nonpublic areas and should take place only by appointment or invitation of the physician.
- Involvement of students and trainees in such individual meetings should occur only for educational purposes and only under the supervision of a faculty member.
- Academic medical centers should develop mechanisms whereby industry representatives who wish to provide educational information on their products may do so by invitation in faculty-supervised structured group settings that provide the opportunity for interaction and critical evaluation. Highly trained industry representatives with M.D., Ph.D., or Pharm.D. degrees would be best suited for transmitting such scientific information in these settings.

Site Access by Device Manufacturer Representatives

- Access by device manufacturer representatives to patient care areas should be permitted by academic medical centers only when the representatives are appropriately credentialed by the center and should take place only by appointment or invitation of the physician.
- Representatives should not be allowed to be present during any patient care interaction unless there has been prior disclosure to and consent by the patient, and then only to provide in-service training or assistance on devices and equipment.
- Student interaction with representatives should occur only for educational purposes under faculty supervision.

SOURCE: AAMC, 2008c.

Drug Samples

Issues

Physicians and patients often value drug samples provided as gifts because they allow physicians to send a patient home with a medication that can be evaluated for its short-term effects and side effects without requiring the patient to fill and pay for a full prescription. For low-income patients, many of whom are treated at academic medical centers and teaching hospitals, samples can provide access to needed medications (Daugherty, 2005).

Some research has, however, suggested that poor or uninsured patients are somewhat less likely than higher-income or insured patients to receive a drug sample (Cutrona et al., 2008). Drug samples may also be used by physicians themselves or their families. In a 1997 survey of residents, 32 percent of all medications used by residents were obtained from drug sample cabinets or directly from drug representatives (Christie et al., 1998). As discussed in Chapter 6, some professional societies approve such use.

Other research points to risks associated with physician acceptance of drug samples. In academic medical centers, drug samples may be associated with the prescription of new brand name drugs in situations in which the sample drugs are different from the physician's preferred drug or are not recommended by evidence-based practice guidelines or in situations in which less expensive drugs or generic equivalents are available for the same indication. One study of a sample of university-based physicians' responses to several clinical scenarios found that from 17 to 82 percent of the physicians would dispense a drug sample, and, in two of three scenarios, a great majority would do so instead of using their usually preferred drug—largely on the grounds that use of the sample would avoid costs to the patient (Chew et al., 2000). Residents were more likely than attending physicians to report that they used drug samples. In a second study, which involved residents in an inner-city clinic, half were randomized to forgo the use of available free drug samples. They were more likely than the control group to choose unadvertised drugs and were more likely to use over-the-counter drugs. The authors concluded that access to drug samples influences residents' prescribing decisions (Adair and Holmgren, 2005). A third study found that physicians who prescribed angiotensin-converting enzyme inhibitors or calcium channel blockers (a departure from the recommendations of the Joint National Commission on High Blood Pressure Treatment) were more likely than other physicians to report that they provided patients with samples of antihypertension medications (Ubel et al., 2003). This relationship persisted even after physician and practice variables were taken into account.

Responses

Concerns about the possible negative effects of drug samples have led some academic health centers to restrict or ban their provision. For example, some medical schools require drug samples to be received and distributed by a medical center pharmacy and prohibit their direct provision to individual physicians (see, e.g., University of Massachusetts [2008]). Other policies may allow donation of products only for purposes of evaluation or education and not to support "patient care purposes on an ongoing basis" (University of California, 2008, p. 4). When the University of Michigan

Health System (2007) prohibited the distribution of drug samples in patient care and non-patient care areas, it provided committee-approved vouchers for starter medications for clinic patients and for limited exceptions if a clinic director believed that a sample of a specific drug was clinically necessary. The most common provision among the policies reviewed by the committee was a prohibition on the personal use of samples by physicians or their family members.

AAMC (2008c) recommends that samples—if their distribution is by the institutions—should be centrally managed, when feasible (e.g., when timely access to the medications is possible). It warns that the "acceptance and use of drug samples transmits the message to students and trainees that information about samples received from industry sales personnel is sufficient without independent critical evaluation" (p. 16). The recommendation does not mention the personal use of samples by physicians or their family members or staff.

In a March 2009 report, the Medicare Payment Advisory Commission recommends that the U.S. Congress require manufacturers and distributors of drugs to report their distribution of drug samples. It also recommends that the secretary of the U.S. Department of Health and Human Services make the information available for analysis through data use agreements.

Gifts from Medical Product Companies

Issues

As noted earlier in this chapter, surveys indicate that almost every medical student has received a meal and a small noneducational gift from a drug company and that other interactions are common as well (see, e.g., Sigworth et al. [2001], Bellin et al. [2004], Sierles et al. [2005], and Fitz et al. [2007]). In one study, residents were asked to empty their pockets of pens, penlights, calipers, and other items (Sigworth et al., 2001). Ninety-seven percent of the residents had at least one item marked by a pharmaceutical insignia, and about half of the items carried by residents were so branded. More than 90 percent of the residents said that they thought that interactions with drug company representatives influenced their prescribing.

The committee found no studies documenting an educational benefit of these kinds of gifts from industry. Although medical students or residents may find the gift of an expensive textbook welcome, nothing similar to the benefits of academic-industry collaboration in biomedical research has been argued for gifts from industry in medical education.

In contrast, studies of medical personnel combined with social science research provide reasons for concern about the risks of industry relationships and gifts, even small gifts. The paper by Jason Dana in Appendix D

reviews this literature. It suggests that even small gifts can be influential. Furthermore, because influence may operate at an unconscious level, it can distort the choices of people who believe that they are objectively making decisions. Disclosure of interests and education about bias may be useful, but they cannot be relied upon to overcome the potential for undue influence and bias associated with conflicts of interest. A number of studies suggest that medical residents, faculty, and other physicians tend to think that they themselves are less likely than others to be influenced by gifts or other interactions (see, e.g., McKinney et al. **[1990], Steinman et al.** [2001], Halperin et al. [2004], Zipkin and Steinman [2005], and Morgan et al. [2006]).

Few studies have specifically investigated the effects of industry relationships on teaching. One study compared the attitudes of internal medicine residents and faculty about the impact of gifts or income from industry on teaching within and outside the institution (Watson et al., 2005). In general, students were more likely than faculty to perceive industry influence in association with gifts or income. Both students and faculty perceived visiting attending faculty as more susceptible to such influence than regular faculty, and both perceived off-site teaching as more subject to influence than on-site activities. For example, residents were more likely than faculty to believe that gifts or income from industry influences how attending physicians teach on rounds (47 versus 34 percent), during in-hospital lectures and journal clubs (58 versus 30 percent), and during out-of-hospital dinner lectures and journal clubs (80 versus 57 percent). For responses about the effects on visiting attending physicians, the numbers were even higher, with 89 percent of residents and 72 percent of faculty reporting that they believed that gifts or income from industry affected teaching by this group during out-of-hospital dinner lectures and journal clubs. Moreover, 62 percent of residents and faculty believed that annual income or gifts of less than $10,000 could influence an attending physician's teaching. Sixty-five percent of residents and 74 percent of faculty preferred that speakers disclose all financial relationships with industry rather than just report relationships that speakers considered relevant to the educational topic. Although these findings are from a single study in a single institution, they do raise particular concerns about presentations given outside the medical school setting.

Responses

AAMC (2008c) recommends that schools ban the acceptance of industry-supplied food or meals, except in association with ACCME-accredited educational programs. This ban should apply both on and off campus. A few universities (e.g., the University of Michigan and Yale University by 2005)

initiated restrictions some years before the AAMC statement. Schools that ban vendor-provided meals on campus (e.g., Stanford University) may not be explicit about the acceptance of meals at off-site locations, although several schools (e.g., Yale University) also discourage this.

As discussed in more detail in Chapter 6, AMA allows gifts of modest value that are viewed as having some benefit to patients (e.g., meals as part of an educational activity) or the physician's practice (e.g., notepads). The policies of several medical centers (e.g., Wake Forest University, Case Western Reserve University, and the University of Minnesota) are similar to this policy.

In addition to policy changes within the academic community, the Pharmaceutical Research and Manufacturers of America (PhRMA) recently revised its voluntary *Code on Interactions with Healthcare Professionals* (PhRMA2008, effective 2009). Except for the section on scholarships and education funds, the document does not refer specifically to interactions in academic settings. As discussed further in Chapter 6, the revised code more strongly discourages "noninformational" physician-company relationships, such as the provision of tickets to sporting events, token consulting arrangements, speaker training programs at resorts, and meals by sales representatives outside a physician's office or other medical setting.

Industry-Sponsored Scholarships and Training Positions

Issues

Little information on the extent of industry funding for undergraduate and graduate medical education is available, although AAMC has stated that medical schools have become increasingly dependent on such funding for such major activities. The committee is aware of industry-funded residencies or fellowships in a few areas, for example, dermatology residencies funded by companies making dermatologic products (Kuehn, 2005); industry-funded fellowships in rheumatology (Goldblum and Franzblau, 2006); and industry support for psychiatry resident fellowships, awards, and the Chief Resident Leadership Conference (APA, 2008).

The rationale for industry funding of residencies and fellowships seems to rest on physician or researcher shortages in certain specialties and the desire to attract more individuals to these areas through additional industry-supported training positions. For example, the American Academy of Dermatology (AAD) launched an initiative in 2004 to fund 10 dermatology residency positions (Kuehn, 2005). The AAD created a fund to accept donations from the academy, pharmaceutical companies, and other interested parties. Awards were assigned to 10 university programs ($60,000

per year for 3 years), and no recipient would be identified as having been funded by a particular company or companies.

Responses

AAMC (2008c) recommends that academic medical centers establish and implement policies requiring that industry funds for scholarships and similar purposes be given centrally to the administration of the medical center. In addition, industry should have no involvement in the selection of recipients, and no "quid pro quo [should] be involved in any way" (p. 21). The objective is to "prevent the establishment of one-on-one relationships between industry representatives and students and trainees" and minimize "the possibility that these funds will be perceived or used as direct gifts" (p. 21). The committee supports the AAMC recommendations. AMA and PhRMA both permit industry funding of scholarships for medical students, residents, or fellows to attend carefully selected educational conferences when the selection of recipients is made by the academic or training institution.

Changing the Environment or Creating Educational Interventions

To the extent that industry influence operates at an unconscious level, the most effective strategies for reducing the risk of undue influence may involve changing the environment in ways that eliminate or reduce the source, especially when the source offers little or no countervailing educational benefit. That is a major rationale for the policies cited above that eliminate gifts, meals, and other noneducational interactions from the learning environment. Some evidence suggests that the learning environment influences attitudes. Two studies have reported that residents who trained in environments that restricted interactions between industry representatives were less likely than residents who trained in environments without such restrictions to view promotional interactions as being beneficial (Brotzman and Mark, 1993; McCormick et al., 2001). One literature review found weak evidence that trainees who were exposed to educational interventions may be "less accepting of pharmaceutical industry marketing tactics" than those who are not (Carroll et al., 2007, p. e1533). The review noted that two studies that involved industry personnel in the design of the educational intervention found that the participants were more positive toward industry and industry representatives than they were before the intervention.

Some research—including research in academic medical centers as well as community settings (see, e.g., Solomon et al. [2001])— suggests the value of "academic detailing" or educational outreach programs provided by clinical pharmacists or other experts as an objective educational alternative

to the activities of medical product companies. Because these programs are aimed at physicians outside academic institutions, this research is reviewed in Chapter 6.

THE LEARNING ENVIRONMENT IN ACCREDITED CONTINUING MEDICAL EDUCATION

Physicians commit to life-long learning to keep pace with new knowledge and skills and to maintain their current skills. Most state licensing boards, specialty boards, and hospitals require accredited continuing medical education for relicensure, recertification, or staff privileges. Thus, it is important to promote a constructive learning environment in this arena as well as in undergraduate and graduate education. This discussion focuses on accredited continuing medical education. (As noted earlier, this report uses the phrase accredited continuing medical education to refer to education that is presented by accredited providers and is certified for course credits.)

Providers of accredited continuing medical education are more numerous and diverse than providers of undergraduate and graduate medical education. The major ACCME-accredited providers are physician membership organizations (n = 270), publishing/education companies (n = 150), medical schools (n = 123), and hospitals and health care delivery systems (n = 93). In 2008, ACCME had 740 accredited providers of continuing medical education, and state medical societies accredited approximately 1,600 additional providers (ACCME, 2008a, 2009). What ACCME calls "publishing/education companies" are often described as "medical education and communication companies," or MECCs, and that term is used here. According to data reported by the Society for Academic Continuing Medical Education (SACME) for 2006, about 40 percent of medical schools held commercially sponsored "satellite" meetings in conjunction with national professional society meetings, and 70 percent of these meetings were managed by communications companies (SACME, 2007).

Table 5-2 shows the shares of total income, participants, hours of instruction, and activities (all providers) accounted for by several types of accredited continuing medical education providers. Medical schools accounted for a considerably larger share of total hours of instruction than might be expected from their share of the total income received by education providers. In contrast, MECCs (publishing/education companies) account for a considerably smaller share of all instructional hours than of total income.

Accredited continuing medical education programs embedded in medical schools are shaped in part by the missions, culture, and challenges of the larger institution. The programs' members are represented by SACME,

TABLE 5-2 Share of Total Accredited Continuing Medical Education Income, Instruction Hours, Participants, and Activities Accounted for by Major Types of ACCME-Accredited Providers

	Share (as %)			
Provider Organization Type	Total CME[a] Income	Total Hours of CME Instruction	Total CME Participants	All CME-Sponsored Activities
Medical school	17	45	31	30
Publishing/education company	33	9	30	30
Physician membership organization (nonprofit)	35	23	26	20
Other providers	15	23	13	20
TOTAL	100	100	100	100

[a]CME = continuing medical education.
SOURCE: ACCME, 2008a, Tables 2, 3, 4, 7.

which describes its mission as promoting "research, scholarship, evaluation and development" of educational and professional development programs "to enhance the performance of physicians . . . for purposes of improving individual and population health" (SACME, 2008a, unpaged). Professional society programs are also shaped by the missions, culture, and resources of the society. Most MECCs are for-profit organizations. They are represented by the North American Association of Medical Education and Communication Companies, which is "dedicated to providing representation, advocacy, and education for its members" (NAAMECC, 2009).

The curriculum for accredited continuing medical education is also diffuse. All states except Colorado, Indiana, Montana, New York, South Dakota, and Vermont have some requirements for accredited continuing medical education for physicians who want to maintain (reregister) their license (AMA, 2008a). The policies are generally not specific about the content of the accredited continuing medical education, although a number of states have certain content requirements, for example, palliative and end-of-life care or patient safety (AMA, 2008a). Medical specialty boards have more specific and coherent requirements. They have also recently adopted a "maintenance of certification" model for ensuring continuing physician competence, and this model has implications for the future content of accredited continuing medical education.[8] Approximately 85 percent of U.S.

[8] The American Board of Medical Specialties and its 24 member boards have been moving from a process of recertification based on an examination taken once every several years to

physicians are board certified, so recertification requirements affect the majority of physicians (ABMS, 2007).

In addition to accredited continuing medical education, physicians also have access to an array of nonaccredited education programs sponsored by a wide range of public and private organizations. Many conferences sponsored by the National Institutes of Health and other government agencies do not offer credit, although some do. Hospitals sponsor a range of medical staff education programs that do not offer credits. The committee heard testimony that a professional society may organize a scientific meeting of research presentations for which it controls the selection of topics and speakers (ASH, 2008; Kaushansky, 2008). The organization may then seek financial support from industry, often small grants from several companies. Because of limited budget and staff, a small society may not pursue the provision of continuing medical education credits even when it provides safeguards against commercial bias consistent with accreditation standards. When medical product companies organize nonaccredited continuing medical education, the offerings may range from dinner seminars to training on the use of a medical device and satellite symposia at professional society meetings (some satellite symposia offer credit). Some nonaccredited programs controlled by companies may be little more than marketing. Others, such as programs that provide training on the use of a complex new medical device, may meet legitimate education needs, although the presentations may still be more positive about the device than presentations by an independent educational source would be. The committee lacked the resources to investigate nonaccredited activities.

Some medical schools have policies that require their faculty to limit participation in industry-supported programs to programs that meet certain conditions. These conditions may be similar or identical to the standards for accredited continuing medical education (see, e.g., Boston University [2007] and the University of Pittsburgh [2007]).

As noted earlier, the committee commissioned a paper on conflict of interest concerns, policies, and practices in other professions. That paper, which is presented as Appendix C, examines conflicts of interest in law, accounting, engineering, and architecture. In general, other professions differ from medicine in that they have no authority similar to that of physicians to prescribe regulated products for client's personal use and, except to various degrees for law, do not have vulnerable clients.

In some respects, the current system of continuing legal education

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a maintenance of certification program that emphasizes continuing self-evaluation of practice and knowledge and other activities to maintain competence. Boards may develop self-assessment programs that also offer continuing medical education credit that will meet state licensing board and other requirements.

resembles the system of continuing medical education in decades past. Much continuing legal education is provided by law schools as part of their service mission, although law firms and commercial companies also offer programs. Programs may be offered at no charge or may be paid for by individual lawyers or their firms or employers. Programs sometimes have corporate sponsorship, but the sponsors' products tend to be resources for the lawyer (e.g., software and information resources) rather than for the lawyer's clients and thus do not present the same concerns about bias in presentations that occur in medicine. Although legal continuing education cannot be seen as an exact model for medicine, it does suggest that alternatives (e.g., higher fees and employer subsidies) to the major role of industry funding for continuing medical education may exist.

Industry Funding in Accredited Continuing Medical Education

Survey data from ACCME show that industry funding of accredited continuing medical education increased by more than 300 percent between 1998 and 2007 (ACCME, 2008a, Table 7).[9] Moreover, profit margins increased substantially, from 5.5 percent in 1998 to 31 percent in 2006 (Steinbrook, 2008b). For the many providers of accredited continuing medical education, this combination of increased reliance on industry funding and increased profitability provides strong incentives to resist efforts to curtail such funding.

The contribution of funding from industry (primarily from drug, medical device, and biotechnology companies) varies by the type of provider of accredited continuing medical education (Table 5-3). Funding from industry provides more than half of the total income for medical schools and almost three-quarters of the total income for MECCs. Professional societies (i.e., physician membership organizations) as well as MECCs show a significant margin of income over expenses.

Although professional societies are not as dependent on industry funding for their accredited educational programs as MECCs or medical schools, they receive nearly equal amounts of funding from commercial sources (24 percent) and advertising and exhibit income (25 percent). ACCME's survey does not count the latter as commercial support.

SACME surveys provide additional data on the significance of industry

[9] One widely cited analysis estimated that every $1.00 of industry spending on physician meetings and events generated an average of $3.56 in increased revenue (cited in Walker [2001]; see also CEJA [2008] and NAAMECC and Coalition for Healthcare Communication [2008]). Descriptions of the reported analysis do not indicate the relative weight of accredited versus nonaccredited activities in the estimate or whether accredited continuing medical education was distinguished from other types of meetings, such as promotions. Nonetheless, it suggests a rationale for industry support of a range of educational activities.

TABLE 5-3 Income, Expenses, and Source of Support as Percentage of Income, by Type of Accredited Provider of Continuing Medical Education, 2007

Organization Type (No. of Organizations)	Total Income	Expenses as % of Total Income	Total Commercial Support (% of Total Income)	Advertising and Exhibits Income (% of Total Income)
Nonprofit (physician membership organization) (270)	$887,181	68	$215,388 (24)	$217,907 (25)
Publishing/Education Company [MECC](150)	830,811	74	594,420 (71)	10,831 (1)
School of medicine (123)	427,668	88	245,790 (57)	23,203 (5)
Hospital/health care delivery system (93)	105,014	95	47,498 (45)	7,407 (7)
Nonprofit (other) (38)	160,397	79	78,412 (49)	11,852 (7)
Not classified (33)	55,188	79	29,263 (53)	2,423 (4)
Government or military (15)	69,452	100	255 (0)	376 (0)
Insurance company/managed care company (14)	3,489	193	318 (9)	35 (1)

NOTE: Monetary data for 2007 are in 1,000s of dollars. Data for a third category of income (other) are not shown here. As categorized by ACCME, other income represents income other than commercial support and advertising and exhibit income. Data for providers accredited by state medical societies are not included, but ACCME survey data show that commercial sources accounted for about 25 percent of their income.
SOURCE: ACCME, 2008a (Table 7).

funding for medical school programs. In 2006, the typical (median) medical school received some commercial support for about 45 courses, which represented almost 70 percent of its educational activities (SACME, 2007). About 7 percent of schools reported that the majority of their courses were supported by a single commercial source, and the mean number of such courses across all respondents was two. Respondents also reported that "if commercial support were no longer provided, the typical school would no longer hold 11 courses, representing 23% of the school's courses" (p. 3).

Because they depend on industry for almost three-quarters of their income, MECCs could be severely challenged by an end to direct commercial funding, which some have proposed (Fletcher, 2008), or by a decision by medical product companies to shift their support to academic institutions, as one company recently did (Loftus, 2008). They could still have a role if academic medical centers continued to contract with them to manage or administer some of their continuing medical education programs.

Providers of accredited continuing medical education may solicit industry support for their programs. For example, a medical education company described opportunities to provide educational grants for a large meeting sponsored jointly with an academic medical center, as shown in Box 5-2. Other organizations sell sponsorship opportunities for everything from meeting coffee breaks to hand sanitizers and flash drives.

In addition to support for organizational programs, industry also provides support to individual physicians. On the basis of the findings from a 2004 survey, Campbell and colleagues (2007a) found that 26 percent of physicians reported that industry paid for their admission to continuing medical education meetings and 16 percent reported payments for serving as a speaker or on a speakers bureau.

Conceptually, industry support may be direct or indirect. Direct funding is from the company to the program provider. Indirect funding may occur in several ways. The company may set up a foundation that it substantially controls to provide the funding, or the provider may set up a foundation to receive the funds. Such arrangements may not provide any protection against the company influencing the content of the accredited continuing medical education. Alternatively, the company may provide funds to an intermediary, such as a central continuing medical education office in an academic health center. These arrangements are intended to separate the funding from decisions about the course content. The committee has heard criticisms that despite ACCME requirements that course directors review the course content for bias, the recipient of industry funds may have an implicit understanding that additional industry funds will not be offered in the future if the course does not present topics of interest to the company and use speakers who are favorable to the company's products.

BOX 5-2
Example of a Solicitation of Industry Support (Educational Grants) for a Large Accredited Continuing Medical Education Program

Several support levels are listed below. Please note that educational support is appreciated at any dollar level. Please contact our office for further details. We appreciate that our supporters recognize the need for [the organization] to maintain authority and autonomy in decisions regarding program format, content, and faculty.

Cornerstone Supporter
Total: $195,000
Foundation Supporter
Total: $135,000
Leadership Supporter
Total: $80,000

Satellite Symposia
Open to Cornerstone and Foundation Supporters

1 Breakfast Symposium	Fee: $15,000
1 Lunch Symposium	Fee: $20,000
1 Breakfast Symposium	Fee: $15,000
1 Lunch Symposium	Fee: $20,000
1 Breakfast Symposium	Fee: $15,000

Symposium fee includes:

- Program listing on the [meeting] website, linking to the program provider's online registration site for the satellite symposium.
- Program listing and schedule in the meeting materials distributed to all meeting attendees.
- One complimentary email to the preregistration mailing list for use in promotion of the satellite symposium.
- One time complimentary use of the preregistration mailing list for use in promotion of the satellite symposium (restrictions apply).
- One insert into the delegate literature bag for use in promotion of the satellite symposium.

SOURCE: Excerpted from Oncology Congress, 2008, 2009.

Concerns About Industry Support for Accredited Continuing Medical Education

The substantial support that industry provides for accredited continuing medical education indirectly subsidizes physicians who pay less

for many accredited continuing medical education programs than they otherwise would. As the preceding section indicates, industry support also contributes to the financial well-being of many educational providers that depend on it for the major part of their income for the provision of accredited continuing medical education.

The committee found little systematic research on other consequences of industry-supported continuing medical education, for example, whether it promotes bias in individual programs or in overall educational offerings. One study published before the adoption of the first ACCME standards for commercial support compared programs funded by rival pharmaceutical companies and found that the programs favored the products of their funders (Bowman, 1986). A study by Orlowski and Wateska (1992) focused on a kind of industry-sponsored activity that provoked considerable criticism and that now is not permitted for accredited education, that is, a program held at a resort with all expenses paid for attendees and with limited time actually devoted to the educational content. The authors found, using actual prescribing data obtained before and after the activity, that this "elaborate promotional technique . . . was associated with a significant increase in the prescribing of the promoted drugs at one institution" (p. 273). The investigators also found that the physicians involved did not believe that the activity would affect their practices.

Another study found that courses on primary care directed by academic faculty covered a broader range of topics than symposia sponsored directly by industry (Katz et al., 2002). Moreover, 91 percent of the industry-sponsored symposia were sponsored by a company that had recently obtained FDA approval for a drug related to the symposium topic. The industry-sponsored symposia did not cover prevention screening, dermatological diagnoses, child abuse, alcoholism, or the technology resources available for clinicians, which were considered important in the academic program. In that study, the university-based accredited continuing medical education courses received funding from multiple companies through a MECC to the university. University faculty determined the content of their courses, and the MECC handled marketing and meeting logistics. During meal breaks at these courses, symposia funded by industry were also offered.

Unfortunately, much information about accredited continuing medical education, particularly that offered by for-profit providers, is not based on good data but, rather, is based on personal experiences with covert relationships with providers or inferences made on the basis of the nearly total dependence of these providers on pharmaceutical, medical device, and biotechnology companies. One 2008 article, based on personal experience, describes how accredited continuing medical education providers can tailor programs to secure company grants (Gilbert, 2008, unpaged). A commer-

cial provider selected a program concept to "provide a platform for one of the sponsors," which was working on a drug covered by the program. The provider also organized informal workshops with experts who were hired on the basis of their support for the sponsor's message.

Using a checklist that they developed to assess bias in education programs, Takhar and colleagues (2007) concluded that 9 of the 17 continuing medical education programs that they assessed were biased (e.g., by limiting the discussion to the sponsor's product and ignoring alternatives). Work is needed to validate this and other instruments that are intended to be used to assess bias in presentations retrospectively or identify presentations at risk of bias during the planning stage (see, e.g., Barnes et al. [2007]).

The Senate Finance Committee staff report on the use of educational grants by pharmaceutical manufacturers noted that ACCME's reports documented numerous cases of undue influence by companies over "supposedly independent educational programs" (Finance Committee, U.S. Senate, 2007, p. 2). For example, during 2005 and 2006, 18 of 76 program providers were found to be out of compliance with at least one of the ACCME standards related to independence, and some were cited for being under the improper influence of industry.

More specific information on industry practices comes from litigation. Prompted in many instances by whistleblower complaints, the U.S. Department of Justice as well as state attorneys general have filed charges against a number of pharmaceutical and medical device companies for illegal practices related to purported educational activities as well as speaking and writing arrangements. In some cases, one focus of litigation has been the giving of educational grants as an inducement to use the company's products, which can be illegal under the Medicare law. In other cases, the focus has been on industry efforts to bias the content of educational programs and presentations, particularly as part of efforts to promote the off-label use of drugs (i.e., for purposes not approved by the FDA), which is also illegal.[10]

Box 5-3 lists some of the cases in which settlements have been reached. Internal company documents that were made public as a result of the first case described in the box provided insights into the use of speakers bureaus (which included chairs of neurology departments), "educational" teleconferences, and grants to medical education companies (with multiple ties to the company) to further marketing objectives for the drug Neurontin (gabapentin) (Steinman et al., 2006; see also Landefeld and Steinman [2009]).

[10] In 1997, the FDA provided guidance on the characteristics of industry-supported educational activities that distinguish them from promotional activities, which are subject to the labeling and advertising provisions of the Federal Food, Drug, and Cosmetic Act (FDA, 1997). This guidance stresses the role of voluntary oversight, for example, through accreditation; it explicitly disavows an interest in regulating programs.

BOX 5-3
Settlements Involving Educational Activities and Speaking and Writing Arrangements

In 2004, Warner-Lambert paid $430 million to settle U.S. Department of Justice charges that the company promoted off-label uses of the drug Neurontin in violation of the Food, Drug, and Cosmetic Act. "This illegal and fraudulent promotion scheme corrupted the information process relied upon by doctors in their medical decision making, thereby putting patients at risk." Tactics included "[paying] doctors to attend so-called 'consultants meetings' in which physicians received a fee for attending expensive dinners or conferences during which presentations about off-label uses of Neurontin were made; . . . [and sponsoring] purportedly 'independent medical education' events on off-label Neurontin uses with extensive input from Warner-Lambert regarding topics, speakers, content, and participants. . . . In at least one instance, when unfavorable remarks were proposed by a speaker, Warner-Lambert offset the negative impact by 'planting' people in the audience to ask questions highlighting the benefits of the drug" (DOJ, 2004, unpaged).

In 2007, Orphan Medical, Inc., agreed to pay $20 million and accept a corporate integrity agreement to settle charges that it had illegally promoted the drug Xyrem (sodium oxybate) for off-label uses. Among other charges, the company was accused of using unrestricted "educational grants" as an inducement for off-label use and paying tens of thousands of dollar in speaker fees to physicians for their promotion of these uses. One of these physicians has been charged criminally for his behavior (DOJ, 2007b). The associated corporate integrity agreement required, among other provisions, that the company create procedures to ensure that sponsored continuing medical education and educational activities be independent and nonpromotional (OIG, 2007).

In 2008, in a stipulated agreement filed in Oregon, Merck & Co, Inc., agreed to pay $58 million to 30 states and to end certain deceptive practices used to promote the drug Vioxx (rofecoxib). The stipulation prohibits, among other practices, company use of ghostwriting of published journal articles and the nondisclosure of promotional ties with speakers at independent continuing medical education programs (Oregon DOJ, 2008a).

The conditions associated with the settlement in the case specified requirements for the company's reporting of its support for continuing medical education and its financial relationships with speakers and participants (OIG, 2004).[11]

[11] The corporate integrity agreement was signed by Pfizer, which had purchased Warner-Lambert, which, in turn, was the parent company of Parke-Davis, the company named in the case.

Responses to Concerns About Bias in Industry-Funded Accredited Continuing Medical Education

Responses by Private Organizations

Expanded industry support for accredited continuing medical education and the involvement of commercial firms began to become a significant concern in the 1980s and led to ACCME-developed guidelines on commercial support in 1987 and then ACCME-developed standards in 1992. These standards have been criticized as doing little to curb industry influence over the content of accredited continuing medical education (see, e.g., Relman [2001, 2003]; see also Ross et al. [2000], Krimsky [2003], and Brody [2007]). In 2004, ACCME issued new, more restrictive standards.

The accreditation standards now require the disclosure of conflicts of interest by meeting planners as well as speakers. They also require the review of the educational content for bias and the resolution of conflicts of interest in some fashion (e.g., by finding an alternative speaker or identifying and eliminating biased content in a presentation). In addition to the standards, ACCME has developed tools (e.g., definitions, frequently asked questions, and slide presentations) to help educational providers with program implementation.

The SACME survey mentioned above reported that academic providers found the 2004 standards to be difficult to implement (SACME, 2007). Only 5 percent of the respondents considered the standard related to resolving conflicts of interest to be easy to implement. Slightly less than half of the respondents thought that the standards had reduced bias a little or somewhat.

In 2008, the ACCME board of directors adopted a statement that indicated that accredited continuing medical education providers "cannot receive guidance, either nuanced or direct, on the content of the activity or on who should deliver that content" (ACCME, 2008b, p. 3). The organization also announced that it was devoting more resources to implementation and enforcement, which would eventually require an increase in member fees (ACCME, 2008b). In addition, ACCME issued a request for comments on a proposal related to commercial support, which included as options the elimination of commercial support, the continuation of the current situation, and the development of a new paradigm (ACCME, 2008d). The executive summary for the November 2008 board of directors meeting states that analysis of the comments is continuing and that action is not anticipated before the end of 2009 (ACCME, 2008c).

Notwithstanding the changes in ACCME standards, criticisms of industry funding and influence continue (see, e.g., Steinbrook [2005, 2008b] and Fletcher [2008]). ACCME's limited resources for monitoring adherence to

its standards (as of early 2008, it had approximately a dozen staff members) are also a concern (Kopelow, 2008).

Other issues involve the monitoring of the content of presentations. Program-by-program and presentation-by-presentation assessments for bias are labor-intensive activities, and instruments for the systematic assessment for bias need further development and validation. The committee found no studies describing or evaluating the effectiveness, burdens, and adverse consequences of such monitoring for bias overall or by category of accredited continuing medical education provider. ACCME requirements for monitoring may stimulate research in this area.

Some critics raise broader questions about the value, goals, and structure of the current system of accredited continuing medical education (see, e.g., Fletcher [2008]). Some have also proposed ending direct industry support for continuing medical education (see, e.g., Brennan et al. [2006], Fugh-Berman and Batt [2006], CEJA [2008], and Fletcher [2008]). In 2008, the AMA House of Delegates referred back to its Committee on Ethical and Judicial Affairs a proposal that physicians and organizations not accept industry funding for professional medical education (AMA, 2008c; see also Relman [2008]). The summary of a 2008 consensus conference held at the Mayo Clinic describes a conclusion that continuing medical education requires a "strategic management process that focuses on the integrity of an enterprise" and that deals "in a convincing, transparent and accountable manner issues such as commercial interest influence, conflicts of interest, bias, sources of evidence and the quality of product, process and delivery" (Kane, 2008, p. 8). It also stressed the need for research (and funding for research) to guide reforms.

In a 2008 report on industry funding of medical education, AAMC recommended that academic medical centers set up audit procedures to assess compliance with ACCME standards. The report observed that given "the heavy dependence by academic medical centers on industry funding" for continuing medical education, it was essential that they comply with "evolving" ACCME standards and take other steps to ensure the independence of their program offerings (AAMC, 2008c, p. 19). The report also recommended that academic medical centers establish a central office through which all requests for industry support and the receipt of funds for continuing medical education would be coordinated and overseen. It further proposed that institutions should prohibit faculty, students, residents, and fellows from participating in non-ACCME accredited industry events that are labeled as continuing medical education. Also, if medical centers allow faculty participation in industry-sponsored, FDA-regulated programs, they should set standards for appropriate faculty involvement.

In its revised code of conduct, PhRMA includes provisions on industry support for continuing educational programs. With an eye to federal

kickback laws, it advises companies to separate decision making about educational grants from sales and marketing units and to "develop objective criteria for making CME grant decisions to ensure that . . . the financial support is not an inducement to prescribe or recommend a particular medicine or course of treatment" (PhRMA, 2008). For nonaccredited educational activities, the code provides that the organizers of the activity should control its content, faculty, materials, and similar details. As noted earlier, one pharmaceutical company announced that it would no longer fund educational programs offered by MECCs.

Most medical school policies reviewed by the committee already state that their programs should meet the standards for commercial support set forth by ACCME. Some have instituted further restrictions. In 2007, Memorial Sloan-Kettering Cancer Center announced a 6-month trial period during which it would no longer accept industry funding for its continuing medical education programs (industry provided about 25 percent of total funding for continuing medical education at that institution). To reduce costs, off-site programs were moved on-site, free lunches were eliminated, advertising was cut, and fewer external speakers were used. Although the fees for external participants were raised by 10 to 20 percent, program attendance stayed the same (Kovaleski, 2008). The ban on industry funding is now permanent. At least one other institution has also announced that it will no longer accept direct industry funding for specific accredited continuing medical education courses either on or off campus, nor will it accept payments from third parties that have received commercial support (Stanford University School of Medicine, 2008). Industry support is, however, permitted if it is not designated to a specific subject, course, or program but is for use in a broadly defined field and is provided through a central university office for continuing medical education.

Responses by Public Agencies

As described above, the U.S. Department of Justice and state attorneys general have charged a number of companies with illegal practices related to the funding of educational programs, including accredited programs in some instances. In addition, in its 2003 compliance guidelines for pharmaceutical manufacturers, the Office of the Inspector General (OIG) of the U.S. Department of Health and Human Services identified the provision of educational grants as an activity that place a company at high risk for violating federal antikickback rules and certain FDA regulations (OIG, 2003). These compliance guidelines advise manufacturers to separate their grant-making activities from their sales and marketing activities to "help insure that grant funding is not inappropriately influenced by sales or marketing motivations and that the educational purposes of the grant are legitimate"

(p. 21). Other activities identified as having a high potential for fraud and abuse include the provision of gifts, entertainment, and personal services compensation arrangements. The OIG guidelines also recommend (pp. 20–21) that manufacturers

1. separate grant-making functions from sales and marketing functions;
2. establish objective criteria for awarding grants that do not take into account the volume or value of the recipient's purchases;
3. establish objective criteria for awarding grants that ensure that the funded activities are bona fide; and
4. refrain from controlling speakers or content of educational activities funded by grants.

The 2007 Senate Finance Committee staff report cited above concluded that most large pharmaceutical companies had established written policies and procedures on educational grants, limited sales representatives from soliciting requests or promising funding, and established a centralized mechanism for administering grants.

GHOSTWRITING, SPEAKERS BUREAUS, AND INDEPENDENCE OF PUBLICATIONS AND PRESENTATIONS

Concerns about Ghostwritten Publications, Participation in Speakers Bureaus, and Other Industry-Controlled Work

Two hallmarks of academic integrity are intellectual independence and accountability for one's work. Certain practices by medical school faculty create a hidden curriculum that subverts the professional values endorsed by the formal curriculum. One example is taking credit as the author of a manuscript prepared by an unacknowledged or inadequately acknowledged industry-paid writer. (An adequate acknowledgment would specify the roles of these writers, for example, as the preparers of the first draft, as well as the roles of the listed authors.) Another example is participating in an industry speakers bureau or other long-term speaking arrangement with a company, regardless of how the relationship is labeled. One concern is that ongoing company payments for presentations (and travel to attractive locations) create a risk of undue influence. A second concern that is frequently tied to the speakers bureau label is that the company exerts substantial control over the content of a presentation. Industry influence in these arrangements may be direct (e.g., when a talk and slides are largely or entirely prepared by someone else or when speakers are instructed to provide the company-prepared responses to questions and avoid the favorable mention of competing products). Influence may also be less direct (e.g.,

when a company-trained and company-paid physician modifies talks to fit the objectives of the company) (see, e.g., Elliott [2006] and Carlat [2007]). The committee recognizes that companies have an interest in some oversight of presentations for a variety of reasons, including the need to comply with FDA prohibitions on promoting the use of drugs for the treatment of conditions not approved by the agency.

Serving on speakers bureaus appears to be common in clinical medicine. A 2006 survey of academic-industry relationships found that 21 percent of clinical department chairs reported being on a speakers bureau (whereas 2 percent of nonclinical department chairs reported being on a speakers bureau) (Campbell et al., 2007b). As reported earlier, another survey, which was not limited to academics and which asked less specific questions, found that 16 percent of physicians reported serving on a speakers bureau or as a speaker, which could have involved a single presentation (Campbell et al., 2007a). ACGME has expressed concern about "a new variation of a promotional activity in which residents and even medical students receive slides, lecture materials and honoraria and subsequently act as 'experts,' delivering the packaged information at continuing medical education events" (ACGME, 2002, p. 3).

Unacknowledged industry influence over publications is also common. In one study, 13 percent of research articles in major biomedical journals had "ghost" authors, that is, people who filled the criteria for authorship but who were not listed as authors (Flanagin et al., 1998). None of these ghost authors was even acknowledged in the paper. A review of documents obtained during litigation against a major pharmaceutical company concluded that review manuscripts were often prepared by writers for medical publishing companies but authorship was "subsequently attributed . . . to academically affiliated investigators who often did not disclose industry financial support" (Ross et al., 2008, p. 1800). One incident illustrates that such ghostwriting may be discovered only by accident. An academic physician reported that a MECC sent her a draft manuscript of a review article commissioned by a drug company and invited her to be its "author." She declined, but she was subsequently asked by a journal to review an article that was similar to that article and that now had another author (Fugh-Berman, 2005; see also Eaton [2005]). The analysis by Steinman and colleagues (2006) of documents obtained through litigation cited earlier found that those documents describe plans for recruiting academic authors of a series of ghostwritten articles to be prepared by a medical education company. Box 5-3 included examples of company settlements with the Department of Justice related to speaking and writing arrangements.

Another concern about industry relationships is that academic authors of research articles may not have full access to the data from an industry-sponsored study. This issue was discussed in Chapter 4.

In the setting of medical education, the question is not whether assistance by professional writers and others may improve publications and help busy researchers get important, objectively presented findings into print; it may do both. The questions are whether the assistance is hidden, whether it is intended to promote a company's interests rather than present unbiased information, and whether the author takes credit for work that he or she did not do and thus misrepresents the provenance of the article. Such arrangements (which are essentially gifts) send the wrong message about the values of intellectual independence, professional ethics, accountability, and evidence-based medicine. In the context of research, they raise questions about the objectivity of research reports that other researchers as well as practitioners and developers of practice guidelines rely on.

Responses to Concerns About Independence and Accountability in Writing and Speaking

Medical journal editors (including the International Committee of Medical Journal Editors and the World Association of Medical Editors) have taken steps to eliminate ghostwriting (see, e.g., Rennie et al. [1997], Davidoff et al. [2001], ICMJE [2008], and WAME [2008]). As stated by the International Committee of Medical Journal Editors, "[a]ll persons designated as authors should qualify for authorship, and all those who qualify should be listed" (ICMJE, 2008, p. 3; see also Ross et al. [2008]). The objective of authorship policies is to eliminate unethical practices and generally not to preclude legitimate and properly acknowledged writing assistance (see, e.g., Lagnado [2002] and Woolley et al. [2006]).

As described in Chapter 3, one journal has revised its conflict of interest disclosure form to include questions intended to detect commercial sponsorship and unacknowledged authors after concluding that such questions were necessary to detect ghostwritten or promotional submissions (AFMI, 2008). In its disclosure form for continuing medical education programs, the same professional society asks several questions about relationships with speakers bureaus (e.g., whether an individual is acting independently or as an agent) as well as questions about the receipt of assistance with manuscript preparation from commercial entities (AAFP, 2006b).

In its 2008 report on medical education, AAMC recommended, "[a]cademic medical centers should prohibit physicians, trainees, and students from allowing their professional presentations of any kind, oral or written, to be ghostwritten by any party, industry or otherwise" (AAMC, 2008c, p. 22). It noted that properly acknowledged collaborations with industry personnel or medical writers is not ghostwriting. The report also recommends that participation in industry-sponsored speakers bureaus be discouraged.

A few medical school policies reviewed by the committee mention speakers bureaus by name. For example, the University of Massachusetts views speakers bureaus as an "extension of the marketing process" and forbids faculty participation in them. The Mayo Clinic has long prohibited faculty from speaking on behalf of industry, and its current policy prohibits participation in the speakers bureaus of commercial firms because the linkage would imply endorsement by the Mayo Clinic (personal communication, Marianne Hockema, Administrator, Office of Conflict of Interest Review, Mayo Clinic, September 19, 2008). Faculty at the University of Louisville (2008) are "strongly discouraged" from serving as speakers hired by vendors (p. 4). A policy recently adopted by the Johns Hopkins University School of Medicine (2009) states that faculty may not participate on-site or off-site in "activities with any of the following characteristics . . . a company has the contractual right to dictate what the faculty member says; a company (not the faculty member) creates the slide set (or other presentation materials) and has the final approval of all content and edits; the faculty member receives compensation from the company and acts as the company's employee or spokesperson for the purposes of dissemination of company-generated presentation materials or promotion of company products; and/or a company controls the publicity related to the event" (p. 7). The policy notes that some of these activities occur in the context of speakers bureaus but it is the conditions of an activity that determine whether it is permissible.

In addition, a few medical schools (e.g., the University of California at San Francisco, the University of Louisville, and the University of Colorado) forbid ghostwriting (using that term). A few other medical schools (e.g., Stanford University, the University of Missouri, Emory University, and the University of Rochester) cover the practice of ghostwriting by forbidding medical school personnel from publishing, under their own name, articles that are written entirely or in significant part by an industry employee.

The ACCME standards for commercial support require that presenters disclose relevant financial relationships. They provide no explicit guidance or reference to the appropriateness of commercial assistance in the preparation of talks.

The 2008 PhRMA *Code on Interactions with Healthcare Professionals* notes that companies and speakers should understand the difference between (accredited) continuing medical education and company-sponsored speaker programs (PhRMA, 2008). For the latter, "[s]peaker training is an essential activity because the FDA holds companies accountable for the presentations of their speakers" (p. 9). This is a reference to FDA's ban on company promotion of the use of a medication for the treatment of conditions that have not been approved by the agency (FDA, 1997). The

PhRMA code specifies that company policies should provide a cap on the total annual amount that it will pay a speaker and address the "appropriate number of engagements for any particular speaker over time" (p. 10).

RECOMMENDATIONS

Medical Schools and Residency Programs

Policies on Relationships with Industry

This chapter has documented the extensive relationships that exist between industry and medical institutions, faculty, students, and residents and the concerns that have been raised about the risks that these relationships pose to the basic educational missions of academic medical centers and the lack of benefits from such relationships, such as those that support academic-industry collaborations in medical research. It has cited research indicating that even small gifts can be influential and has reviewed the recommendations of organizations such as AAMC and PhRMA. The committee concluded that it is time for medical schools to end a number of long-accepted relationships and practices that create conflicts of interest, threaten the integrity of their missions and their reputations, and put public trust in jeopardy. The risks are substantial and are not offset by meaningful benefits.

RECOMMENDATION 5.1 For all faculty, students, residents, and fellows and for all associated training sites, academic medical centers and teaching hospitals should adopt and implement policies that prohibit

- **the acceptance of items of material value from pharmaceutical, medical device, and biotechnology companies, except in specified situations;**
- **educational presentations or scientific publications that are controlled by industry or that contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged;**
- **consulting arrangements that are not based on written contracts for expert services to be paid for at fair market value;**
- **access by drug and medical device sales representatives, except by faculty invitation, in accordance with institutional policies, in certain specified situations for training, patient safety, or the evaluation of medical devices; and**
- **the use of drug samples, except in specified situations for patients who lack financial access to medications.**

Until their institutions adopt these recommendations, faculty and trainees at academic medical centers and teaching hospitals should voluntarily adopt them as standards for their own conduct.

This recommendation has several targets, most of which focus on promotional relationships. One target is the acceptance by faculty or trainees of items of material value (including small gifts and meals) from industry except in certain situations. These situations, which should be defined in institutional policies, include (1) appropriate payment for legitimate services (such as contracts, grants, and consulting arrangements); (2) charitable donations, which should be given to the institution; and (3) sharing of research materials or data. Under appropriate transfer agreements, the sharing of research materials or data is encouraged, as it promotes medical research. This recommendation covers not only physical gifts, such as pens, notepads, and meals, but also preferences, such as paid speaking engagements that are intended as rewards or inducements. Consulting arrangements and drug samples are discussed further below.

The second target of this recommendation is the involvement of faculty or trainees in presentations or publications for which they cannot ethically claim credit or intellectual independence. Although no physician or researcher should accept authorship of a ghostwritten academic publication (see the discussion earlier in this chapter), failure to meet this standard is particularly troublesome when it involves faculty who have a special obligation to demonstrate intellectual independence and to act as role models. For similar reasons, faculty should not participate in speakers bureaus and similar promotional activities in which they either present content directly controlled by industry or formulate their remarks to win favor and continued speaking fees. If institutions fail to adopt these recommendations, then acceptance of authorship for ghostwritten publications or industry-controlled presentations would constitute a gift to be disclosed to the institution even if the institution's policies do not explicitly mention these arrangements as gifts.

The recommendation's third target is consulting arrangements. Faculty should engage only in bona fide consulting arrangements that require their expertise, that are based on written contracts with specific tasks and deliverables, and that are paid for at fair market value. As part of their administration of conflict of interest policies, university review of faculty consulting and other contracts is prudent and desirable.

The fourth target of this recommendation concerns access to educational environments by sales representatives of pharmaceutical, medical device, or biotechnology companies. Clinical teaching should be done by faculty, not by marketing agents. The recommended restrictions on site access should not discourage appropriate and productive research collabora-

tions between industry and academic researchers. In addition to promoting scientific progress and the development of useful products, collaborations can provide educational benefits to medical students, graduate students, and postdoctoral fellows who might participate in legitimate collaborative research projects with industry under proper supervision.

As described earlier, the AAMC recommendations and some medical school policies set stringent restrictions on access by pharmaceutical sales representatives but establish slightly less restrictive conditions for access by representatives of medical device companies. The recommendations and policies reflect assessments that access by device representatives—if they are properly managed and appropriately limited—can contribute to patient safety. Nonetheless, the expectation is that faculty will quickly learn how to use complex new devices, including relevant surgical techniques, and will then instruct and supervise residents and fellows rather than rely on company representatives to do so. Access under these circumstances would occur after the institutional purchase of a complex device. For the purposes of device evaluation, access by the device representatives would occur before purchase of the device.

The fifth target of this recommendation, which covers drug samples, presents difficult issues. Caring for patients who cannot afford needed drugs is frustrating for physicians who are trying to meet their professional obligations to act in their patients' best interests. Despite the aid provided through Medicaid and Medicare, other public programs, and the patient access initiatives of pharmaceutical companies, many patients are not eligible for such aid and cannot afford to continue to take medications after they have used a sample. Moreover, although physicians and others may believe that drug samples allow low-income patients access to drugs that they could not readily obtain otherwise, this chapter has cited research that suggests that most samples are not, in fact, given to indigent patients and that access to samples may change trainee behavior such that they move away from practicing evidence-based and lower-cost care. Drug samples are not a satisfactory answer to the serious problem of the lack of affordability of medications for many patients, but the committee was reluctant to call on physicians to abandon them completely in the short term.

For academic medical centers, the use of drug samples may often be managed without a direct interaction between a physician and a company representative. Thus, AAMC recommends and this committee agrees that samples (if the institution permits them) should, whenever possible, be centrally managed in ways that allow timely and appropriate patient access.

In the absence of such centralized arrangements, institutions should limit the provision of free drug samples and provide them only to patients who lack financial access to medications in situations in which generic alternatives are not available and the sample medication can be continued at

little or no cost to the patient for as long as it is needed. They should also help physicians and patients use alternative public and private resources to obtain the needed medications. The proposal by the Medicare Payment Advisory Commission for company reporting and U.S. Department of Health and Human Services analysis of data about the distribution of drug samples cited earlier in this chapter could, if it is adopted, produce helpful information to guide future policies.

The elements of this recommendation apply both to campus settings and to off-site settings, for example, off-site locations for professional meetings and educational programs. They also apply to volunteer faculty who provide clinical education in their offices or in community hospitals. Chapter 6 presents a parallel recommendation (Recommendation 6.1) for physicians who are not affiliated with academic institutions. That chapter also presents a comprehensive recommendation (Recommendation 6.2) that calls for medical product companies to change their policies to be consistent with these recommendations. The committee recognizes that it takes time for academic medical centers to develop policies. It recognizes the value of policy development processes that involve the assessment of local conditions, the inclusion of those who will be affected, and investigation of the experiences of similar institutions.

Until institutions act, faculty, students, and trainees should still change their own behavior so that it is in line with the recommendations presented above. In addition, consistent with Recommendation 9.1, the committee encourages AAMC, AMSA, and similar membership organizations to continue or initiate survey, monitoring, and other activities to promote the reform of conflict of interest policies in medical education.

Education on Relationships with Industry

RECOMMENDATION 5.2 Academic medical centers and teaching hospitals should educate faculty, medical students, and residents on how to avoid or manage conflicts of interest and relationships with pharmaceutical and medical device industry representatives. Accrediting organizations should develop standards that require formal education on these topics.

Changing the environment within educational institutions is important, but medical schools also need to prepare trainees for practice in environments that may be characterized by more permissive standards of conduct regarding drug and device marketing. Faculty will continue to experience a range of situations in which they will interact with industry representatives and will also need to be prepared to act as educators and role models on industry relationships.

The committee recognizes that the evidence on the effectiveness of educational programs of this sort on physician attitudes and behaviors is not strong, but it believes that a basic level of education supports the development of core competencies and prepares students and trainees for future practice. The establishment of educational standards will help ensure that such education is of high quality and receives appropriate attention.

Accredited Continuing Medical Education

The members of the committee had extensive internal discussions about industry support for accredited continuing medical education. Overall, there was general agreement that continuing medical education has become far too reliant on industry funding and that such funding tends to promote a narrow focus on products and to neglect the provision of a broader education on alternative strategies for managing health conditions and other important issues, such as communication and prevention. Given the lack of validated and efficient tools for preventing or detecting bias, industry funding creates a substantial risk of bias, to the extent that industry-reliant providers want to attract industry support for future programs. Although the committee did not reach agreement on a specific path to reform, it concluded that the current system of funding is unacceptable and should not continue.

RECOMMENDATION 5.3 A new system of funding accredited continuing medical education should be developed that is free of industry influence, enhances public trust in the integrity of the system, and provides high-quality education. A consensus development process that includes representatives of the member organizations that created the accrediting body for continuing medical education, members of the public, and representatives of organizations such as certification boards that rely on continuing medical education should be convened to propose within 24 months of the publication of this report a funding system that will meet these goals.

One option is for this broad-based consensus development process to be convened by the member organizations of ACCME. As described earlier in this chapter, they represent medical specialty boards (American Board of Medical Specialties), hospitals (AHA and the Association for Hospital Medical Education), organized medicine (AMA), medical schools (AAMC), medical specialty societies (CMSS), and state licensure boards (Federation of State Medical Boards). Although these organizations have interests in continuing medical education and in ensuring that continuing education is

free of bias and supports core competencies, they do not all have a vested interest in the current system of funding that education.

The consensus development process convened by this or another group should be broad based and should also include representatives of other medical education accrediting bodies (LCME and ACGME), other interested state and federal agencies, public interest and patient advocacy groups, and organizations such as specialty certification boards that rely on continuing medical education. It should also include providers of accredited continuing medical education and industry funders. The deliberations should take into account the findings of other groups that have analyzed funding for continuing medical education or that have made recommendations about improving continuing medical educational methods.

Most committee members believed that a near-term end to industry funding would be unacceptably disruptive for the major providers of accredited continuing medical education, including medical schools and professional societies, which together provide 68 percent of the total number of hours of this type of education (see Table 5-2). A SACME survey found that 77 percent of respondents said that immediate elimination of commercial support would substantially reduce the number of courses at their academic centers and the scope of their programs and could potentially lead to the elimination of programs (SACME, 2008b). Eliminating all industry funding without having in place an alternative model could have other adverse consequences. For example, a surgical society may hold a premeeting accredited workshop involving hands-on teaching of surgical techniques, typically supported by indirect funds from industry. In the committee's experience, the costs of setup and materials for multiple simultaneous workshops can be several million dollars and would be hard to cover by payments from attendees. Furthermore, other innovative educational formats—for example, Internet-based training, simulation-based training, and performance improvement learning activities—also require funding for start-up and updating costs that could be prohibitive for providers to self-fund or fund entirely through nonindustry sources.

A majority of the committee supported the use of a consensus development process to develop a new funding system for accredited continuing medical education that would be free of industry influence but that would leave open the possibility of certain forms of indirect industry funding under conditions that minimized the risk of undue influence on program content. Some committee members supported the use of a consensus development process to develop an alternative funding model but believed that no form of direct or indirect industry funding was acceptable.

Among the options that the consensus development activity could consider are proposals for some kind of pooled funding mechanism. For example, companies could grant funds to some independent central or regional

entity that would establish educational priorities and make decisions—perhaps within broad categories—about the distribution of funds on the basis of an independent review of applications from education providers.

Both direct company funding to institutions for specific continuing medical education programs and direct company provision of unrestricted grants to institutions offer clear opportunities for undue influence, particularly for continuing medical education providers that also receive the great majority of their funding overall from companies. A plan for a system free from industry influence would exclude such funding as well as funding from company-controlled foundations.

The committee recognizes that industry willingness to provide funds under a restructured system of funding accredited continuing medical education might be quite limited. Thus, the consensus development process would also need to consider alternative means of financing, steps to reduce program costs, and other strategies that would support high-quality continuing medical education. Options include increased fees for attendees; subsidies from academic medical centers as part of their educational missions; elimination of expensive program locales and amenities; reduced payments to speakers; collaboration among education providers to share the costs of developing certain expensive programs; and rethinking the purpose and methods of continuing medical education, as is already being done in the development of programs for the maintenance of certification by specialty societies. Higher fees might be a particular burden for physicians with lower-than-average professional incomes, including rural physicians and physicians serving disadvantaged populations.

The committee members who opposed any industry funding of continuing medical education through any mechanism believed that physicians (or their employers) should bear the entire cost of accredited continuing medical education that is required for renewal of licensure and specialty certification. Even giving industry funding and program decision-making responsibility to a central office within a medical school, MECC, or other institution would unnecessarily retain conflicts of interest over the choice of course topics, directors, content and speakers, and the leadership of the continuing medical education office. In the view of these committee members, all industry support for accredited continuing medical education should be rejected, just as it is for most undergraduate and graduate medical education.

In the process of hearing testimony relevant to the issue of funding of continuing medical education, many committee members came to the conclusion that a number of other fundamental problems about the focus and the effectiveness of continuing medical education warranted attention. These issues were outside of the purview of the committee. Some will be considered by another committee of the Institute of Medicine, which is

charged with making recommendations about the promotion of more effective methods of life-long education for health professionals (IOM, 2009). Analyses of the financing of continuing medical education are planned in conjunction with that project. Those analyses may provide a better understanding of the implications of different proposals about financing in the context of other changes in the system.

The committee focused on accredited continuing medical education. As noted earlier, some nonaccredited activities with industry support are educational rather than promotional and apply safeguards to prevent bias in the selection of topics, speakers, and materials presented. One example is the scientific symposium that is organized and controlled by a professional society and supported by unrestricted grants from companies. Such meetings may be particularly important for fields with many Ph.D. researchers and relatively restricted budgets. Another example is training in the use of complex medical devices provided by medical device companies under the conditions outlined elsewhere in this report (e.g., no gifts or inducements to use the product).

Other Recommendations in This Report

In addition to the recommendations in this chapter, other recommendations in this report would affect institutions that provide undergraduate, graduate, or continuing medical education. The standardization of institutional disclosure policies and formats (Recommendation 3.3) would require work to change policies and information systems, but in the long term, it should make institutional policies less burdensome across all educational institutions—as well as for individuals who must disclose potential conflicts of interest. Academic medical centers, which have repeatedly been embarrassed by revelations of incomplete and inaccurate faculty disclosures of payments from industry, would benefit from a national program of company reporting of payments to physicians and researchers that would allow the verification of certain disclosures (Recommendation 3.4). Because that reporting program would also cover payments to academic medical centers and other providers of medical education, it could provide an incentive for the adoption of institution-level conflict of interest policies, as recommended in this report (Recommendation 8.1). Accrediting organizations, membership groups such as AAMC and CMSS, and government agencies should also develop incentives for institutions to adopt and implement conflict of interest policies (Recommendation 9.2).

Adoption of the recommendation related to the conduct of research in which an investigator has a financial interest would encourage the development of management plans to protect trainees involved in such research if the institution concludes that the participation by the investigator with a

conflict of interest in the research is essential (Recommendation 4.1). To the extent that physicians embrace Recommendation 6.1 to reject gifts and similar ties, it would reduce dissonance when students, trainees, and faculty interact with others in the medical community at professional society meetings and in other contexts. Further steps by companies to reform their policies and practices on gifts and payments to physicians (Recommendation 6.2) would allow medical centers to focus more attention on other issues, for example, consulting and other contractual arrangements. Finally, academic institutions can play an important role in implementing a program of research on conflict of interest (Recommendation 9.2).

6

Conflicts of Interest and Medical Practice

A position statement of the American College of Physicians (ACP) observed that "[p]hysicians meet industry representatives at the office and at professional meetings, collaborate in community-based research, and develop or invest in health-related industries. In all of these spheres, partnered activities often offer important opportunities to advance medical knowledge and patient care, but they also create an opportunity for the introduction of bias" (Coyle et al., 2002a, p. 397). This chapter examines these relationships and the sources of conflicts of interest in the context of practicing physicians' primary professional obligations.

Professionals are granted important privileges—including the power to set educational and ethical standards—in return for maintaining competence, being trustworthy and ethical, and working to benefit patients and society. The power to set standards creates certain tensions. As Pellegrino and Relman (1999) have written, "[t]oo often, ethical goals have been commingled with protection of self-interest, privilege, and prerogative. Yet, effacement of self-interest is the distinguishing feature of a true profession that sets it apart from other occupations" (p. 984).

In the realm of patient care, threats to professionalism and questions about conflicts of interest may arise in several situations, some of which involve pharmaceutical, medical device, and biotechnology companies and some of which do not. This chapter focuses on physician financial relationships with industry that usually are not intrinsic to medical practice and that can be avoided. These relationships create conflicts of interest when physicians

- accept company gifts of various kinds, including meals and drug samples;

- act as promotional speakers or writers on behalf of companies; or
- have a financial interest in a medical product company whose products they prescribe, use, or recommend.

In addition, conflicts of interest arise from the ways in which physicians are paid for their services. These conflicts are inherent in any payment system, although each payment method raises different concerns. Physician ownership of health care facilities and self-referral practices also present important and widespread conflicts of interest that have challenged government in its efforts to manage, limit, or eliminate them.

This chapter begins with a brief discussion of physician payment and facility ownership interests as parts of the broader context of medical practice. As planned by the Institute of Medicine, this study was not intended to consider recommendations on physician payment; that is a primary charge of the Medicare Payment Advisory Commission (MedPAC; a body that advises the U.S. Congress). The committee also was not constituted to consider physician ownership and self-referral issues, which would have involved the in-depth examination of a complex regulatory and commercial environment. Therefore, the discussion of these topics is only brief.

The chapter then examines industry promotional activities aimed at practicing physicians and also reviews the responses to concerns about physician financial relationships with industry from private organizations and public agencies. Because the committee considered financial relationships with industry in the context of physicians' professional obligations, the chapter includes a discussion of professional codes of conduct and statements on conflicts of interest in medical practice from professional societies. The chapter concludes with recommendations for the physician community; health care providers; and pharmaceutical, medical device, and biotechnology companies.

THE BROADER CONTEXT: PHYSICIAN PAYMENT, SELF-REFERRAL, AND CONFLICTS OF INTEREST IN MEDICAL PRACTICE

The environment of medical practice has changed significantly in recent decades. Physicians providing patient care have experienced reduced autonomy, increased administrative burdens, and declining incomes. As shown in Figure 6-1, the real income of physicians from medical practice declined about 7 percent from 1995 to 2003, a pattern that contrasts with that for other professional and technical workers. Flat or declining fees from public and private payers appear to be a major contributor to the trend (Tu and Ginsburg, 2006). Although the committee did not locate a

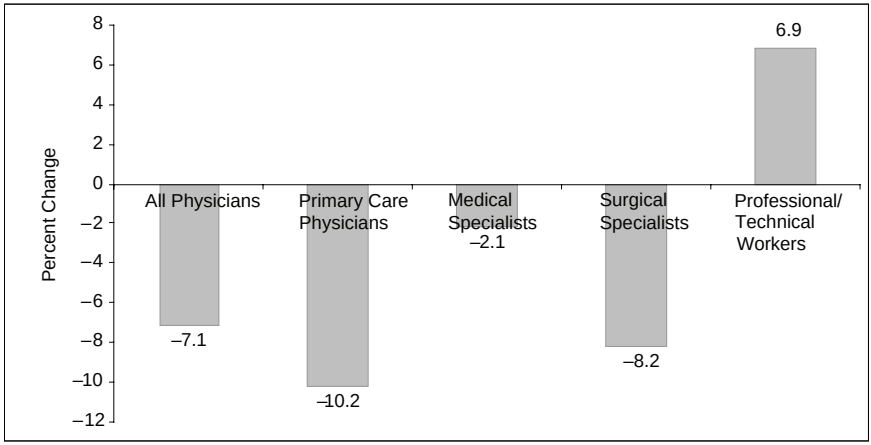

FIGURE 6-1 Percent change in average net physician income, adjusted for inflation, 1995 to 2003. Physician income data are based on reported net income from the practice of medicine (after expenses and before taxes). SOURCE: Tu and Ginsburg, 2006.

more recent analysis of trends, some data (e.g., comparisons of Bureau of Labor Statistics physician and surgeon income data for 2006 and 2007) suggest a more favorable income picture in recent years.

Physician Payment and Conflicts of Interest

Researchers and policy makers have devoted considerable attention to the day-to-day incentives for inappropriate clinical practice related to physician payment arrangements. Each major method of paying physicians has the potential to put physicians' primary interest in promoting the best interests of their patients at odds with their secondary financial interests.

Many studies have concluded that paying physicians for each service that they provide creates incentives for physicians to increase the volume of services, which also increases their income and society's spending for health care (see the reviews by CBO [1986], OTA [1986], PPRC [1987], Smith [1992], and Hsiao et al. [1993]). In addition, the appropriate pricing of specific services and categories of services is a concern (see, e.g., Ginsburg and Grossman [2005] and Bodenheimer et al. [2007]). Higher levels of reimbursement for procedures (e.g., surgeries, invasive procedures, diagnostic imaging, and chemotherapy) compared with the level of reimbursement for non-procedure-related services (e.g., history taking, medical evaluations, and counseling) have contributed to an escalation in the use of procedures and to the shift in the performance of certain lucrative procedural services

from hospitals to physicians' offices. One analysis of information from national surveys and long-term, in-depth studies of 12 local markets concluded that physicians' business practices contribute to higher costs and that "policymakers may need to revisit regulation of physicians' conflicts of interest and consider how their financial incentives could be realigned" (Pham et al., 2004, p. 70).

Payments to physicians on a capitated basis (i.e., a fixed, per person payment for a patient population) and managed care restrictions on referrals and certain services raise concerns about the underprovision of needed care (see, e.g., Hillman [1987], GAO [1995], Rodwin [1996], and Sulmasy et al. [2000]). In general, payment methods have become more complex as public and private health insurers have offered incentive payments to physicians related to quality standards, patient satisfaction, and better patient outcomes (see, e.g., Epstein et al. [2004], MedPAC [2005c], Rosenthal et al. [2007], and Nicholson et al. [2008]).

Self-Referral and Physician Ownership of Health Care Facilities

A former editor of the *New England Journal of Medicine* observed that "[p]hysicians have been conflicted about their dual roles as professionals and businessmen for millennia, but this dilemma has sharpened in recent years as income from the practice of medicine has faltered" (Kassirer, 2001, p. 159). The dilemma is particularly evident, first, in the growth of physician ownership of (or other business arrangements with) outpatient diagnostic or treatment centers and specialty hospitals to which they refer patients and, second, in the increase in expensive in-office ancillary equipment (e.g., equipment used for imaging and other diagnostic services ordered by the physician owner). As described by Pham and Ginsburg (2007)

> The allure of profitable services has led to increased physician ownership of ambulatory surgical, imaging, and endoscopy centers and other free-standing facilities such as specialty hospitals. For example, the number of cardiac and orthopedic specialty hospitals serving Medicare patients grew from twenty-one in 1998 to sixty-seven in 2003, the majority of which were for-profit and owned in part by physicians. The number of ambulatory surgery centers (ASCs) grew more than 35 percent between 2000 and 2004, with 83 percent of existing centers partly or wholly owned by physicians. In addition, physicians have brought the capacity for more diagnostic and therapeutic procedures into their practices. (p. 1591)

Physicians' ownership interests in facilities to which they refer patients constitute a conflict of interest. Their secondary interest (i.e., increased income from increased services) has the potential to bias physicians' primary interest in their patients' welfare. Such conflicts of interest may harm

patients who receive unnecessary services and may also harm society, which is burdened by excess spending on these services. In fact, some research has contradicted claims that physician ownership improves access for underserved populations (see, e.g., OIG [1989], Hillman et al. [1990], and Mitchell and Scott [1992]).

Concerns about physician self-referral have prompted the passage of complex federal legislation and the implementation of regulations (often collectively referred to as the "Stark laws," after the sponsor of relevant provisions in the Omnibus Budget Reconciliation Act of 1989 and other legislation). In general, federal law prohibits physicians from referring Medicare or Medicaid beneficiaries to entities for "designated health services" if the physicians or their immediate family members have ownership or investment interests in the entities or have compensation arrangements with the entities (42 USC 1395nn and 42 USC 1396b(s)).[1]

In 2008, the Centers for Medicare and Medicaid Services issued a new rule requiring physicians to disclose to patients the physician's ownership of or investment in hospitals (CMS, 2008). It is too early to evaluate the experience with this requirement, although the discussion reviewed in Chapter 3 suggests that the need for caution in assuming the effectiveness of disclosure alone as a safeguard against making biased recommendations. In 2009, MedPAC recommended that Congress require hospitals and other entities that bill Medicare to report physician ownership interests (direct and indirect) and that this information be posted on a public website (MedPAC, 2009). MedPAC also recommended that the secretary of the U.S. Department of Health and Human Services submit a report on the types and prevalence of financial arrangements between physicians and hospitals.

INDUSTRY PROMOTIONAL ACTIVITIES AND PRACTICING PHYSICIANS

Scope and Nature of Marketing Activities

Marketing is a major expense for pharmaceutical companies. A recent analysis estimated that pharmaceutical company expenditures for promotional activities were $57.5 billion in 2004, including $20.4 billion for

[1] "Whole" hospitals are not included under the law, which some suggest has been a factor spurring the growth of physician-owned specialty hospitals (Mitchell, 2008). The law also does not cover the purchase and use of imaging and other ancillary equipment within a physician's office. Designated health services include clinical laboratory services; inpatient and outpatient hospital services; diagnostic radiology services; radiation therapy services and supplies; durable medical equipment and supplies; prosthetics, orthotics, and prosthetic devices and supplies; home health care services; physical therapy services; outpatient prescription drugs; occupational therapy services; and parenteral and enteral nutrients, equipment, and supplies.

detailing (sales visits) by drug company representatives, $15.9 billion for drug samples, and $2.0 billion for meetings (Gagnon and Lexchin, 2008). Little information is available on the marketing of medical devices and biologics.

Pharmaceutical company representatives use a variety of interpersonal techniques, including gift giving, to establish relationships with physicians and promote their products.[2] They may calibrate their approach to their assessments of the physician's personality and intellectual style (see, e.g., Roughead et al. [1998], Fugh-Berman and Ahari [2007], and Greene [2007]). In addition, companies have information on individual physician prescribing practices that they can use to target physicians and then monitor the effects of their relationships (Steinbrook, 2006). As described in Chapter 1 and discussed further in this chapter, some of that information is compiled from physician data sold by the American Medical Association (AMA).

Companies may also use physicians as marketing agents. For example, an article in the *Wall Street Journal* reported data from a market research firm showing that in 2004 pharmaceutical companies sponsored some 237,000 meetings or talks that featured physicians and 134,000 meetings or talks conducted by sales representatives, up from about 60,000 talks of each type in 1998 (Hensley and Martinez, 2005). The same article also cited an internal study conducted by Merck that estimated that discussion groups led by physicians yield almost twice the benefit in terms of additional prescriptions as discussion groups led by sales representatives.

A specific example of the use of physicians for marketing involved a new vaccine for human papillomavirus and cervical cancer. The project signed up "hundreds of doctors and nurses . . . as unofficial spokesmen" who were trained by the pharmaceutical company and were "provided with a multimedia presentation and paid $4,500 for each 50-minute talk, delivered" at company-sponsored meals (Rosenthal, 2008, unpaged).

The scope of pharmaceutical company payments for speeches given by physicians is suggested in a report by the Vermont attorney general based on information received under the state's payment disclosure law (see Chapter 3). Between July 1, 2006, and June 30, 2007, pharmaceutical companies in that state spent almost $3,140,000 on payments to physicians and other providers; 52 percent of the payments were for speaker fees and 30 percent were for food (Sorrell, 2008). As discussed below, companies may

[2] A press release from PeopleMetrics Rx about a study of the influence of drug sales representatives on physician prescribing practices stated that the study found "that sales representatives must develop personal relationships with their physicians to achieve the highest levels of engagement" and that "emotional components such as friendship with the reps are the strongest indicators of Fully Engaged physicians [which] . . . has a positive impact on the duration and frequency of meetings and physician prescribing patterns" (*Business Wire*, 2008).

also market to community physicians through "seeding trials" of medications approved by the Food and Drug Administration.

Surveys of Physician Relationships with Industry

Surveys show that relationships with industry are common among physicians across the nation. In a national probability sample of more than 3,100 physicians, 94 percent reported that they had had some type of relationship with industry during the preceding year. These relationships were primarily the receipt of food in the workplace (83 percent) or drug samples (78 percent) (Campbell et al., 2007a). Thirty-five percent received industry reimbursement for costs associated with professional meetings or continuing medical education; and 28 percent received payments for activities such as consulting, serving on a speakers bureau, or enrolling patients in clinical trials. Cardiologists were more than twice as likely as family practitioners to receive payments, but family practitioners met more frequently with industry representatives than physicians in other specialties. Physicians in solo/dual or group practices met more frequently with representatives than physicians practicing in hospitals and clinics. In sum, relationships between physicians and industry are common and vary by specialty, practice type, and professional activities.

Another national survey of physicians also found that relationships with industry are common: 92 percent of physicians had received free drug samples; 61 percent had received meals, tickets to entertainment events, or free travel; and 12 percent had received financial incentives to participate in drug trials (KFF, 2002). The survey found that 15 percent of respondents thought that drug representatives provided "very useful" information, with another 59 percent describing the information as "somewhat useful." Only 9 percent thought that the information was "very accurate," whereas 72 percent thought that it was "somewhat accurate" (KFF, 2002).

A study of community obstetricians-gynecologists reported that most physicians believed that it was appropriate for physicians to accept drug samples (92 percent), a lunch at which information was provided (77 percent), or an anatomical model (75 percent) (Morgan et al., 2006). Just over half (53 percent) thought that it was appropriate for a physician identified as a "high prescriber" to accept a representative's invitation "to sit in" on a market research meeting as a well-paid consultant. In response to a question about whether interactions with industry should be more strictly regulated, 40 percent disagreed, 34 percent agreed, and 26 percent were neutral. As was found in a number of other studies, the respondents thought that other physicians were more likely (probably or almost surely) to be influenced by receiving a drug sample than the respondents were (38 percent for other physicians versus 33 percent for the respondents). The researchers found no

association between the responses and familiarity with the codes of conduct of professional societies.

The studies reported here and in Chapter 5 occurred before the Pharmaceutical Research and Manufacturers of America (PhRMA) revised its *Code on Interactions with Healthcare Professionals* in 2008. These revisions, which set some limits on gift giving and other relationships and which are discussed further below, took effect in January 2009. The Advanced Medical Technology Association (AdvaMed) adopted similar revisions in its *Code of Ethics on Interactions with Health Care Professionals*, effective in July 2009. Thus, it is too early to gauge the effects of these changes on physician relationships with pharmaceutical and medical device companies.

Participation of Community-Based Physicians in Clinical Trials

As mentioned in Chapter 4, physicians in private office settings are increasingly participating in clinical trials that are sponsored by industry and managed by contract research organizations or research site management organizations. The percentage of clinical trials conducted in academic health centers has decreased, and academic health centers are now in the minority among the locations for clinical trials (Klein and Fleischman, 2002). The marketing aspects of some of these trials were described above. The involvement of practicing physicians in clinical trials in the community has potential benefits. For example, their patient pool may be more representative of all patients with the condition being studied than the patient pool of academic physicians, so the results may be more generalizable. Furthermore, the recruitment of participants and the conduct of the study may be more rapid and less expensive in the community setting than in academic medical centers. In addition, such trials may be educational for the participating physicians.

Several concerns have, however, been raised about conflicts of interest in industry-sponsored trials involving community physicians. First, payments to participating physicians may provide incentives to enroll and retain patients, but they may also exceed actual expenses. In guidance provided to pharmaceutical companies, the Office of the Inspector General of the U.S. Department of Health and Human Services has cautioned against payments that exceed fair market amounts for "legitimate, reasonable, and necessary services" (OIG, 2003, p. 21). Second, practicing physicians may have a powerful influence over their patients, perhaps more so than physicians in academic centers, which have high rates of turnover of residents, fellows, and faculty and which allow investigators studying common diseases to recruit participants who are not their personal patients.

In addition, some clinical trials in community practices may be "seed-

ing" trials that companies design to change prescribing habits rather than to gather scientifically useful information (Hill et al., 2008; see also Psaty and Rennie [2006] and Sox and Rennie [2008]). As described in an analysis of documents obtained during litigation, the strategy of such trials is to "target the [clinical] trial to a select group of customers—in this case, primary care physicians; use the trial to demonstrate the value of [the drug] to these physicians; integrate the marketing division and those responsible for trial-related operations in the field with the highest level of precision; and carefully track marketing-related results, that is, rates of [product] prescriptions written by study physicians" (Hill et al., 2008, p. 253). The company in the case under litigation described the physicians as "key customers" (p. 255) and provided them with materials to market their involvement in the study. It also "hid the marketing nature of the trial from participants, physician investigators, and institutional review board members" (Hill et al., 2008, p. 251). As an additional marketing tool, companies may sometimes employ physician opinion leaders as consultants on the use of a drug under study.

A study by Andersen and colleagues (2006) found that general practitioners involved in industry-sponsored studies increased their use of the trial sponsor's drugs, which is consistent with the purpose of using the seeding strategy. Whether the increased use was medically appropriate was not evaluated, but seeding studies subvert ethical standards for research conduct and can put patients at risk.

As part of a broad policy that prohibits or limits many types of company payments to physicians and requires disclosure of other payments, Massachusetts recently issued regulations that require disclosure by companies of payments to physicians for studies "that are designed or sponsored by marketing departments of manufacturers or that are undertaken to increase sales of a particular drug, biologic or medical device" (Lopes, 2009, p. 8). Payments for scientific research need not be disclosed.

Community Versus Academic Practice Environment

Chapter 5 reported on the extensive relationships between academic physicians and industry and discussed industry promotional activities undertaken in the context of graduate and undergraduate medical education. It reported on studies that suggest that industry relationships and promotional activities (e.g., detailing visits) in both academic and general practice settings may influence physician prescribing patterns and requests for additions to hospital formularies. It also reported on studies—conducted mostly in academic settings—that indicate that the provision of free drug samples to physicians may contribute to inappropriate prescribing practices, lower

rates of use of generic and over-the-counter drugs, and increased drug costs.

Chapter 5 also noted that trainees in academic settings have ready access to the latest scientific information through faculty experts and advanced information technologies that they may use to search the medical literature; they do not require interactions with company sales representatives to obtain information on a new drug or its use. Faculty members—in addition to being in the forefront of knowledge development and evaluation in their own fields—also have ready access to the expertise of their colleagues. In contrast, community physicians have less access to such expertise, and that has been one argument in support of visits to community physicians by drug company sales representatives. Sales representatives are, however, tasked with promoting their company's products and not with providing a balanced assessment of the evidence for the use of different clinical options, including nonpharmacologic approaches.

One response to the informational needs of community physicians has been the development of accredited continuing medical education programs. Nevertheless, a recent historical review of pharmaceutical marketing and physician education suggested unintended consequences, that is, the provision of "novel sites of intersection between pharmaceutical marketing and physician education" (Podolsky and Greene, 2008, p. 833). Concern about such consequences has, in turn, produced new approaches, including the "academic detailing" programs described later in this chapter.

In research, the community practice environment is clearly different from the environment in academic medical centers and major teaching hospitals. Although the research may be reviewed in advance by an institutional review board, community physicians may receive no training in the standards of the ethical conduct of research, may have little contact with experienced clinical researchers, and may lack the knowledge needed to review contract or research descriptions provided by a company. In sum, the environment in which community physicians interact with industry may be quite different from the environment of academic physicians discussed in Chapter 5.

RESPONSES TO CONCERNS ABOUT INDUSTRY RELATIONSHIPS AND CONFLICTS OF INTEREST IN COMMUNITY PRACTICE

Responses to concerns about physician financial relationships with industry date back many years. For example, in 1972 the U.S. Congress acted to outlaw certain industry payments or other inducements to physicians. The discussion below focuses on the responses to those concerns made by professional societies, industry, and government. It does not examine responses by provider organizations, such as multispecialty group

practices or hospitals. The committee found no systematic information on the responses by such organizations but identified examples of conflict of interest or other policies that restrict certain individual or organizational relationships with industry (see, e.g., Kaiser Permanente/TPMG [2004], Vesely [2005], and Henry Ford Health System [2007]). Consistent with the emphasis on professional values in this chapter, this section begins with a review of professional society policies.

Professional Societies

Several medical professional organizations have adopted guidelines, codes, or other statements that cover physician relationships with industry, but the committee found no comprehensive overview of statements (or the absence of statements) from professional societies. A selective review of society policies suggests that statements about gifts are fairly common, whereas statements about promotional speaking, ghostwriting, and consulting arrangements are not. A number of professional groups have endorsed a charter for medical professionalism that identifies "maintaining trust by managing conflicts of interest" as 1 of 10 key responsibilities of physicians (ABIM Foundation et al., 2002, p. 245).

Box 6-1 includes excerpts from general statements by AMA and ACP on gifts from industry to physicians. The AMA statement, which was first adopted in 1990, has been endorsed or used as a model by a number of other professional societies, including the American Academy of Pediatrics (Fallat and Glover, 2007), the American College of Obstetricians and Gynecologists (Morgan et al., 2006), and the American College of Rheumatology (ACR, 2007). AMA has also made specific recommendations regarding medical device representatives. It emphasizes that information from or training by such representatives should not be a substitute for the appropriate training of physicians and should be subject to facility policies that govern the presence of such representatives (e.g., informing patients, protecting privacy, and credentialing) (AMA, 2007).

Although ACP strongly discourages the acceptance of gifts and poses some pointed questions for physicians to consider before accepting them, it acknowledges that many physicians feel more comfortable with gifts than the tone of its position statement would imply (Coyle et al., 2002a). The statement observes that "[i]deally, physicians should not accept any promotional gifts or amenities, whatever their value or utility, if they have the potential to cloud professional judgment and compromise patient care" but "[a]s a practical matter, many physicians are comfortable" accepting gifts of modest value that may enhance medical practice or knowledge (p. 398).

BOX 6-1
Excerpts from Statements on Gifts by American Medical Association and American College of Physicians

American Medical Association

Ethical Opinion E-8.061: "Ultimately, it is the responsibility of individual physicians to minimize conflicts of interest that may be at odds with the best interest of patients and to access the necessary information to inform medical recommendations. . . . (1) Any gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value. Accordingly, textbooks, modest meals, and other gifts are appropriate if they serve a genuine educational function. Cash payments should not be accepted. The use of drug samples for personal or family use is permissible as long as these practices do not interfere with patient access to drug samples. . . . (2) Individual gifts of minimal value are permissible as long as the gifts are related to the physician's work (e.g., pens and notepads). . . . (7) No gifts should be accepted if there are strings attached. For example, physicians should not accept gifts if they are given in relation to the physician's prescribing practices" (AMA, 2002 [updated]).

American College of Physicians

"The acceptance by a physician of gifts, hospitality, trips, and subsidies of all types from the health care industry that might diminish, or appear to others to diminish, the objectivity of professional judgment is strongly discouraged. As documented by some studies, the acceptance of even small gifts can affect clinical judgment and heighten the perception and/or reality of a conflict of interest. Accordingly, physicians need to gauge regularly whether any gift relationship is ethically appropriate and evaluate any potential for influence on clinical judgment. In making such evaluations, it is recommended that physicians consider such questions as 1) What would the public or my patients think of this arrangement? 2) What is the purpose of the industry offer? 3) What would my colleagues think about this arrangement? 4) What would I think if my own physician accepted this offer? In all instances, it is the individual responsibility of each physician to assess any potential relationship with industry to assure that it enhances patient care and medical knowledge and does not compromise clinical judgment" (Turton and Snyder, 2007, p. 469, revising Coyle et al., 2002a).

With respect to consulting, the ACP policy also advises physicians to "guard against conflicts of interest when invited to consult or speak for pay on behalf of a company" because "[i]t is likely that a company will retain only individuals who make statements or recommendations that are favorable to its products, thus compromising the physician's scientific objectivity" (Coyle et al., 2002a, p. 399). Furthermore,

> Physicians should also be circumspect if asked to deliver educational programming developed by a medical education and communication company. Such companies, which are largely financed through the pharmaceutical industry, are for-profit developers and vendors of continuing medical education. It is important that physicians retained as lecturers in such settings control the content of the educational modules they deliver rather than allow their presentations to be scripted by the company. Lecturers should screen industry-prepared presentation aids (such as slides and reference materials) to ensure their objectivity and should accept, modify, or refuse them on that basis. Presenters using such materials should disclose their source to audience members. Paid efforts to influence the profession or public opinion about specific medical products are particularly suspect. It is unethical, for example, for physicians to accept commissions for articles, editorials, or medical journal reviews that are actually ghostwritten by industry or public relations firms in an attempt to "manage the press" about certain products or services. (Coyle et al., 2002a, p. 399)

During the course of the committee's work, the Council of Medical Specialty Societies (CMSS) initiated a project to collect best practices on disclosure and limitation of conflict of interest and develop a statement on conflict of interest (The Associated Press, 2008). A CMSS task force recently recommended elements that specialty society policies should include, and it also proposed the development by CMSS of a template for such policies. The task force recommended that societies post their policies and provide information about the financial support that they receive from industry (CMSS, 2008). The CMSS earlier adopted a consensus statement on medical ethics that, among other provisions, states that:

- Physicians should resolve conflicts of interest in a way that gives primacy to the patient's interests.
- Physicians have an ethical obligation to preserve and protect the trust bestowed on them by society (CMSS, 1999, unpaged).

Although this chapter focuses on individual physicians, professional societies as organizations may also have financial relationships with industry. Such relationships include unrestricted educational grants, income from exhibitions and meetings, industry advertisements in the journals of professional societies, and funding for the development of practice guidelines. As discussed further in Chapter 8, such relationships can constitute institutional conflicts of interest, and the committee recommends the adoption of policies on such institution-level conflicts.

The committee found little information about the positions of state medical societies on individual or organizational relationships with medical product companies. The Wisconsin Medical Society announced in 2008 that

its policy (which is not binding on physicians) is now that physicians should not accept gifts from companies whose products they prescribe to their patients. It noted that a "complete ban eases the burdens of compliance, biased decision making, and patient distrust" (WMS, 2008, unpaged).

Industry Codes and Company Actions

As mentioned above, the PhRMA *Code on Interactions with Healthcare Professionals* was revised in 2008 (and was effective in January 2009) and the AdvaMed code was also revised in 2008 (and was effective in July 2009). Some of the PhRMA code's provisions are summarized in Box 6-2. Overall, the revised code discourages noninformational physician-company relationships, such as speaker training programs at resorts and meals provided by sales representatives outside a physician's office or other medical setting. In addition, the revised code provides that the chief executive officers and compliance officers of companies certify yearly that they have a process in place to implement the code. Companies that do that will be identified on the association's website; AdvaMed has announced similar plans.

The 2008 revisions to the PhRMA code also include provisions about contracting arrangements. The document describes several factors as relevant to determining the legitimacy of such arrangement, including whether

- a written contract specifies the nature of the consulting services to be provided and the basis for payment of those services;
- a legitimate need for the consulting services has been identified in advance of requesting services and entering into arrangements with consultants;
- the criteria for selecting consultants are directly related to the identified purpose and the persons responsible for selecting the consultants have the expertise necessary to evaluate whether the particular health care professionals meet those criteria;
- the number of health care professionals retained is not greater than the number reasonably necessary to achieve the identified purpose;
- the retaining company maintains records concerning and makes appropriate use of the services provided by consultants; and
- the venue and circumstances of any meeting with consultants are conducive to the consulting services, and activities related to the services are the primary focus of the meeting; specifically, resorts are not appropriate venues (PhRMA, 2008, p. 8).

Partly in response to U.S. Department of Justice litigation and guidance from the Office of the Inspector General of the U.S. Department of Health

BOX 6-2
Summary of Selected Recent Revisions in the PhRMA *Code on Interactions with Healthcare Professionals*

Companies should not

- offer health care professionals any entertainment or recreational items or any gifts (e.g., notepads, mugs, and pens) that "do not advance disease or treatment education";
- create consulting arrangements as inducements or rewards for prescribing or recommending a particular medicine or course of treatment;
- create speaking engagements as inducements or rewards for prescribing a particular medicine or course of treatment or provide speaker payments above fair market value;
- fund continuing medical education programs as inducement to prescribe or recommend a particular medicine or course of treatment;
- directly subsidize the participation of a health care professional in such a program or in other conferences or professional meetings or create token consulting arrangements to do so indirectly; and
- directly provide meals at continuing medical education events.

Companies may, subject to certain standards,

- have sales representatives make informational visits to physicians and provide modest meals in connection with the visit;
- provide financial support to providers of continuing medical education so that they may reduce registration fees for programs;
- support professional and scientific meetings at appropriate locations in accord with the guidelines of the organizations supported;
- arrange for expert consultants on topics such as the marketplace, patient care, and products;
- sponsor speaker programs and provide training and reasonable compensation for speakers;
- provide scholarships for students and professionals to attend educational conferences; and
- provide educational and practice-related items of modest value to physicians.

and Human Services, some pharmaceutical companies have already revised their contracting practices. In addition, some individual pharmaceutical companies have announced that they will voluntarily post information about a range of payments to individual physicians. For example, Eli Lilly announced that it would create a publicly accessible registry of its payments to physicians beginning in 2009 (Lilly, 2008). Pfizer has released information about its grants and educational awards to medical, scientific, and

patient organizations and has announced that it is eliminating grants to commercial providers of continuing medial education (Pfizer, 2008).

Government Responses

Chapters 1, 3, and 5 discussed various responses by federal and state governments to concerns about financial relationships involving physicians and industry. At the state level, these responses range from laws requiring company disclosure of certain payments to physicians to laws restricting or prohibiting certain relationships. As noted above, some federal agency policies require disclosure of certain physician ownership interests in health care facilities, and MedPAC has proposed a substantial expansion of disclosure of such interests.

As discussed in Chapter 2, conflicts of interest do not necessarily involve actual undue influence, but they may. In some cases, they may be illegal. Federal law prohibits "any remuneration (including any kickback, bribe, or rebate) directly or indirectly, overtly or covertly, in cash or in kind" in return for ordering, purchasing, or referring patients for services or items covered by a federal health care program (42 USC 1320a-7b(b)). Such remuneration has sometimes been disguised as payments to physicians for education, consulting, or research.

In 2003, the Office of the Inspector General of the U.S. Department of Health and Human Services issued guidance for pharmaceutical companies on complying with federal laws and regulations. The guidance included a discussion of how marketing and other relationships with physicians may be designed to reduce the risk of violations of the antikickback laws (OIG, 2003). It advised, for example, that payments for research, consulting, and advisory services be set at fair market value. The guidance also noted that certain practices that are common in other business areas may be illegal in the context of federal health care programs.

For the most part, prosecutions under the statute have been directed at the companies that offer inducements rather than at the individual physicians who accept them. Cases typically do not go to trial but end in financial settlements and compliance and monitoring arrangements (corporate integrity agreements) of some sort. Box 6-3 summarizes a few illustrative settlements of cases that involved various types of financial relationships between companies and physicians.[3]

[3] At the state level, state attorneys general have reached settlements with companies that are similar to those reached by the U.S. Department of Justice. For example, Oregon was the lead state in a $58 million settlement that involved 30 states and a 3-year investigation of deception in the marketing of rofecoxib (Vioxx), and the state was also involved in another multistate settlement involving charges of deceptive marketing of valdecoxib (Bextra) and celecoxib (Celebrex) (Oregon DOJ, 2008a,b).

BOX 6-3
Examples of Prosecutions Involving Kickbacks to Physicians

In 1997, a physician at the Tufts University health maintenance organization reported to federal investigators that a marketer for TAP Pharmaceuticals had offered him an educational grant if he would reverse a health plan decision to list a competing drug in the plan's formulary. Investigators taped company employees offering the physician $65,000 in "education" grants that he could use for any purpose. To settle these and other charges, the company agreed to pay the government $875,000 and enter into a corporate integrity agreement (DOJ, 2001; Studdert et al., 2004).

In 2006, Medtronic agreed to pay $40 million and enter into a corporate integrity agreement to settle charges of improper payments to physicians to promote the company's spinal devices. The improper payments included payments for physicians' attendance and expenses at medical education events and payments made under the guise of consulting, fellowship, royalty, and research activities (DOJ, 2006).

In 2007, the U.S. Department of Justice announced deferred prosecution agreements with four major orthopedic device manufacturers—Zimmer, Depuy, Biomet, and Smith & Nephew—that paid $311 million to settle allegations that they used consulting agreements and other payments as illegal inducements for physicians to use their products during the period from 2002 to 2006. The companies also entered into corporate integrity agreements that would involve extensive monitoring of their consulting needs and arrangements for an 18-month period (DOJ, 2007a).

In 2008, an Arkansas neurologist settled a U.S. Department of Justice civil suit for $1.5 million and also pled guilty to accepting kickbacks—gifts, funds for phony research studies, and sham consulting agreements—from Blackstone Medical, a medical device company (Demske, 2008).

In 2008, Merck reached an agreement with the U.S. Department of Justice to pay $650 million to settle charges that it overcharged Medicaid for three popular drugs and that its sales representatives had devised a variety of illegal arrangements (e.g., payments disguised as being for training, consultation, or market research) to induce physicians to use its products. The company also agreed to a 5-year corporate integrity agreement to prevent future improper conduct (DOJ, 2008).

For the orthopedic device companies mentioned in Box 6-3, the deferred prosecution agreements with the U.S. Department of Justice had some features that are similar to those in some of the conflict of interest policies and proposals discussed in this report. One was that the companies agreed to post on their websites the names of physician consultants and the

payments made to them. In addition, new consulting agreements with physicians would require the physicians to agree to reveal the arrangement to their patients. For the 18-month period that they were in place, the deferred prosecution agreements provided that each company must undertake an assessment of its reasonable needs for educational consulting services and new product development consultants. They also provided for a federal monitor at each company to review compliance for all new and existing consulting relationships with the companies.

Academic Detailing and Other Prescriber Outreach Strategies

As one alternative to physician reliance on company sales representatives for information, "academic detailing" incorporates techniques that pharmaceutical company representatives use. Programs may use in-person visits to physicians by a clinical pharmacist or physician, provide educational materials and branded items, and offer individualized feedback on performance. The goal is to reduce inappropriate prescribing of targeted drugs, for example, inappropriate antibiotics and less effective vasodilators and analgesics. Randomized controlled trials have shown that such educational interventions are effective and have not found adverse clinical consequences (see, e.g., Soumerai and Avorn [1990], Solomon et al. [2001], van Eijk et al. [2001], and Simon et al. [2005]; but see also Lu et al. [2008]). These trials support other studies that suggest that the techniques that pharmaceutical company representatives commonly use are indeed effective in changing physician prescribing behavior.

Some states, including Pennsylvania, South Carolina, and Vermont, have initiated programs using such academic detailing. Pennsylvania's program has an operating budget of approximately $1 million per year, which funds about 1,000 detailing visits by a paid staff (Reck, 2008). Members of the U.S. Congress have proposed the creation of a federal program that would "provide grants or contracts for prescription drug education and outreach for healthcare providers and their patients" (HR 6752, July 31, 2008).

RECOMMENDATIONS

As described in this chapter, relationships between physicians in practice and drug and medical product companies are extensive and have prompted a range of responses from professional societies, government officials, and others. The environment of community medical practice presents challenges different from those posed in academic and research settings. In particular, physicians in community practice often have weaker ties with institutions than academic physicians and a greater degree of autonomy. In addition,

although Chapters 3 and 5 cite questions about the implementation of conflict of interest policies by academic institutions, these institutions are generally in a stronger position to enforce employee adherence to conflict of interest policies than professional societies are to enforce member adherence to their policies and codes of ethics.

Voluntary Action by Individual Physicians

The committee's first recommendation on conflict of interest in medical practice generally parallels that made for academic medical centers, except that it is directed in the first instance at voluntary action by individual physicians. The recommendation also calls on professional societies and health care providers (including hospitals, nursing homes, and hospices) to adopt supportive policies; but the committee believed that it was appropriate to call on physicians directly to adopt practices that are consistent with high standards of professionalism.

RECOMMENDATION 6.1 Physicians, wherever their site of clinical practice, should

- **not accept items of material value from pharmaceutical, medical device, and biotechnology companies except when a transaction involves payment at fair market value for a legitimate service;**
- **not make educational presentations or publish scientific articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged;**
- **not enter into consulting arrangements unless they are based on written contracts for expert services to be paid for at fair market value;**
- **not meet with pharmaceutical and medical device sales representatives except by documented appointment and at the physician's express invitation; and**
- **not accept drug samples except in specified situations for patients who lack financial access to medications.**

Professional societies should amend their policies and codes of professional conduct to support these recommendations. Health care providers should establish policies for their employees and medical staff that are consistent with these recommendations.

The teaching mission of academic medical centers—which includes helping learners at all levels to think critically and appraise the evidence and

providing appropriate role models and mentoring—provides strong arguments for the corresponding recommendations in Chapter 5. Furthermore, physicians in academic settings have ready access to objective, up-to-date information about new therapies, which is often not the case in community practice. The committee recognized the differences in academic and community environments but viewed critical thinking and the appraisal of evidence as key components of life-long learning and medical professionalism for all physicians, wherever their site of practice. The committee believes that entering into the relationships listed in Recommendation 6.1 creates unwarranted risks of compromising physician judgment and undermining public trust—risks that are not outweighed by prospective benefits for patients or society.

Evidence cited in earlier chapters and Appendix D suggests that gifts and drug samples can be influential even when their economic value is small. They primarily serve to create goodwill and a sense of reciprocity and partiality toward the marketing representatives who give them. (Gifts include meals provided to physicians and their employees as part of sales visits.) Moreover, some evidence suggests that they are associated with prescribing patterns that are inconsistent with evidence-based practice guidelines. Other evidence cited in Chapter 5 suggests that patients may have more negative attitudes toward such gifts and their potential impact on behavior than physicians do. The committee sees no convincing professional reasons to justify the acceptance of gifts or other items of material value from industry but does see the risk of bias and the loss of public trust.

To the extent that physicians outside academic institutions make educational presentations and prepare scientific publications, they should—like their counterparts who are faculty at academic institutions—refrain from participation in speakers bureaus and similar promotional activities and refuse authorship of ghostwritten articles. A physician should participate in consulting arrangements on the basis of a company's need for the physician's expertise. Such arrangements should be documented in contracts with specific tasks and deliverables and should be paid for at fair market value.

The recommendations about interactions with sales representatives are slightly different for academic and nonacademic physicians. The committee recognizes that physicians in academic settings have different responsibilities as educators and also have excellent access to information about the latest scientific and clinical developments. Physicians in busy community-based practices need objective information about new drugs and devices, as well as information that compares new drugs and devices with existing drugs and devices and that provides alternatives to drugs and devices. By making visits to physicians' offices, company representatives may provide this information in a convenient manner. In the future, however, with the

continued growth of Internet resources and the development of prescriber outreach and other educational programs, alternative sources of timely, objective, up-to-date information should become more available and readily usable.

If a physician chooses to meet with pharmaceutical and device company representatives, certain conditions should apply. Meetings should be at the invitation of the physician and by appointment and should not involve gifts, including meals provided at the physician's office. In limited cases, it may be appropriate for meetings to take place in the presence of patients (with their informed consent), primarily when representatives are providing in-service education or assistance with devices or equipment.

A related issue is drug company access to physician prescribing information. Currently, drug companies can buy coded prescribing information from pharmacy benefits programs and pharmacy chains. Companies can also purchase data from the AMA Masterfile, which links physician license numbers with their names, addresses, and phone numbers. Some physicians and others have objected to this practice (Steinbrook, 2006). In response, AMA now allows physicians who do not want their identifying information to be provided to companies to fill out a form to request that their data not be made available to company sales representatives and their supervisors (O'Reilly, 2006). (Other company personnel could still have access to the information.) It would be preferable and a lesser burden on physicians for AMA to set the default option so that identifying information would not be provided unless a physician affirmatively agrees.

As discussed in Chapter 5, the committee recognizes that access to affordable medications is a serious problem for many Americans, but it believes that reliance on drug samples is an unsatisfactory response. Samples are typically available only for newer and heavily marketed drugs, which may have no proven clinical benefits over alternatives, including less expensive equivalent drugs or generics. Although a sample may be convenient for the patient, it may not be the most appropriate medication. Many samples are provided to patients with insurance coverage and to physicians and their families, groups that do not have impaired access to medications. In such situations, the convenience of samples is outweighed by their potential to undermine evidence-based, cost-effective prescribing. For patients with chronic illnesses who lack the ability to pay for medications, a sample should be a stopgap that is accompanied by referral of the patient to a public or pharmaceutical company assistance program that can provide continuity of treatment. If physicians decide to accept drug samples, they should be given to patients who lack financial access to medications in situations in which appropriate generic alternatives are not available and the medication can be continued at little or no cost to the patient for as long as the patient needs it. The committee recognizes that physicians in

community practice may not have the option of using a centralized system of administration of drug samples, which is available in many academic medical centers. Some committee members were in favor of banning the acceptance of drug samples altogether and advocating for other mechanisms for providing access to drugs for indigent patients.

Recommendation 6.1 does not mention physician disclosure of financial relationships to patients. Patients could obtain that information, however, if the U.S. Congress were to require companies to disclose payments to physicians and to place that information on a searchable public database and also requires hospitals and other health care providers to report physician ownership interests. This option would avoid the interpersonal complexities involved with patients directly requesting or physicians directly providing such information. Patients and their families would need to be informed about the database, possibly through the use of brochures or notices in medical offices. Studies of patient use of the database would be a potential topic for the research agenda recommended in Chapter 9.

Continued Actions by Industry

The next recommendation promotes continued actions by pharmaceutical, medical device, and biotechnology companies to support the core values and missions of medicine. Some but not all of the recommended actions are covered by the revised codes issued by PhRMA (2008) and AdvaMed (2008) and by federal agency guidance to pharmaceutical companies (OIG, 2003).

RECOMMENDATION 6.2 Pharmaceutical, medical device, and biotechnology companies and their company foundations should have policies and practices against providing physicians with gifts, meals, drug samples (except for use by patients who lack financial access to medications), or other similar items of material value and against asking physicians to be authors of ghostwritten materials. Consulting arrangements should be for necessary services, documented in written contracts, and paid for at fair market value. Companies should not involve physicians and patients in marketing projects that are presented as clinical research.

The committee is encouraged that some companies have already taken steps to end company provision of certain gifts and meals and to develop new procedures for contracting with physicians for their consulting work. The revisions in the PhRMA and AdvaMed codes are also encouraging steps, especially if provisions to track and publicize adherence are meaningful. Public disclosure of commitment to the codes should put pressure on

noncomplying companies and should also reduce any competitive disadvantage to those companies that do comply. The committee would, however, like to see the provisions on gifts extended, consistent with Recommendation 6.1. The adoption of Recommendation 3.4 (which proposes that the U.S. Congress establish a program that requires companies to report their payments to physicians, researchers, and institutions) should allow monitoring of some company practices.

If the levels of adherence to the policies and practices recommended here are low, governments may enact legislation to limit physician ties to companies, as the state of Massachusetts has. In general, committee members believed that voluntary limits should be given an opportunity to work and that legislation and regulation should be held as options if they do not. The reasoning was that this approach is more likely to reinforce professional values and allow more nuanced policies and standards that take into account the possibility of unintended consequences and that create fewer administrative burdens to be developed.

Other Recommendations in This Report

Other chapters of this report also offer some recommendations that could affect community physicians. To the extent they are involved in multiple activities that require the disclosure of financial interests (Recommendation 3.3), community physicians might face more specific disclosure requests but also more consistency in requests. If federal legislation requires pharmaceutical, device, and biotechnology companies to publicly report payments to physicians (Recommendation 3.4), some community physicians might choose to forgo certain relationships with industry that they find difficult to explain and justify. Community physicians who teach medical students or residents off-site would be affected by reforms in the policies of medical schools and teaching hospitals (Recommendation 5.1). A new system of funding continuing medical education (Recommendation 5.3) could lead to higher fees for attendees and reductions in the numbers, variety, and locations of course offerings. In addition, physicians who participate in professional society or other clinical practice guideline development activities might be limited in their involvement if they had conflicts of interest, especially conflicts involving promotional activities (Recommendation 7.1).

7

Conflicts of Interest and Development of Clinical Practice Guidelines

Clinical practice guidelines lie at the intersection of medical research, education, and practice. They build on medical research and serve an educational function. In clinical care, they may influence patient and physician decisions about health care interventions, health plan coverage for medical services, and assessments of the performance of individual physicians and institutions that provide health care.

Ideally, clinical practice guidelines are based on valid scientific evidence, critical assessment of that evidence, and objective clinical judgment that relates the evidence to the needs of practitioners and patients. Arguably, the most significant problem in the development of sound clinical practice guidelines is the lack of research that can be used to guide the development of comprehensive recommendations on clinical practice. Clinical trials often exclude children, older adults, and patients with multiple or uncommon diagnoses or complex personal situations. Given the lack of evidence on many clinical topics and patient populations and the frequent lack of consistent research findings, expert judgment based on clinical experience remains a significant element in the development of evidence-based practice guidelines. As the methods manual of the American College of Cardiology and the American Heart Association states, it is not often that there is "an abundance of evidence available that leads directly to an indisputable recommendation" (ACC/AHA, 2009, p. 27).

Financial relationships with pharmaceutical, medical device, and biotechnology companies may create conflicts of interest and a risk of undue influence on judgment both for entities that sponsor the development of clinical practice guidelines and for the individuals who participate in their development. In addition to financial relationships with industry, other potential sources of bias in the development of clinical practice guidelines

include professional affiliations and practice specialization, reimbursement incentives, intellectual preconceptions and previously stated positions, and the desire for recognition and career advancement (see, e.g., Kahan et al. [1996], Ayanian et al. [1998], Murphy et al. [1998], Fitch et al. [1999], and Detsky [2006]).

This chapter begins with definitions and a brief historical overview and description of groups that develop clinical practice guidelines. It then reviews what the committee learned about the nature and the effects of sources of funding on the development of clinical practice guidelines, the financial interests of individual participants, and policies on financial relationships and conflicts of interest. A later section reviews other methods for promoting objectivity in the development of clinical practice guidelines and trust in those guidelines. The final section presents recommendations on how to reduce conflicts of interest in the development of clinical practice guidelines.

BACKGROUND AND CONTEXT

Definitions

As defined in an earlier Institute of Medicine (IOM) report, *clinical practice guidelines* are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (IOM, 1990, p. 8). The IOM report emphasized the role of formal evaluations of the evidence base for clinical practice guidelines and the linking of recommendations to those reviews. *Systematic reviews*, the common term used today for formal evaluations of the evidence, are highly structured assessments of the research literature that use explicit, previously defined methods and tools to identify, select, assess, and summarize research studies relevant to a technology, treatment of a clinical condition, or similar topic (see, e.g., OTA [1994] and Cochrane Collaboration [2005]). A *meta-analysis* is a quantitative summary of the data examined in a systematic review. As explained below, various groups have devised tools for assessing the extent to which a set of guidelines are based on systematic, evidence-based procedures.

Evolution of Clinical Practice Guidelines

The American College of Cardiology, the American College of Physicians, the National Institutes of Health (NIH) Consensus Development Program,[1] the U.S. Preventive Services Task Force, the Blue Cross and

[1] Since 1977, the Consensus Development Program at NIH has sponsored "an unbiased, independent, evidence-based assessment of complex medical issues" (NIH, undated). It orga-

Blue Shield Association, ECRI (now the ECRI Institute), and the RAND Corporation were, among others, leaders in devising systematic methods for assessing the evidence and developing clinical recommendations for practitioners, patients, payers, and others (see, e.g., IOM [1985, 1988] for contemporary descriptions of such activities). In 1989, the U.S. Congress created the Agency for Healthcare Policy and Research (AHCPR) and gave it responsibility for creating a public-private partnership to develop, disseminate, and evaluate clinical practice guidelines (P.L. 101-239). In 1995, the Congress came close to defunding the agency in response to lobbying by back surgeons who disagreed with the agency's guidelines for the treatment of low back pain developed by an AHCPR Patient Outcomes Research Team (Deyo et al., 1997; Gray et al., 2003; see also Clancy [2003], Gaus [2003], and Wennberg [2003]). Other government bodies charged with some aspect of technology assessment have also been defunded under circumstances that underscore the political sensitivity of this activity (for example, the National Center for Health Care Technology in 1982 and the congressional Office of Technology Assessment in 1995) (see, e.g., Bimber [1996], Rettig [1997], Eisenberg and Zarin [2002], and Keiper [2005]).

After its close call, AHCPR—rechristened the Agency for Healthcare Quality and Research (AHRQ)—withdrew from the work of developing clinical practice guidelines. Instead, the agency supports evidence-based practice centers that conduct systematic reviews that government agencies, professional societies, and other groups can request and use to develop guidelines and other recommendations. In 2008, AHRQ supported 14 such centers, 5 of which focused on assessments for the Centers for Medicare and Medicaid Services. One evidence review (performed under a grant from AHRQ) by the RAND Corporation's Evidence-Based Practice Center concluded that the quality of practice guidelines suffered as a result of the retreat of the agency from guideline development (Hasenfeld and Shekelle, 2003; see also Grilli et al. [2000]).

The U.S. Preventive Services Task Force, which was created several years before AHCPR/AHRQ but which is now part of the agency, continues to develop evidence-based guidelines for preventive services. It is currently supported by one evidence-based practice center. Other federal agencies, such as NIH and the Centers for Disease Control and Prevention, also develop practice guidelines.

To support the dissemination of the clinical practice guidelines developed and submitted by others, AHRQ sponsors the National Guideline

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nizes conferences that are jointly sponsored and administered by one or more NIH institutes or centers and the Office of Medical Applications of Research, which is located in the Office of the Director of NIH. Other federal agencies may participate if their expertise is relevant to the topic. Currently, the Agency for Healthcare Research and Quality provides a systematic review of the conference topic from one of its Evidence-Based Practice Centers.

Clearinghouse. The guidelines posted by the clearinghouse are summarized in a common format that includes headings for information about the source(s) of funding and about financial disclosures or conflicts of interest.[2] Although the clearinghouse is the most comprehensive source of information on the funding of guideline development activities and on financial disclosures and conflicts of interest, its data have some significant limitations. The analysts who compile the guideline summaries primarily rely on source documents provided by the guideline sponsor, and those documents may be incomplete. For example, because the source documents are silent on the topic, "Not stated" entries for "financial relationships/conflict of interest" may be found in clearinghouse summaries of guidelines for groups such as the American College of Physicians and the U.S. Preventive Services Task Force. These two groups do, in fact, have a process of disclosing, evaluating, and managing conflicts of interest.[3] Given these and other limitations in the clearinghouse database, the committee used information from the database on funding sources and disclosures with caution.

The guideline initiatives described above and other initiatives have gradually but not fully replaced less rigorous guideline development efforts that lacked formal procedures, clear reporting of the authors involved with and the methods used for the systematic review of the evidence, and explicit links between the recommendations and the supporting evidence. Shortcomings in the processes for the development and reporting of clinical practice guidelines persist. These shortcomings include the incomplete disclosures of the financial relationships of the participants and the funding sources and informal procedures, which increase the opportunity for undue influence and bias (see, e.g., Shaneyfelt et al. [1999], Burgers et al. [2003], Harpole et al. [2003], Hasenfeld and Shekelle [2003], Shiffman et al. [2003], Boluyt et al. [2005], Guyatt et al. [2006], Poitras et al. [2007], Nix [2008], and Nuckols et al. [2008]).

[2] The criteria for the inclusion of a guideline in the clearinghouse relate to sponsorship, evidence of some kind of literature review, adoption of the guideline within the last 5 years, and print or online availability of the complete text of the guideline.

[3] To cite one example of how such omissions may occur, when U.S. Preventive Services Task Force guidelines are published in journals that require disclosures, they include a statement (compare, e.g., the guidelines on screening for lipid disorders in children as published in *Pediatrics* at USPSTF [2007a] and as published online at USPSTF [2007b]). In contrast, guidelines presented on the agency's website do not routinely include information about the group's conflict of interest policies and procedures or about the authors' financial relationships (see, e.g., guidelines on screening for sickle cell disease in newborns at USPSTF [2007c]). The processes for developing the guidelines were the same, but the information in the clearinghouse varies because the source documents varied in the information that they provided. A discussion of task force policies can be found online in the procedure manual, but the site does not highlight it (USPSTF, 2008).

Systematic Process for Developing Clinical Practice Guidelines

The adoption of explicit, systematic methods for reviewing evidence and developing and documenting practice guidelines is, as discussed further below, an important strategy for reducing the opportunities for bias, whether the source might be intellectual and professional preconceptions, financial interests, or something else. Table 7-1 depicts a generic process for developing evidence-based guidelines that is similar to that used by a number of government and professional societies. (Sponsor means the entity developing the guideline.)

At each step in this process, financial relationships may create conflicts of interest. Any of the responsible parties identified in Table 7-1 could have financial relationships with industry that could unduly influence recommendations—even when systematic reviews and other safeguards are employed. Thus, some groups have conflict of interest policies that apply not only to the expert panels that develop guidelines but also to some or all of the other responsible or involved parties. As described in Chapter 4, the evidence base itself can be biased to the extent that the publication of

TABLE 7-1 Basic Elements of Process for Developing Evidence-Based Practice Guidelines

Responsible Party	Activity
Sponsor	Select topic and provide financial and other resources
Sponsor	Appoint a panel to develop the guideline that balances relevant expertise and perspectives and that is subject to conflict of interest policies throughout the process
Panel	Develop a work plan and specify clinical questions and outcomes of interest
Panel or contractor	Conduct a systematic review of the relevant evidence by using standardized methods for selecting studies, analyzing and rating the evidence, identifying and evaluating benefits and harms, and presenting conclusions
Panel	Develop and agree on a draft guideline with recommendations explicitly linked to the evidence and expert judgment
Panel or sponsor	Distribute a draft for internal and external review
Reviewers	Review of guideline by external reviewers and internal reviewers (e.g., the governing board of a professional society)
Panel	Revise a draft and produce the final guideline
Sponsor or journal	Publish and disseminate the guideline
Sponsor	Monitor new research findings and determine whether a guideline should be updated

negative findings or findings unfavorable to a product have been delayed or suppressed.

Professional societies and other groups sometimes rely on evidence reviews conducted by AHRQ's Evidence-Based Practice Centers. (Professional societies and other groups can nominate topics for reviews. In late 2008, the agency's website listed 11 evidence reports on clinical topics as under development.) Others groups may use a combination of staff and expert panel members to conduct reviews. One reason for the latter course is the expense. Systematic reviews for a complex clinical topic may cost in the range of $300,000 to $350,000 or more (personal communication, Beth A. Collins Sharp, director, Evidence-Based Practice Centers Program, Agency for Healthcare Research and Quality, November 14, 2008). On the basis of the committee's review of descriptions of the systematic review process for several professional and patient advocacy groups, groups that rely on staff or volunteer experts vary considerably in the resources that they devote to such reviews, the rigor of their evidence review processes, and the products of these reviews.

Possible Benefits and Risks of Industry Involvement in Guideline Development

The committee found little systematic information about the funding of guidelines, the financial relationships of participants, or the effects of both. In developing this discussion and the recommendations in this chapter, it drew on testimony at its meeting and a convenience sample of information available on the Internet, as well as its experience and judgment.

Potential Benefits of Industry Relationships

Industry funding for the development of clinical practice guidelines may allow some groups to create guidelines on new topics when they otherwise would not. Groups that develop practice guidelines may also benefit from presentations by industry employees as part of the evidence consideration process, and industry employees may be asked to review evaluations of the evidence for their technical accuracy. Individual panel members who have financial relationships with industry often have expertise that is pertinent to the development of a guideline.

Risks of Industry Relationships

As observed above, relationships with industry and conflicts of interest in the development of clinical practice guidelines may exist at both the individual level (i.e., participants may have industry ties) and the institu-

tional level (i.e., the sponsoring group may rely on industry funding for guidelines). These relationships raise the possibility of conflicts of interest and undue influence at each step in the guidelines development process.

Selection of topics Groups that require industry funding for the development of practice guidelines may propose topics that will attract industry funding (e.g., a guideline on how to use a product but not whether it should be used). Among the topics proposed to potential funders, companies may favor topics and questions for which the evidence is most likely to support conclusions favorable to a particular company.

Review of evidence Studies examining the association between industry ties and the outcomes of systematic reviews or meta-analyses raise concerns.[4] Although these studies do not deal explicitly with the entire process of developing clinical practice guidelines, they examine a key element. In one study, industry-sponsored meta-analyses of drug trials were less transparent about the methods that they used, were much more likely than Cochrane Collaboration reviews to recommend the experimental drug without reservation, and had fewer reservations about the methodological limitations of the trials included in the analysis (Jorgensen et al., 2006).[5] All of the industry-sponsored reviews but none of the Cochrane Collaboration reviews recommended the experimental drug without reservation.

Another study examined review articles on the health effects of secondhand smoke (Barnes and Bero, 1998). Ninety-four percent of the review articles written by individuals affiliated with the tobacco industry concluded that passive smoking is not harmful to health, whereas 13 percent of the reviews written by authors without such an affiliation made that conclusion. The association between the conclusion that secondhand smoke is not harmful and an affiliation with the tobacco industry persisted even after the analysts took into account the methodological quality of the review, the year of publication, the clinical topics examined, and whether the review was subject to peer review.

[4] As described in materials prepared for the Cochrane Collaboration (2002, unpaged), "meta-analysis is a two-stage process. The first stage is the extraction of data from each individual study and the calculation of a result for that study (the 'point estimate' or 'summary statistic'), with an estimate of the chance variation we would expect with studies like that (the 'confidence interval'). The second stage involves deciding whether it is appropriate to calculate a pooled average result across studies and, if so, calculating and presenting such a result. Part of this process is to give greater weight to the results from studies which give us more information, because these are likely to be closer to the truth we are trying to estimate."

[5] The authors identified 24 Cochrane Collaboration reviews for which another meta-analysis studied the same two drugs in the same disease and was published within 2 years of the Cochrane Collaboration review. (Eight of the 24 comparison guidelines were industry supported; 9 had no declared source of support; 7 reported nonprofit support or self-funding.)

As discussed in Chapter 4, which describes additional studies, a review of meta-analyses on hypertensive drugs found that financial ties to a single pharmaceutical company were not associated with findings that favored the company but were associated with favorable conclusions (Yank et al., 2007). The authors further noted that peer reviewers and journal editors did not prevent the publication of biased conclusions.

Expert panel deliberations The committee found no systematic studies of the relationship between participant financial relationships and the content of guidelines. One study did find, however, that only 7 percent of participants in guideline development surveyed believed that their own relationships with industry influenced their recommendations, but 19 percent believed that their coauthors' recommendations were influenced by such relationships (Choudhry et al., 2002). Because more than half of the participants reported no process for disclosing financial relationships, it is not clear how well informed the respondents were about their colleagues' relationships. (The extent of the relationships identified in the study is discussed below.)

Dissemination of guidelines Even if industry support is limited to the dissemination of guidelines, such support could influence the overall strategy for dissemination in ways that unduly favor a company's product. This is one interpretation of the controversy over guidelines related to sepsis summarized in Box 7-1 below.

GROUPS THAT DEVELOP CLINICAL PRACTICE GUIDELINES

A range of public and private groups develop or collaborate in the development of clinical practice guidelines (Table 7-2). On the basis of guidelines included in the National Guideline Clearinghouse, medical specialty societies are the most common developers of the guidelines; they accounted for almost 40 percent of the guidelines in the clearinghouse database in April 2008. Professional societies report that practice guidelines are among the most valued services that they provide (see, e.g., Bennett et al. [2003], Masur [2007], and Sagsveen [2008]). Evaluations of specialty society guidelines have sometimes been critical of their lack of systematic reviews of the evidence and other characteristics (see, e.g., Grilli et al. [2000]); but the committee's review indicates that many specialty societies have taken steps to make their procedures more systematic, transparent, and evidence based by hiring knowledgeable staff and developing methods, process manuals, and policies that include conflict of interest policies and procedures. The committee found less information about the clinical guideline development-related activities of disease-specific groups.

TABLE 7-2 Number of Clinical Practice Guidelines in the National Guideline Clearinghouse by Selected Types of Sponsors, as of March 16, 2009

Type of Sponsor	Number of Guidelines
Medical specialty society (U.S. and other)	959
Professional association (U.S. and other; mostly nonphysician or mixed groups)	408
Government agency (non-U.S.)	214
Federal/state/local government agency	165
Nonprofit organization	142
Independent expert panel	97
Academic institution (U.S. and other)	98
Disease-specific society (U.S. and other)	202
Hospital/medical center (U.S. and other)	26
For-profit organization	21
Managed care organization	11
Total, all guidelines, all sponsors	2,343

NOTE: Some guidelines are developed collaboratively by more than one type of sponsor. For example, a guideline may list as developers one or more professional societies and one or more disease-specific societies. The National Guideline Clearinghouse (NGC) search option does not generate unduplicated counts by category of sponsor. The unduplicated count presented here was provided by NGC staff. Nineteen of the 26 guidelines from a hospital or medical center were submitted by a single institution.
SOURCE: Personal communication, Mary Nix, Health Scientist Administrator, National Guideline Clearinghouse, March 22, 2009.

Public agencies also develop practice guidelines. U.S. federal and state agencies and public agencies from other countries accounted for more than 500 of the guidelines in the National Guideline Clearinghouse.

Some groups involved in guideline development have sought partners. For example, the American College of Cardiology and the American Heart Association have collaborated in their guideline development program since the 1980s (ACC/AHA, 2009). Several groups are investigating an international collaboration to develop guidelines for the care of respiratory diseases (personal communication, Holger Schunemann, M.D., Ph.D., chair, Department of Clinical Epidemiology and Biostatistics, McMaster University, February 19, 2009). Compared with the complexity of simply adding individuals with different professional and other backgrounds to a guideline development panel, the management of partnerships between and among agencies tends to be more complicated because each partner usually has, for example, its own policies and procedures. Nevertheless, the

potential benefits of collaboration include the sharing of costs, broadening of the scope of the questions examined, and reductions in the number of dueling guidelines that may undermine the credibility and acceptance of recommendations.

FINANCIAL RELATIONSHIPS IN GUIDELINE DEVELOPMENT

Sources of Funding for Guidelines and Systematic Reviews

The committee found no systematic assessment of the public or private sources of funding for the development of clinical practice guidelines (see, e.g., Boyd [2008]) or systematic reviews of funding sources (Jorgensen et al., 2006). Nearly all (98 percent) of the summaries of more than 2,000 guidelines included in the National Guideline Clearinghouse as of April 21, 2008, contained a statement about the funding source, usually indicating that the group that developed the guideline had funded it (Nix, 2008). Some information is inconsistent. For example, in the summary statement for guidelines on bronchial intraepithelial neoplasia/early central airways lung cancer, the section on the source of funding states that a professional society funded it, whereas the section on financial disclosures/conflict of interest states that funding came from five pharmaceutical or biotechnology companies (NGC, 2009c; see also Kennedy et al. [2007]). Similarly, a guideline on the prevention and treatment of mucositis listed the two authoring groups as the source of funding, but the information on financial disclosures/conflicts of interest referred to unrestricted grants from unnamed companies (NGC, 2009h; see also Keefe et al. [2007]).

Some professional societies, such as the American College of Physicians, the American Academy of Neurology, the American Society of Hematology, and the American Society for Clinical Oncology, fund their guideline development programs from general revenues and, in some instances, grants from independent nonprofit organizations (ASCO, 2008; Sagsveen, 2008; personal communication, Martha Liggett, executive director, American Society of Hematology, February 24, 2008; personal communication, Vincenza Snow, director, Clinical Programs and Quality of Care, American College of Physicians, February 23, 2009). As discussed in Chapter 6, a society's general revenues may include a significant share from industry, for example, income generated by journal advertising or by pharmaceutical or device company exhibits at professional society meetings.

The committee is aware that some smaller professional societies that have sought to fund clinical guideline development and systematic reviews without industry support have found it difficult to do so (personal communication, Roger Chou, assistant professor of medicine and medical informatics and clinical epidemiology, Oregon Health Sciences University, April 2, 2008). Professional societies can, however, nominate topics for

AHRQ-supported systematic reviews, and if such a topic is selected, even a resource-limited society will have an evidence-based review with which to work.

Most, if not all, guidelines developed by government agencies in the United States (e.g., the U.S. Preventive Services Task Force) and elsewhere (e.g., the National Institute for Health and Clinical Excellence in the United Kingdom) are publicly funded. One controversial exception involving a Texas state agency is described in Box 7-1, which cites several controversies involving financial relationships in practice guidelines.

Practice guidelines are sometimes developed by ad hoc groups, which by their nature are not likely to have a well-developed infrastructure for the performance of evidence-based reviews and other activities, including procedures for identifying and managing conflicts of interest. Box 7-1 described one ad hoc initiative related to heart disease screening guidelines that provoked concerns about bias and conflict of interest.

The Cochrane Collaboration (an independent, nonprofit, international organization that produces systematic reviews, among other activities) does not allow industry funding for a review. It does, however, allow commercial contributions to a central pool of funds to be used for certain other activities, such as the translation of reviews into different languages (Cochrane Collaboration, 2006).

Although the committee found no systematic information, industry involvement in the dissemination of guidelines appears to be fairly common. For example, companies may buy copies of the journal issue in which a guideline is published. They may also develop derivative materials (e.g., summaries for lay audiences) based on the guideline. The committee was unable to systematically investigate whether dissemination activities resulted in materials that altered or elaborated on a guideline in ways that departed from the conclusions in the guideline itself.

Nature and Extent of Individual Relationships with Industry

The committee found little systematic study and documentation of financial relationships between industry and the individuals who author clinical practice guidelines. A 2002 study reported that the authors of practice guidelines had widespread financial relationships with the pharmaceutical industry (Choudhry et al., 2002).[6] Of 44 practice guidelines that Choudhry et al. initially reviewed, only 2 included disclosures of the authors' financial relationships with industry. A follow-up survey of 100 authors involved with 37 of the guidelines found that 87 percent of the authors had some

[6] The study covered guidelines that were published between 1991 and 1999, that had identifiable authors, and that had been endorsed by a "recognized" North American or European professional society.

BOX 7-1
Cases and Controversies Involving Conflicts of Interest in Guideline Development

In an investigation of pharmaceutical companies' use of educational grants (based on information provided by 23 companies), staff of the Finance Committee, U.S. Senate (2007) found that "several companies helped fund the Texas Medical Algorithm Program (TMAP) run by the Texas Department of State Health Services to develop psychiatric treatment algorithms" (p. 12). A whistleblower complaint led to the dismissal of the state employee who headed the effort and had served as a paid consultant to a company that benefited from the treatment guidelines (Waters, 2006, unpaged).

In 2006, the *Boston Globe* reported that an ad hoc group of physicians had solicited nearly $56,000 from several pharmaceutical companies to have their heart disease screening guidelines published in a supplement of a leading cardiology journal (Smith, 2006; see also, e.g., Naghavi et al. [2006]). The guidelines were subsequently criticized by an official of the National Heart, Lung, and Blood Institute, who pointed out that the supplement had been financed by a company that stood to profit from implementation of the recommendations, that the authors of the guidelines failed to reveal their relevant financial relationships with that company and others, and that the process for developing the guidelines was not evidence based or subject to rigorous review (Lauer, 2007).

Eichacker and colleagues (2006) alleged that industry funding was used to support a "three-pronged marketing strategy" to increase sales of drugs for the treatment of sepsis (p. 1640). They cited a marketing document, which is no longer available online, that described a strategy "to first raise awareness about rationing and then the disease state as a means of enhancing prospects of utilization" and then employ "highly-specific marketing initiatives to physicians and the medical trade media"; a grant would then be used to create a task force to study health care rationing in the intensive care unit; and lastly to "[r]aise awareness of severe sepsis and generate momentum towards development of treatment guidelines for the infection through establishment of the Surviving Sepsis Campaign" (AHRP, 2006, unpaged). The Infectious Diseases Society of America chose not to endorse the sepsis guidelines on the basis of concern about "the manner in which the guidelines were developed, the use of a suboptimal rating system, and their sponsorship by a drug company" (Eickhacker et al., 2006, p. 1642; see also Masur [2007]). A recent set of revisions to the guidelines reported no industry funding for guideline development meetings, and 7 of the 24 authors reported no "potential" conflicts of interest (Dellinger et al., 2008).

financial relationship or interaction with industry and that 59 percent had relationships with companies whose products were considered in the guideline. The most frequent relationship with companies involved honoraria for speaking (64 percent of the respondents, who reported an average of 7.3 companies as sources of the honoraria). Thirty-eight percent of the authors had an employee or consultant relationship with one or more companies. The majority of the authors surveyed reported no discussion of financial relationships during the guideline development process.[7]

Journal articles and other publications that contain practice guidelines vary greatly in the extent to which they include disclosures of the relevant financial relationships of the participants in the guideline development process. For the most part, disclosures emphasize financial relationships with pharmaceutical and device companies, although some describe ties to other kinds of organizations (e.g., federal research agencies and managed care organizations). Some guideline documents do not indicate whether the participants with no listed disclosures were explicitly asked to declare if they had no relevant relationships. The categorizations of the relationships are also not consistent across guideline disclosures. Some lump together relationships (e.g., research and consulting or honoraria and participation in speakers bureaus) that others report separately.

When guidelines include financial disclosure statements, the content is quite variable, as Box 7-2 illustrates. An analysis of the guideline summaries in the clearinghouse as of April 2008 found that almost half (47 percent) indicated "Not stated" under the summary heading for financial disclosure/conflict of interest (Nix, 2008). An earlier analysis found that the proportion of summaries that included some information on financial relationships or conflict of interest increased from just over 20 percent to approximately 50 percent from 1999 to 2006 (Tregear, 2007). (Most summaries in the clearinghouse are based on the source document cited for the guideline, but some reflect supplementary information provided by the groups submitting the guidelines.) In a later section, Box 7-3 provides additional examples of disclosures about conflict of interest policies.

[7] The committee also located an article reporting on a review by the Dutch Health Care Inspectorate of the influence of pharmaceutical companies in the development of practice guidelines in The Netherlands (Smulders and Thijs, 2007). As summarized in the English-language abstract, the agency concluded that "virtually all opinion leaders are financially supported by pharmaceutical companies, and therefore, potential conflicts of interest are unavoidable" (p. 2429). The agency recommended making potential conflicts more transparent by full disclosure of all relationships, especially financial relationships. It also suggested that allowing companies to review draft guidelines might reduce "undesirable initiatives" to influence guidelines, that individuals with certain kinds or levels of relationships might be precluded from participation in guidelines development, and that an independent review process might be instituted to assess guidelines for signs of interference by pharmaceutical companies.

BOX 7-2
Examples of Financial and Conflict of Interest Information Excerpted from Summaries in the National Guideline Clearinghouse

Example A
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
Not stated. [This is the most common entry for the period from 1999 to 2006.]

Example B
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
All participants involved in guideline development have disclosed potential conflicts of interest to their colleagues, and their potential conflicts have been documented for future reference. *They will not be published in any guideline, but kept on file for reference, if needed*. Participants have been asked to update their disclosures regularly throughout the guideline development process. [emphasis added; NGC, 2009e; see also NASS, 2008]

Example C
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
All members of the Expert Panel complied with the Infectious Diseases Society of America (IDSA) policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested about employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Potential Conflicts of Interest: L.A.P. has served as a speaker and consultant to Schering-Plough and Pfizer. P.G.P. has received grant support from Schering-Plough, Pfizer, Merck, and Astellas; has been an ad hoc consultant for Pfizer; and has been a speaker for Pfizer and Astellas. C.A.K. has received research grants from Merck, Astellas, and Schering-Plough and serves on the speakers bureau for Merck, Astellas, Pfizer, and Schering-Plough. All other authors: no conflicts. [NGC, 2009d; see also Chapman et al. 2008]

Indirect evidence for widespread relationships with companies is presented in a study of participants involved with the development of the *Diagnostic and Statistical Manual of Mental Disorders* (Cosgrove et al., 2006). These diagnostic criteria, like practice guidelines, are based on expert reviews of the relevant evidence. (An AHRQ-funded study on conflicts of interest in commercial drug compendia should be published soon. Many

health plans, including Medicare, use evidence summarized in compendia as a basis for payment and coverage decisions.)

The committee also found a few assessments of the adequacy of disclosures in studies that have applied the standardized evaluation tool AGREE (Appraisal of Guidelines Research and Evaluation), which is further described below. One of the evaluation criteria (Item 23) is whether a guideline document includes information about participant conflicts of interest. Another criterion (Item 22) is whether the guideline is editorially independent from the funding source. Studies have found shortcomings in reporting on conflicts of interest by participants and editorial independence in a wide array of clinical practice guidelines, including guidelines on stroke rehabilitation (Hurdowar et al., 2007), occupational medicine (Cates et al., 2006), pediatrics (Boluyt et al., 2005), lung cancer (Harpole et al., 2003), low back pain (Arnau et al., 2006), and nonsteroidal anti-inflammatory drug and acetaminophen treatment of osteoarthritis of the hip or knee (Wegman et al., 2004). It is not clear whether a lack of disclosure was related to the policies of the group developing the guidelines (e.g., no policy on disclosure or disclosures were not revealed) or the policies of particular journals (e.g., no request for disclosure). A study of 191 guidelines published in six leading journals in 1979, 1984, 1989, 1994, and 1999 found reporting of conflicts of interest only in the most recent year (1999) and then for only 7 of the 40 guidelines and 18 authors for that year (Papanikolaou et al., 2001). Although all the disclosures were in journals that had disclosure policies, only 4 percent of the articles in those journals included disclosures.

Consequences of Financial Relationships

The committee found no systematic studies that investigated the association between the funding source and the development process or the content of the clinical practice guidelines. As illustrated in Box 7-2, it did find cases that raised concerns about the influence of industry funding.

The committee also found no systematic studies of the relationship between participant financial relationships and the content of the guidelines.[8] As described above, a study by Choudhry and colleagues (2002) found that

[8] In a possibly relevant study of a different kind of panel, Lurie and colleagues (2006) examined the financial relationships and decisions reached in 221 meetings of 16 advisory committees of the Food and Drug Administration. They reported that in nearly three-quarters (73 percent) of the meetings at least one committee member had a financial link to the maker of a drug being considered by the committee or had a link to a competitor company. Overall, approximately one-quarter (28 percent) of the members reported conflicts. They concluded, "A weak relationship between certain types of conflicts and voting behaviors was detected, but excluding advisory committee members and voting consultants with conflicts would not have altered the overall vote outcome at any meeting studied" (p. 1921).

only 7 percent of participants in guideline development surveyed in their study believed that their own relationships with industry influenced their recommendations, but 19 percent felt that their coauthors' recommendations were influenced by such relationships. Also as described above, studies examining industry ties and the outcomes of systematic reviews raise concerns about undue influence.

A few case studies examine conflicts of interest for specific guidelines or guideline development programs. For example, in 2006, 14 of 16 members of a group that worked on the development of guidelines for the treatment of anemia in patients with chronic kidney disease received consultant fees, speaking fees, research funds, or some combination thereof from at least one company that could be affected by the guidelines (Coyne, 2007). The principal funder of the guidelines was a company that would be affected by the guidelines, and the chair and cochair of the work group had financial relationships with that company (KDOQI, 2007). The work group recommended that the dosage of a drug made by the company be raised, which could have substantially increased costs to the Medicare program. By coincidence, the guidelines were announced at the same time that research that showed adverse patient outcomes associated with the approach recommended by the guidelines was published. The lead investigator of the research allegedly informed the guideline development work group that the study in question had been terminated early, and he advised that they wait for the results before issuing the new guidelines. The group, however, chose not to wait. The entity that sponsored the work group recently described changes in its conflict of interest policies, which it described as providing "an even higher level of transparency" by providing that financial disclosures would be discussed at the meetings of guideline development groups, that those reviewing the evidence would be "empowered to assure that all guideline recommendations are supported by the evidence," that the organization's compliance officer would monitor guideline development activities and report to the organization's board on issues relating to conflict, and that no future guideline could be funded by a single industry sponsor (NKF, 2007).

POLICIES ON CONFLICTS OF INTEREST IN CLINICAL PRACTICE GUIDELINE DEVELOPMENT

Characteristics of Policies

The committee examined a convenience sample of conflict of interest policies identified through the National Guideline Clearinghouse, presentations at committee public meetings, organizational websites, documents describing guidelines, assessments of specific guidelines, other publications,

and discussions with staff or members of organizations involved with guideline development. It found no systematic information on the conflict of interest policies of groups that develop clinical practice guidelines. Reviews by Boyd and Bero (2006) and Boyd (2008) likewise found no systematic descriptions or assessments of these policies.

The availability, representativeness, and quality of the available information are limited in several important ways. As noted above, even if the developers of guidelines have conflict of interest policies, they may not refer to them in individual guideline documents. This in turn means that the summaries in the National Guideline Clearinghouse are likely to have no information either. A number of groups have recently revised aspects of their policies, and the committee is aware of other groups that are considering changes. In some cases, these changes may not be reflected on websites or in publications.

From the policies examined, the committee identified several variations in organization conflict of interest policies and procedures. They vary in the

- information required for disclosure, including how detailed the information disclosed must be, how often disclosure is requested, and whether a panel member needs to explicitly state that he or she has no relationships to disclose;
- management of disclosed information, including who reviews it and whether other panel members are told of conflicts;
- procedures for managing the relationships disclosed, including limitations of participation by members with conflicts (such as serving as chair or cochair or voting);
- provisions for public disclosure of conflict of interest policies, funding sources, and individual financial relationships;
- procedures for managing relationships with companies that provide funding for guidelines development; and
- assignment of explicit responsibility for monitoring whether institutional policies are followed.

The frequent lack of transparency of conflict of interest policies limits the ability of guideline readers to consider financial relationships and conflicts of interest as part of their assessment of the credibility of a set of guidelines. To give a sense of what readers of guidelines may encounter, Box 7-3 includes additional examples of the range of summary statements in the National Guideline Clearinghouse. (See also Box 7-2.)

The committee found few descriptions of the policies used to manage the relationship between guideline developers and industry for groups that accept industry funding for guideline development. One exception is the

BOX 7-3
Examples of Conflict of Interest Policy Descriptions Excerpted from Summaries in the National Guideline Clearinghouse

Example A
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
Not stated. [This is the most common entry for the period from 1999 to 2006.]

Example B
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
To assure the integrity of the Advisory Committee on Immunization Practices (ACIP), the U.S. Department of Health and Human Services has taken steps to assure that there is technical compliance with ethics statutes and regulations regarding financial conflicts of interest. Concerns regarding the potential for the appearance of a conflict are addressed, or avoided altogether, through both pre- and postappointment considerations. Individuals with particular vaccine-related interests will not be considered for appointment to the committee. Potential nominees are screened for conflicts of interest, and if any are found, they are asked to divest or forgo certain vaccine-related activities. In addition, at the beginning of each ACIP meeting, each member is asked to declare his or her conflicts. Members with conflicts are not permitted to vote if a conflict involves the vaccine or biologic being voted upon. [NGC, 2009g; see also ACIP, 2007]

Example C
FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST
The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were

American College of Chest Physicians, whose policies are summarized in Box 7-4.

Effectiveness of Policies

The committee identified no evaluations of the impact of conflict of interest policies on the content of guidelines or other outcomes. The review by Boyd and Bero (2006) also found no rigorous assessments of conflict of interest policies for guideline development and no evaluations of different strategies for implementing or enforcing them.

obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. With regards to this specific report, all authors have stated that they have nothing to disclose. One of the authors performs epidural steroid injections. [NGC, 2009b; see also Armon et al., 2007]

Example D

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Standards and guidelines are to insure that individuals participating in professional activities are aware of author relationships with commercial companies that could potentially affect the information presented. The American Thyroid Association has endorsed the requirement that authors disclose any significant financial interest or affiliations they may have with the manufacturers of products or devices that may be discussed in the development of guidelines. In compliance with this policy, a superscript number placed by the name of an author denotes an author who has indicated an affiliation with organizations which have interests related to the content of these guidelines. The intent of this policy is to openly identify potential conflicts of interest so that physicians may form their own judgments about the guidelines with full disclosure of the facts; it remains for the audience to determine whether an author's outside interest may reflect a possible bias in either the exposition or the conclusions presented. [NGC, 2009f; see also Cooper et al., 2006a]

NOTE: As explained in the text of this chapter, the documents on which guideline summaries are based may not include references to organizational policies that have governed the development of the guideline. Thus, a "Not stated" response does not necessarily indicate that a group has no policy.

Other Strategies to Limit Bias in the Development of Clinical Practice Guidelines

Those committed to the development and implementation of sound, credible, and useful guidelines have devised a number of methods and tools that can be used to support the creation of such guidelines. Several are listed in Box 7-5, roughly according to the step in the process of guideline development described in Table 7-1. Arguably, the most important steps are the conduct of a systematic review of the evidence and the linking of recommendations to the evidence in an explicit fashion. The strategies—and continuing areas of debate and methodological refinement—are described in depth elsewhere (see, e.g., Higgins and Green [2008] and IOM [2008]).

BOX 7-4
Policies of American College of Chest Physicians on Industry Funding of Guideline Development

- Fund development activities are undertaken by the organization's executive office without the involvement or knowledge by the organizational unit responsible for guideline development, and each guideline ideally is either self-funded or funded by at least three to five outside sources.
- Names of sponsoring companies are not revealed to staff, society members, and other participants in guideline development until the information is disclosed in the final publication.
- Sponsors do not nominate topics, participate in meetings, or review drafts. They see the guideline only upon publication.
- The organization does not inform sponsors of the participants involved in developing a guideline, the specific questions investigated, the methodologists or evidence-based practice center involved in the evidence review, the reviewers, or meeting times or places.
- Guidelines refer to pharmaceuticals only by their generic names and not by their brand names.

SOURCE: Baumann et al., 2007; Lever and Lewis, 2008.

In general, they reinforce conflict of interest policies by limiting the opportunity for secondary financial interests to exert undue influence on the primary interest of developing sound guidelines.

Unfortunately, as Steinberg and Luce (2005) have observed, rigorous methods for clinical practice guideline development and reviews of the clinical evidence are not applied consistently, and the conclusions of evidence reviews are not always interpreted appropriately. Furthermore, given that the evidence base is weak in many areas, they advise, "physicians, policymakers, and others acting on the basis of judgments, recommendations, or measures . . . should not blindly assume that the label [evidence-based] truly applies" (p. 91).

As noted earlier, in addition to developing methods to limit bias, individuals and groups have been developing tools for standardizing the presentation of guidelines and assessing the quality of guidelines across several domains (see, e.g., IOM [1992], the AGREE Collaboration [2003], and Shiffman et al. [2003]). Methodologists have also developed tools that can be used to assess the quality of systematic reviews (Shea et al., 2007; see also Oxman et al. [2006a]). The 23-item AGREE instrument, which was developed by experts from 13 countries with funding from the European Union, includes two elements that relate to conflict of interest, specifically, that the "guideline is editorially independent from the funding

BOX 7-5
Other Strategies for Limiting Bias in Clinical Practice Guideline Development

Using an explicit process to select topics for clinical practice guideline development. Various groups and individuals have recommended a formal process and the use of explicit criteria for the selection of topics for guideline development (see, e.g., Battista and Hodge [1995], IOM [1995], and Oxman et al. [2006a]). Although the primary rationale is to use limited resources to evaluate areas that offer the greatest potential to improve the quality or effectiveness of health care, another potential benefit is a reduction in the opportunity for financial relationships and other sources of bias to influence the selection of topics.

Creating a diverse expert panel. The inclusion of individuals with a range of relevant professional and other backgrounds on guideline development panels can help check financial, professional, and other sources of bias; promote the fuller consideration of potential outcomes, relevant evidence, and aspects of implementation; and help win broader acceptance by professionals, consumers or patients, health care plans, and others who play roles in the successful implementation of guidelines (see, e.g., IOM [1990, 1992, 2008] and AGREE Collaboration [2003]).

Systematically reviewing relevant evidence. As summarized by Higgins and Green (2008, Section 1.2.2) for the Cochrane Collaboration, key elements of this critical step include

- "a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example, through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies."

Using systematic procedures to evaluate the evidence, employing expert judgment, and linking recommendations to the evidence. Methodologists have developed and tested formal processes for developing consensus and otherwise structuring the expert judgment process (see, e.g., Fink et al. [1984], Murphy et al. [1998], Verkerk et al. [2006], and Renfrew et al. [2008]). In addition, considerable effort has been invested in developing and testing explicit methods for reporting and rating the evidence relevant to guidelines and for rating the strength of the recommendations (see, e.g., Guyatt et al. [1995], Lohr [2004], and Schünemann et al. [2006], and Schünemann [2008]).

Obtaining expert reviews. An independent, expert review of the guidelines and related documents is an important tool that can be used to improve the identification, evaluation, and use of the evidence. The process used to select expert reviewers should explicitly identify and assess reviewer ties with potentially affected companies.

body" (Item 22) and that "[c]onflicts of interest of guideline development members have been recorded" (Item 23). In addition, the Conference on Guideline Standardization (COG) proposed a somewhat similar 18-item checklist for reporting (documenting) guidelines (Shiffman et al., 2003). The COG list includes the identification of the funding source or sponsor, its role in developing or reporting the guideline, and the disclosure of conflicts of interest.

These and other instruments are not intended to be used to assess the full substance of the guidelines. In and of themselves, they will not identify, for example, whether key evidence has been overlooked or incorrectly assessed, whether relevant benefits or harms have been ignored or improperly weighed, or whether critical barriers to implementation have been missed. Notwithstanding some shortcomings of guideline assessment tools, their development and application underscore that it is important for documents containing clinical practice guidelines to provide potential users of the guidelines with informative descriptions of the development process, the evidence base, the participants, and the applicable conflict of interest policies. When users of guidelines confront guidelines that lack such descriptions, they would be prudent to treat the guidelines with caution and search for other guidelines that provide appropriate documentation.

Even when the developers of clinical practice guidelines use sound methods, they are often limited by shortcomings in the evidence base. A review of the guidelines in the National Guideline Clearinghouse reveals recommendation after recommendation that is supported by weak, mixed, or no evidence. Both to support the development of practice guidelines and for other purposes, many groups in the United States and elsewhere have called for greatly increased public investments in comparative effectiveness research and analysis for at least two decades (for a small sampling, see IOM [1985, 2007, 2008], OTA [1994], CBO [2007], and MedPAC [2007]). At the end of the next section, the committee endorses the recommendations for such investments that another IOM committee made recently. Overall, the combination of a better evidence base for clinical practice guidelines and better tools for assessing that evidence not only strengthens the usefulness of practice guidelines but also reduces the potential for conflicts of interest to bias guidelines.

RECOMMENDATIONS

Given the important role that clinical practice guidelines play in many aspects of health care, it is important that these guidelines be free of industry influence and be viewed by clinicians, policy makers, patients, and others as objective and trustworthy. The committee found substantial variation in the extent to which different groups disclosed their conflict of interest

policies and the financial ties to industry of the sponsoring group and the members of the guideline panel. It also found little systematic descriptions or assessments in the literature. On the basis of its judgment and experience (including experience with conflicting guidelines and guidelines not based on formal reviews of the evidence), the committee believes that the risk of undue industry influence on clinical practice guidelines is significant, and that risk justifies that strong steps be taken to strengthen conflict of interest policies governing the development of guidelines. Recommendation 7.1 proposes several such steps.

RECOMMENDATION 7.1 Groups that develop clinical practice guidelines should generally exclude as panel members individuals with conflicts of interest and should not accept direct funding for clinical practice guideline development from medical product companies or company foundations. Groups should publicly disclose with each guideline their conflict of interest policies and procedures and the sources and amounts of indirect or direct funding received for development of the guideline. In the exceptional situation in which avoidance of panel members with conflicts of interest is impossible because of the critical need for their expertise, then groups should

- **publicly document that they made a good-faith effort to find experts without conflicts of interest by issuing a public call for members and other recruitment measures;**
- **appoint a chair without a conflict of interest;**
- **limit members with conflicting interests to a distinct minority of the panel;**
- **exclude individuals who have a fiduciary or promotional relationship with a company that makes a product that may be affected by the guidelines;**
- **exclude panel members with conflicts from deliberating, drafting, or voting on specific recommendations; and**
- **publicly disclose the relevant conflicts of interest of panel members.**

Transparency is one key element of Recommendation 7.1. Groups should disclose their conflict of interest policies and their process for seeking members without conflicts of interest and its results. The disclosure of the relevant financial interests of members of guideline development panels should be sufficiently specific and comprehensive that it helps others judge the severity of the conflicts of interest, including allowing the identification of fiduciary interests (e.g., membership on company boards) and promotional relationships (e.g., participation in industry speakers bureaus).

Groups that develop guidelines should also disclose the sources and the amounts of funding provided for guideline development, including unrestricted company grants. Some committee members also wanted groups that develop guidelines to report publicly all their sources, amounts, and purposes of funding because industry contributions to general revenues (e.g., from journal advertising or unrestricted grants) could also create undue influence. The committee did not reach a consensus on this point. Other committee members were also concerned about the overall reliance of some professional and patient groups on industry funding, but they believed that this reporting of all sources and purposes of funding is not necessary, provided that groups developing guidelines adopt and implement rigorous evidence-based procedures, report indirect and direct funding sources for each guideline, and institute the conflict of interest policies and procedures recommended in this report. Another safeguard would be the continued development of processes for rating guidelines development processes, as described above. Moreover, if the U.S. Congress requires companies to report payments not only to individuals but also to a range of medical organizations, that information, in combination with the annual reports that many professional society and patient groups issue, should allow the calculation of industry funding as a share of total revenues.

Transparency also involves the inclusion of the specified information with each guideline that a group sponsors. Preferably, the information would accompany the written text, but it could—particularly if it is very lengthy—be provided by an Internet link that is maintained through the life of the guideline.

In addition to expanded disclosure about funding, the committee recommends an end to direct industry funding of clinical practice guidelines. It recognizes that this step might have the undesirable effect of reducing the involvement of professional societies in guideline development but believes that it is necessary to avoid the conflicts that come from industry financing. It is also likely that an increase in public support for systematic reviews of the evidence would buffer such effects because these reviews are an expensive part of the process of developing evidence-based guidelines. Professional societies and other groups with a shared interest in certain clinical problems could also collaborate on the development of guidelines and spread the costs. In addition, a pooling mechanism might be created—as has been suggested by some for continuing medical education—to support indirect industry funding of the development of clinical guidelines in certain broad categories.

Another important step is to exclude or substantially limit the participation of individuals with conflicts of interest on panels that develop clinical practice guidelines. As more academic institutions and other groups as well as individual professionals take the steps recommended in Chapters 5

and 6 of this report, it should be easier to find individuals who are free of conflicts of interest involving promotional relationships (e.g., participation in speakers bureaus). If groups conclude that participants with conflicts of interest are essential to provide the necessary expertise, they should demonstrate to the public that they have made a good faith but unsuccessful effort to find individuals with the required expertise and without conflicts of interest. They should also preclude individuals with conflicts of interest from chairing guideline development panels, restrict the number of individuals with conflicts of interest on panels to a distinct minority (e.g., to 25 to 30 percent of the membership), and prohibit members with conflicts of interest from drafting and deciding specific recommendations.

In addition to actions by the institutions directly involved in the development of guidelines, organizations with an interest in unbiased clinical practice guidelines can create incentives for groups that develop guidelines to adopt the recommendations presented in this report. The committee understands that the National Guideline Clearinghouse will be phasing in a requirement for the disclosure of conflicts of interest, but the committee recommends that it extend the requirement to include the disclosure of funding and policy information, consistent with Recommendation 7.1. It would also be desirable for the clearinghouse or some other entity to begin substantive assessments of the quality of clinical practice guidelines.

RECOMMENDATION 7.2 Accrediting and certification bodies, health insurers, public agencies, and other similar organizations should encourage institutions that develop clinical practice guidelines to adopt conflict of interest policies consistent with the recommendations in this report. Three desirable steps are for

- **journals to require that all clinical practice guidelines accepted for publication describe (or provide an Internet link to) the developer's conflict of interest policies, the sources and amounts of funding for the guideline, and the relevant financial interests of guideline panel members, if any;**
- **the National Guideline Clearinghouse to require that all clinical practice guidelines accepted for posting describe (or provide an Internet link to) the developer's conflict of interest policies, the sources and amounts of funding for development of the guideline, and the relevant financial interests of guideline panel members, if any; and**
- **accrediting and certification organizations, public and private health plans, and similar groups to avoid using clinical practice guidelines for performance measures, coverage decisions, and similar purposes if the guideline developers do not follow the practices recommended in this report.**

The committee expects that the adoption of the committee's recommendations will reduce the probability of undue influence from industry funding and may also reduce the number of conflicting and competing clinical practice guidelines. Some groups that have operated with undisclosed industry support or that have been unwilling to disclose the financial relationships of guideline development panel members may remove themselves from the guideline development process. Other groups may collaborate to share the costs of developing guidelines on topics of common interest.

Although the committee believes that an expanded role for public-sector sponsorship of the development of systematic reviews and clinical practice guidelines would be desirable, an examination of this issue is beyond its scope. The committee endorses the recommendation in a recent IOM report for expanded federal support for assessments of the effectiveness of clinical services (IOM, 2008). That report called for the U.S. Congress to direct the U.S. Department of Health and Human Services to designate a single entity with the responsibility and capacity to "to ensure production of credible, unbiased information about what is known and not known about clinical effectiveness" (p. 171). That entity would establish priorities for and manage the development of systematic reviews of clinical effectiveness, develop standards for such reviews and for clinical guidelines, and address conflicting guidelines. The report also recommended that accreditation organizations and other groups preferentially use guidelines developed by using the standards described in the report. In addition, it recommended that guideline development panels minimize bias by including a balance of competing interests, prohibit voting by participants with conflicts of interest, and publish conflicts that have been disclosed.

Other Relevant Recommendations in This Report

In addition to the two recommendations in this chapter, recommendations elsewhere in this report are relevant to institutions that develop clinical practice guidelines. Consensus standards on disclosure elements and procedures would make disclosures more informative as well as less burdensome for those making disclosures to multiple institutions (Recommendation 3.2). A national system for public reporting by companies of their payments to individuals and organizations would allow the easier verification of certain disclosures (Recommendation 3.4). Limitations on certain industry ties and practices (e.g., the receipt of gifts and participation in speakers bureaus) should reduce conflicts of interest among the pool of experts considered for participation in clinical practice guideline development (Recommendations 5.1, 6.1, and 6.2).

The adoption of explicit policies and procedures on institutional conflict

of interest would challenge professional societies, patient advocacy groups, and other entities that develop clinical practice guidelines to confront the scope and appropriateness of their financial ties with industry, eliminate questionable ties, and prudently manage others (Recommendation 8.1). The next chapter discusses conflicts of interest at the level of institutions.

8

Institutional Conflicts of Interest

Financial relationships with industry exist at the institutional level as well as the individual level and may create conflicts of interest for academic medical centers, professional societies, and other institutions that carry out medical research, medical education, clinical care, or practice guideline development. Some of these relationships may generate significant benefits to an institution's primary missions. For example, gifts to endow named professorships or fund the construction of research facilities support the core teaching and research missions of academic medical centers. The committee heard testimony that new kinds of institutional relationships between academia and industry—beyond relationships involving individual faculty members—could promote the translation of basic discoveries into new therapies and thereby benefit society (Benz, 2008; Moses, 2008). The question for institutions as well as individuals is whether a relationship with industry can be maintained in a way that achieves the desired benefits but avoids the risks of undue influence on decision making and the loss of public trust.

Although several cases reported by the news media have called attention to institutional conflicts of interest in medicine, institutional conflicts of interest have generally received less attention than individual conflicts of interest. Institutional conflicts of interest often involve the financial interests of both the institution and its senior officials (Box 8-1).

The risks to core missions posed by institutional conflicts of interest can be as serious as those created by individual conflicts. Moreover, if institutions do not prudently manage relationships with industry and are exposed to public criticism for inadequately or improperly managing conflicts, the work of many individual researchers, educators, and clinicians associated

BOX 8-1
Cases and Controversies Involving Institutional Conflicts of Interest

After the 1999 death of Jesse Gelsinger during a clinical trial involving a gene transfer intervention conducted by a University of Pennsylvania research institute, various investigations raised questions about the university's oversight of the study and the research institute (Stolberg, 2000; Steinbrook, 2008c). The university and several past and present officials had financial interests in the biotechnology company that developed the intervention. The company contributed $25 million to the research institute's annual budget and had exclusive rights to develop products emerging from the trial and related research. In addition, the director of the institute, who was also the lead researcher, had founded the company and maintained a financial interest in it.

In 2005, reporters revealed that the Cleveland Clinic and its chief executive officer had undisclosed financial interests in a medical device firm (Armstrong, 2005). The firm's heart surgery device was used at the hospital and was promoted by its surgeons. Patients were not informed of the conflicts of interest. The board of the Cleveland Clinic subsequently adopted new policies on institutional conflict of interest.

Amgen, the manufacturer of epoetin, a drug that increases hemoglobin levels, was the founding and primary sponsor of the Kidney and Dialysis Outcomes Quality Initiative carried out by the National Kidney Foundation (Coyne, 2007; see also Chapter 7). This project issued practice guidelines recommending an increase in the target hemoglobin level for patients with chronic kidney disease, which would entail the use of higher doses of epoetin and increased sales of the sponsor's product.

In 2008, the chair of the Psychiatry Department at Emory University resigned that position after congressional investigators reported that he had failed to disclose the receipt of substantial consulting payments from pharmaceutical companies, in violation of university and federal government rules, and had also failed to comply with an agreement with the university that he limit such payments. One of the documents cited was a letter he sent to a university official pointing out that his multiple ties to pharmaceutical companies had benefited the university by attracting company funding for department career awards, an endowed chair, and other gifts (Harris, 2008).

with the institution may unfairly be called into question, even though they were not involved in the conduct that was criticized.

This chapter begins by defining institutional conflicts of interest and describing what has been documented about the extent of such conflicts. The discussion then reviews responses to institutional conflicts of interest

and examines some of the challenges in managing such conflicts. The chapter concludes with recommendations, including a recommendation that the National Institutes of Health (NIH) require its grantees to adopt and apply policies on institutional conflicts of interest.

WHAT ARE INSTITUTIONAL CONFLICTS OF INTEREST?

Institutional conflicts of interest arise when an institution's own financial interests or those of its senior officials pose risks of undue influence on decisions involving the institution's primary interests. For academic institutions, such risks often involve the conduct of research within the institution that could affect the value of the institution's patents or its equity positions or options in biotechnology, pharmaceutical, or medical device companies. Conflicts of interest may also arise when institutions seek and receive gifts or grants from companies, for example, a gift of an endowed university chair or a grant for a professional society to develop a clinical practice guideline.

In addition, institutional conflicts of interest exist when senior officials who act on behalf of the institution have personal financial interests that may be affected by their administrative decisions. For instance, a department chair or dean who has a major equity holding in a medical device company could make decisions about faculty appointments and promotions or assignment of office or laboratory space in ways that favor the interests of the company but compromise the overall research, educational, or clinical mission of the institution. Similarly, a hospital official with such a holding would be at risk of undue influence in making decisions about the use of the company's products for patient care. In situations like these, an individual's financial relationship also implicates the institution's interests.

As emphasized in Chapter 2, conflicts of interest are defined in terms of the risk of undue influence and not actual bias or misconduct. Whether they are at the individual or the institutional level, conflict of interest policies seek to prevent compromised decision making rather than to try to remedy its consequences.

Institutional interests can be evaluated for the likelihood of undue influence and the seriousness of potential harms in ways analogous to those applicable to individual conflicts (see Chapter 2). Thus, assessments would consider the nature of the primary interest, the value and scope of the secondary interest, the extent of institutional accountability and discretion involving decisions about the primary interest at stake, and the seriousness of potential harms in relation to potential benefits (see also Emanuel and Steiner [1995]).

EXTENT OF INSTITUTIONAL RELATIONSHIPS WITH INDUSTRY

Because institutional conflicts of interest have not received as much attention as individual conflicts of interest, there is less evidence about their characteristics or impacts. The committee found little comprehensive information about the scope and nature of the ties of academic medical centers, professional societies, patient advocacy groups, and other institutions to pharmaceutical, medical device, and biotechnology companies. Such ties may involve various kinds of payments and gifts to an institution, institutional ownership interests in companies, patents, and the relationships of senior officials (for example, service on a company's board of directors). Most reports focus on prominent and usually egregious cases of misconduct, as illustrated in Box 8-1.

Chapter 4 reviewed the results of a survey of department chairs in medical schools and large independent teaching hospitals that found that 27 percent of preclinical departments and 16 percent of clinical departments received income from intellectual property licensing (Campbell et al., 2007b). (This income may be seen as a benefit of the provisions of the Bayh-Dole Act, which allow institutions to patent discoveries resulting from federally funded research and to grant exclusive licenses for others to develop those discoveries.) The survey also found that ties to industry were common among department chairs, who served as consultants (27 percent), members of a scientific advisory board (27 percent), paid speakers (14 percent), company officers (7 percent), and company board members (11 percent). The committee did not locate institution-level data on company funding of biomedical research, but Chapter 4 reported that the majority of such research in the United States is commercially funded.

For institutions as well as individuals who provide health care, conflicts of interest also arise from provider reimbursement methods, whether these involve fee for service, prospective payment per case, pay for performance, or other arrangements. In addition, conflicts may arise from provider ownership interests, for example, hospital ownership of subsidiary specialty centers to which the hospital's physicians refer patients. As noted in Chapter 6, however, consideration of payment methods and ownership interests in medical facilities are beyond the scope of this report.

Among universities, a Congressional Research Service report concluded that patents typically account for a small percentage of university research and development funding and that most significant income from patents has tended to come from single "blockbuster" patents (Schacht, 2008). The report did not look specifically at biomedical research institutions. The Association of University Technology Managers, which conducts an annual survey of technology transfer activities (including the licensing of patents

and the launching of start-up companies), does not report information by scientific field.[1]

Most professional societies and disease-focused or patient advocacy groups do not make public the details of funding received from industry, but it appears that many groups depend on medical product companies for a significant share of their overall revenues and for specific activities (e.g., continuing medical education and the development of clinical practice guidelines). In connection with congressional inquiries about its relationships with pharmaceutical companies, the American Psychiatric Association (APA) reported that medical companies supplied about 28 percent of its annual income. An informal APA survey of other medical specialty societies indicated that this figure was about in the middle of the range of the income that companies provide these groups (from 2 to nearly 50 percent) (Stotland, 2008). An Associated Press story on pharmaceutical company spending to promote the awareness of fibromyalgia reported that companies contributed funds that amounted to 40 percent of the annual budget of the National Fibromyalgia Association (Perrone, 2009). Many groups list corporate donors but do not report how much of their income is derived from these donors. Groups that report sources of funding for activities such as clinical practice guideline development usually do not report the amount of company funding for an activity or what percentage of an activity's cost was accounted for by company funds. These data would assist with assessments of the risk of undue influence.

In a 2006 report for its board of directors, the American Academy of Family Physicians (AAFP) analyzed its resources and activities and concluded that it was not financially possible to forgo industry funding for any of its activities without imposing unacceptable cuts in services to members or increases in member costs. For its fiscal year 2006–2007 budget, AAFP projected that less than 38 percent of its income ($31 million of a total budget of $80 million) would come from dues and sales of products and services to members. Approximately 42 percent ($34 million) would come from the pharmaceutical industry, of which about 60 percent would come from advertising in the academy's journal and 13 percent would come from payments for exhibits at meetings (AAFP, 2006a). The report noted that the organization had sought to broaden its base of nondues funding beyond pharmaceutical companies by seeking grants from government and foundations for various activities and

[1] On the basis of its 2006 survey, the Association of University Technology Managers reported 12,672 actively managed licenses from patents as well as the introduction of 697 new products and 553 start-up companies (AUTM, 2007). It did not report the extent to which the institutions had financial stakes in the new products and companies. The survey covered 190 institutions, including 161 universities and 28 teaching hospitals and research institutions.

had also taken other steps to limit the influence of industry. If it stopped accepting all funding from industry, however, including journal advertising, the organization would have had to increase member dues by about $600 (to about $1,000 per year) to maintain the levels of service and the programs (e.g., existing educational activities at the same per program cost to members) that existed at that time (AAFP, 2006a).

The data presented in Chapter 6 showed that physician membership organizations obtained 49 percent of their income for accredited continuing medical education from a combination of commercial funding for activities, advertising, and exhibits at meetings. Medical school continuing medical education programs received about 62 percent of their income from these sources; for publishing and education companies, the figure was 73 percent.

RESPONSES TO INSTITUTIONAL CONFLICTS OF INTEREST

Federal regulations and laws have not consistently targeted institutional conflicts of interest. The U.S. Public Health Service (PHS) regulations on conflict of interest, which were issued in 1995 and which are included in Appendix B, cover only individual conflicts of interest and relationships with industry. Institutional conflicts of interest were deliberately not addressed (NIH, 1995). The guidance on financial relationships in research with human participants published by the U.S. Department of Health and Human Services discusses the identification and management of institutional as well as individual financial interests (HHS, 2004). The document suggests questions and procedures for institutional review boards (IRBs), investigators, and institutions to consider in evaluating institutional relationships. Federal antikickback rules apply to illegal payments to institutions as well as individuals. The recommendation by the Medicare Policy Advisory Commission (see Chapter 3) for industry reporting of consulting and other payments covers not only payments to physicians but also payments to medical schools, professional societies, and providers of continuing medical education (MedPAC, 2009). A bill introduced in the U.S. Congress in 2007 (S. 2029) and reintroduced in 2009 (Grassley, 2009) covers payments to individual physicians.

Several academic organizations have issued reports on institutional conflicts of interest, including the Association of American Medical Colleges (AAMC, 2002; AAMC-AAU, 2008), the Association of American Universities (AAMC-AAU, 2008), and the Council on Government Relations (COGR, 2003). The 2002 AAMC and 2008 AAMC-AAU reports dealt with institutional conflicts of interest in research with human participants.

The 2008 AAMC-AAU report was in part a response to evidence that academic medical centers had not implemented the recommendations set

forth in the 2002 AAMC report. In an AAMC survey of its members, only 38 percent of the institutions that responded reported that they had a conflict of interest policy that applied to the institution's financial interest, although another 37 percent reported that they were developing such a policy (Ehringhaus et al., 2008). For institutions that had policies, the documents typically covered equity in nonpublicly held companies (90 percent) or publicly held companies (77 percent), royalties (80 percent), payments for reaching designated milestones in the course of a study (73 percent), and substantial gifts from a research sponsor (73 percent). The majority of institutions that had policies applied them to senior officials (71 percent), governing board members (66 percent), and members of the IRB (81 percent). In addition, the majority of respondents reported creating organizational arrangements to separate institutional responsibility for research from responsibility for investment management (94 percent) or technology transfer (61 percent). Although the most serious problem identified in the survey was the lack of policies at a majority of institutions, another concern was the incomplete coverage by policies of significant institutional interests.

In addition to reiterating the importance of such policies, the 2008 AAMC-AAU report set forth several guiding principles for institutional conflict of interest policies. They were

- "research and financial decision-making processes and agents must be separated";
- "decisions about whether or not to pursue a particular human subjects research project in the presence of an institutional conflict of interest should be governed by a 'rebuttable presumption' against doing the research at or under the auspices of the conflicted institution" unless a compelling case can be made to justify an exception; and
- institutional conflict of interests "will be addressed consistently throughout the institution, such that those subject to institutional financial conflict of interest policies, specifically officials of the institution and the institutions themselves, are subject to substantive reporting, disclosure, and management of their financial interests." (pp. 14–16)

The report also recommended the creation of a standing institutional conflict of interest committee and discussed procedures for the reporting of institutional financial interests and the managing of relationships that were determined to be conflicts of interest. Strategies could involve divesting the institution of an equity interest in a company, requiring senior officials to remove themselves from involvement with making decisions that might affect their conflicting interest, declining to perform research in which the

institution has a financial stake (beyond the funding of the research itself), asking the IRB at another institution to review such research, or disclosing the institutional conflict of interest to research participants.

One university's policy lists several issues to be considered in evaluations of the circumstances that might justify institutional involvement in a human subjects research project despite a conflict of interest (University of Rochester, 2006). The case for the institution's participation in the project is stronger to the extent that

- the work is carried out at multiple sites (e.g., under the auspices of several institutions);
- the institution takes a relatively passive role in the conduct of the project (e.g., the gathering of data);
- the number of research subjects under the institution's supervision is small;
- an adverse effect on research subjects appears more likely if the institution is not used as a research site; and
- the investigators conducting the research or the university resources supporting the project are essential and are not readily available elsewhere.

In a position statement on organizational aspects of physician relationships with industry, the American College of Physicians (ACP) advised that "[m]edical professional societies that accept industry support or other external funding should be aware of potential bias and conflicts of interest" (Coyle et al., 2002b, p. 405). It recommended the adoption of explicit institutional policies on industry relationships, including policies that "avoid reliance on outside sources of support" and that guide the acceptance and disclosure of funding from industry and other outside sources. The ACP position on educational programs is that "it is unethical for academic institutions and educational organizations to accept any support that is explicitly or implicitly conditioned on industry's opportunity to influence the selection of instructors, speakers, invitees, topics, or content and materials of educational sessions" (Coyle et al., 2002b, p. 405).

In a 2006 statement, the Society for General Internal Medicine (SGIM) reported limits on the share of its annual operating budget that could come from external sources (SGIM, 2006). The limit on external sources of funding was 33 percent overall, with limits of 10 percent from health care-related for-profit entities in combination and 5 percent for any single such entity. (Thus, 67 percent of the operating budget must come from internal sources, such as member dues and fees.) Furthermore, the statement declared that the organization should not accept funds from

> for-profit companies (or not-for-profit entities funded largely by for-profit companies) for research or educational projects (including *individual* precourses, workshops or other presentations at the SGIM national or regional meetings) related to specific diseases, or to pharmaceuticals, medical devices, diagnostics, or other products or services purported to have direct health benefits to patients (regardless of whether the products are sold by that particular external funder). (p. 2)

The statement described such funds as "problematic" because their intent would seem to be "primarily promotional; that is, to directly or indirectly (through greater recognition of the disease in the population) encourage wider use of medical products, to the benefit of the sponsor" (p. 2). The statement stated that general meeting support may be solicited after program planners have determined the content of the meeting.

Chapter 6 discussed the actions that the Accreditation Council for Continuing Medical Education initiated to limit industry influence associated with providers' solicitation and acceptance of industry funding. Chapter 7 described the steps taken by some professional societies to insulate activities such as clinical practice guideline development from influence associated with industry funding. It also noted that some societies do not accept industry funding for guideline development.

SPECIAL CHALLENGES IN MANAGING INSTITUTIONAL CONFLICTS OF INTEREST

Although the committee found no systematic research on institutional conflicts of interest or the effects of institutional policies, it identified several challenges in managing such conflicts. One challenge is that identifying relevant institutional financial interests and conflicts may be difficult. Particularly in universities or other large institutions, no single individual or office may have knowledge of all such interests. Those responsible for identifying relationships may have to survey various parts of the institution to develop an inventory of relevant interests and relationship. In an academic medical center, for example, this inventory could cover the office responsible for technology transfer and intellectual property, the office or body that manages investments, the offices responsible for purchasing medical equipment, academic departments and other units that may receive gifts, and perhaps other offices or units as well. For senior officials, the usual process for disclosing individual financial interests will apply, although the review of disclosures will be at a higher level, for example, through a committee of the governing board, as recommended below.

Dealing with institutional conflicts of interest may be more difficult in some respects than dealing with individual conflicts of interest. In the case of individual conflicts in large institutions such as universities, medical

schools, and major teaching hospitals, opportunities for review usually exist at multiple levels of the institution and involve authorities who are relatively independent and do not stand to gain personally from the secondary interests in question. In contrast, an independent review for institutional conflicts of interest may be difficult because the institutional officers themselves may stand to benefit indirectly from the conflict of interest and may be reluctant to question current or proposed relationships with companies that seem likely to improve the institution's financial welfare. For example, the reputation and tenure of chief executives and other high-level officials may depend on their success in strengthening the financial health of their institution. If senior officials who oversee technology transfer, intellectual property, and research grants are also charged with managing institutional conflicts of interest, they may find it difficult to resist pursuing a grant or may be reluctant to divest the institution of a property interest even if such actions are necessary to manage the conflict. The leaders of professional societies and patient advocacy groups that depend significantly on member dues or individual contributions may be reluctant to reject grants from industry, even though they create a risk of undue influence over activities such as the development of clinical practice guidelines or educational programs.

The potential for conflicts of interest among senior institutional officials is one reason for the committee's recommendation below that the key responsibility for oversight of institutional conflicts of interest be lodged with an institution's governing body. It is also a reason for the recommendation that independent members—individuals not affiliated with the institution—be included on board committees that review and manage institutional conflicts of interest.

Because the potential financial gain from a secondary institution-level interest may not be personal for institutional officials, their decisions may be more easily rationalized as serving the institution rather than themselves—even when officials also stand to gain in personal reputation. In fact, the gains often do serve the institution's primary mission, for example, when returns on investments or licenses are distributed to worthy research, educational, or patient care activities. Nonetheless, it is precisely because this argument for benefit is so plausible (and often valid) that serious institution-level conflicts of interest may be ignored or may not be reviewed carefully to assess whether they might, on balance, undermine rather than promote the primary missions of the institution.

For similar reasons, the public may—at least initially—be more tolerant of institutional conflicts of interest than individual conflicts of interest and may expect that institutions will pursue relationships to advance research, expand educational activities, or increase clinical resources. This tolerance may, in turn, reinforce the inclination of institutional leaders to downplay

or ignore the resulting conflicts of interest. Because it is clear that universities and other health care institutions require resources to fulfill their missions and because society has encouraged institutions to pursue such resources, "[s]ociety may not view this as self-interested behavior and consequently may erroneously be more tolerant of circumstances in which an institution's financial interests may compromise the integrity of its missions than of similar situations involving individual conflict of interest" (Emanuel and Steiner, 1995, p. 263).

RECOMMENDATIONS

Because no decision maker in an institution is fully free of conflict in the case of institutional conflicts of interest, it is not possible to establish a fully independent process for assessing such conflicts. Although no perfect solution exists, the committee concluded that, on balance, the most suitable authority for making judgments about institutional conflicts is the board of trustees or an equivalent governing body.

In their fiduciary role, members of the board are responsible for giving priority to the longer-term interests of the institution. Because they stand at a greater distance from the daily pressures of decision making than an institution's senior officials, they should be able to assess more judiciously the positive or negative effects of financial interests on the institution's core mission. Board members also have access to comprehensive information about the finances of the institution, some of which may be confidential and not revealed to senior institutional officials. They may also be better positioned to help an institution's chief executive resolve disputes about conflicts of interest that involve different units within the institution. For example, in a university, faculty in the school of public health may be more concerned than faculty in the school of business about the potential for investments in certain products to create a risk to the missions of the whole institution.

In addition, the decisions made by a governing board are more salient within and beyond the institution than decisions made by staff. When the board takes up an issue, the concerned public is more likely to take notice.

RECOMMENDATION 8.1 The boards of trustees or the equivalent governing bodies of institutions engaged in medical research, medical education, patient care, or practice guideline development should establish their own standing committees on institutional conflicts of interest. These standing committees should

- **have no members who themselves have conflicts of interest relevant to the activities of the institution;**
- **include at least one member who is not a member of the board or an employee or officer of the institution and who has some relevant expertise;**
- **create, as needed, administrative arrangements for the day-to-day oversight and management of institutional conflicts of interest, including those involving senior officials; and**
- **submit an annual report to the full board, which should be made public but in which the necessary modifications have been made to protect confidential information.**

The standing board committee (or subcommittee) would regularly review the financial relationships of the institution itself to identify conflicts of interest with its primary mission or missions and would likewise review the financial relationships of senior officials. The board committee would also evaluate the adequacy of the policies and procedures established to deal with these relationships. This board committee would be different from the committee established to address individual conflicts of interests, as suggested in Recommendation 3.1.

Although the board should be accountable for institutional conflicts of interest, the committee recognizes that board members may not be well suited to carry out day-to-day oversight or conduct special investigations, especially in academic medical centers and other large institutions. The board may therefore decide to establish a mechanism for the day-to-day oversight of institutional conflicts of interest. This mechanism could take different forms at different institutions. For example, as AAMC and AAU have recommended, an academic institution might establish a faculty-staff committee that would oversee institutional conflicts of interest and that would be separate from any committee responsible for individual conflicts of interest. Such a committee (and any other support staff) could report to the board committee or to an officer of the institution who is not directly responsible for institutional investments, technology transfer, or research. Various options are reasonable; and the choices made may depend in part on the size, organization, and scope of an institution. In any case, the option selected should be consistent with the objectives of establishing and supporting governing board oversight of institutional conflicts of interest.

The recommended annual report from the board committee will provide an incentive for that committee to report on both what it has decided with respect to newly identified conflicts of interest and how its previous decisions (e.g., plans for eliminating or managing an institutional conflict of interest) have been implemented. Such reporting will also provide an incentive for rigorous review and accountability. The board committee is

more likely to be diligent in its reviews if its members know that if they miss potential problems, their failure may be publicized for all to see, should these problems become the subject of official investigations or media reports. In certain cases, a tension may exist between the countervailing goals of public disclosure and keeping confidential certain personnel information and certain facts about current or pending intellectual property. Thus, the board's public reports may exclude some details because the information is confidential, but such exclusions should be rare.

To speed the adoption of institutional conflict of interest policies, NIH should extend the 1995 PHS regulations on conflict of interest to cover institutional as well as individual financial interests for institutions that receive PHS research grants. Such rules would also call attention to the issue and encourage institutions that do not receive research funds but that are engaged in medical education, clinical care, or the development of practice guidelines to voluntarily take action to avoid and oversee potential conflicts of interest. Ideally, the development of new PHS rules would be harmonized with corresponding revisions in the regulations of the National Science Foundation.

RECOMMENDATION 8.2 The National Institutes of Health should develop rules governing institutional conflicts of interest for research institutions covered by current U.S. Public Health Service regulations. The rules should require the reporting of identified institutional conflicts of interest and the steps that have been taken to eliminate or manage such conflicts.

Although the new PHS rules should be consistent with the recommendation in Recommendation 8.1 and other recommendations in this report, they need not be highly prescriptive or rigid, particularly given that experience with institutional conflict of interest policies appears to be more limited and is less well documented than policies governing individual conflicts. Provisions for monitoring and enforcement are, however, important both at the level of the NIH extramural program and within research institutions. Consistent with current PHS rules on individual conflicts of interest, Recommendation 8.2 calls for grantee reporting to NIH of identified institutional conflicts of interest.

NIH can encourage the appropriate and reasonably consistent implementation of the regulations by providing supplementary explanations and guidance, as it has recently done for its policies and regulations on individual conflicts of interest (see Chapter 3). It can also bring grantee representatives together to discuss their experiences and identify good practices in policy development and implementation. In addition, NIH can develop or commission case studies on common situations that raise concerns over

conflicts of interest, such as institutional stakes in start-up companies that seek to sponsor research at the institution.

Although the 2008 AAMC-AAU report did not explicitly recommend governing board responsibility for policies on institutional conflicts of interest, their report can still provide useful guidance to NIH and to grantee institutions and a model for developing case studies to provide education on the evaluation of conflicts of interest. Because experience with and evaluations of institutional conflict of interest policies are limited, the investigation of such policies should be one focus of the research agenda recommended in Chapter 9. In addition, continued attention to this area—for example, further surveys of policy adoption—by AAMC would also be constructive.

The intent of the recommendations in this report is to promote a culture in which conflicts of interest are taken seriously by institutions and individuals engaged in medical research, education, and practice and practice guideline development. For this to happen, institutions must effectively manage their own conflicts and be seen to be doing so. The board and the senior officials set the tone for the institution. They should be accountable for making sure that their own institutional interests are in order.

9

Role of Supporting Organizations

Physicians, researchers, and the institutions that carry out medical research and education, provide patient care, and develop practice guidelines do not act in isolation but, rather, as part of complex intersecting systems. These systems can support or interfere with the adoption, implementation, and improvement of sound conflict of interest policies and can amplify or reduce the probability that financial relationships with industry may undermine primary professional or institutional obligations. Within these systems, a variety of organizations—public and private—can influence the policies and practices of institutions and uphold norms of professional integrity.

Chapter 1 distinguished between institutions that carry out medical research, education, clinical care, and practice guideline development and supporting organizations. Supporting organizations include accreditation and certification bodies, health insurance plans, membership groups such as the Association of American Medical Colleges (AAMC) and the World Association of Medical Journal Editors (WAME), and government agencies such as the National Institutes of Health (NIH). These entities may be seen as supporting organizations because they are in a position to influence the conflict of interest policies of the institutions that are the primary subject of this report. They can establish incentives for academic and other institutions to create more effective responses to conflicts of interest, including adopting and implementing the recommendations presented in this report. Some supporting organizations can also create incentives for individual physicians and researchers to follow conflict of interest policies and related codes of conduct. They can, more broadly, help create a culture of accountability that supports the integrity of professional judgment and sustains public confidence in that judgment.

The opportunities for supporting organizations to exert influence arise in different ways, depending on the roles and authority of the organization. Accrediting organizations set standards for medical schools, residency and fellowship programs, and institutions that provide health care. State agencies establish rules for the licensing and relicensing of individual physicians, and specialty boards design rules to certify and recertify physician specialists. The National Guidelines Clearinghouse sets conditions for the posting of clinical practice guidelines developed by professional societies and other groups. Public and private health insurers use a variety of financial and other incentives to influence the practices of institutions and individual physicians. The U.S. Department of Justice and the Office of Inspector General of the U.S. Department of Health and Human Services enforce antikickback and self-referral laws that prohibit or limit certain conflicts of interest. NIH promotes and oversees adherence to U.S. Public Health Service (PHS) regulations on conflict of interest for grantees. Professional societies and associations of health care and educational institutions articulate norms and ethical standards for their members. (Some professional societies are both organizations in this sense and also institutions that carry out research, education, and practice guideline development.) Although the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Advanced Medical Technology Association (AdvaMed) represent companies, they establish codes of conduct for their members that may indirectly support medical professionals and institutions by discouraging member companies from interactions that create a risk of undue influence. (As described in Chapter 6, PhRMA and AdvaMed have indicated that they will publicly report on the companies that adopt their recently revised codes.)

Previous chapters have identified various shortcomings in the policies and practices of academic and other institutions. For example, as discussed in Chapter 3, some research institutions have been slow to adopt or adequately implement PHS requirements for conflict of interest policies, some academic medical centers have not adopted key AAMC policy recommendations, and some medical journals have not followed recommendations on conflict of interest from WAME and the International Committee of Medical Journal Editors (ICMJE). Furthermore, it may be difficult to determine a particular institution's policies. Postings on institutional websites may be incomplete or not up to date, and some institutions choose not to reveal their policies. Such a lack of transparency makes it difficult to assess whether an institution's policies are consistent with regulations or with recommendations of groups such as AAMC and WAME. As a result, opportunities to strengthen the institution's accountability for conflict of interest policies may be lost. Supporting organizations may promote consensus on the content of policies and also, in some situations, draw attention to the

failure of institutions to adopt and implement the policies, which may then stimulate corrective action.

This chapter discusses ways in which these diverse supporting organizations can cooperate with and influence the academic and other institutions that have the primary responsibility for dealing with conflicts of interest in medical research, education, and practice. The chapter begins by considering some of the productive forms that support and cooperation can take. The discussion emphasizes the roles of collaboration, consensus building, and incentives in making conflict of interest policies more effective and compliance with them less burdensome. It also recognizes that policies need to be backed by enforcement and sanctions. The chapter concludes with two recommendations that supplement the mostly mission-specific recommendations of earlier chapters. The first calls on supporting organizations to develop incentives for medical institutions to become more accountable for preventing, identifying, and managing conflicts of interest. The second calls for more research to provide a stronger evidence base for evaluating and improving conflict of interest policies.

HOW SUPPORTING ORGANIZATIONS CAN INFLUENCE MEDICAL INSTITUTIONS

Consensus Building and Collaboration

Consensus building and collaboration can operate within the institutions that are the focus of this report. Such efforts seek to engage those affected by policies in the process of developing them to improve the policies (e.g., by identifying and understanding obstacles to the success of the policies) and to win acceptance or buy in by those affected. Supporting organizations may likewise be more successful if they engage research, educational, and other institutions in the process of designing incentives and setting standards and if they give those institutions some discretion on how to reach specific performance goals. The leaders of those institutions are often in the best position to identify barriers to accountability (including burdensome or confusing administrative procedures) and to suggest ways to overcome those barriers. They are also well situated to identify and reduce the unintended negative consequences of proposed policies or procedures.

Some lessons for collaborative efforts that can be made to improve conflict of interest policies and practices are suggested by quality improvement initiatives within health care organizations. The typical quality improvement program in health care actively engages frontline caregivers and managers in an interdisciplinary process of identifying and analyzing problems in the quality of care, devising preventive or corrective interventions, monitoring outcomes, and modifying interventions on the basis of

the observed outcomes (Berwick, 1998). In this approach, the gathering and monitoring of outcomes data are crucial to identifying and reducing inappropriate variations in outcomes. In some cases, cross-institutional collaborations have helped institutions develop effective quality improvement programs. Some programs use transparency—the public reporting of organizational performance in relation to benchmarks—as a means of enhancing accountability and promoting competition to improve the quality of care. Accreditation agencies and voluntary groups have also encouraged this quality improvement process, and some universities have applied quality improvement models to university administration. The University of Wisconsin, for example, has an office of quality improvement that supports process improvement activities in administrative as well as academic areas, and its website showcases examples of activities that are potentially relevant for conflict of interest programs (University of Wisconsin, 2008).

There are, of course, significant differences between quality improvement procedures and conflict of interest policies. Nonetheless, the mechanisms of collaboration, consensus building, and outcome measurement can usefully guide the relationships between outside supporting organizations and institutions directly involved in medical research, education, and practice.

Some supporting organizations have been able to promote a consensus on important and often contentious aspects of conflict of interest policies. As described in earlier chapters, AAMC convened a broad group of affected parties that made recommendations about financial ties with industry in medical education (AAMC, 2008c). The parties included academic medical centers, teaching hospitals, industry, professional organizations, government agencies, and consumer groups. AAMC and the Association of American Universities convened another consensus development process to develop recommendations for improving the adoption and implementation of conflict of interest policies in human subjects research (AAMC-AAU, 2008). Over time, these and other initiatives have forged agreement on goals and recommendations regarding a number of controversial issues. Such collaborative consensus-building activities can address the practical concerns of individuals and institutions affected and make recommendations more credible and acceptable.

Incentives

Supporting organizations can devise incentives for institutions to adopt and implement conflict of interest policies. An example of an incentive for change in institutional policies and practices is the policy of the National Library of Medicine mentioned in Chapter 3. It will not cite or index articles from certain types of company-sponsored journal supplements unless they

include specific disclosures about any financial relationships that guest editors and authors have with the company or with the commercial products discussed in the supplement.

Just as the Medicare program and private health insurers have turned to pay-for-performance programs to provide incentives for quality improvement, so could insurance organizations offer incentives to institutions to adopt and maintain effective conflict of interest policies and to individuals to refrain from engaging in undesirable relationships with pharmaceutical, medical device, and biotechnology companies. For example, if preferred provider organizations publicly identified those participating physicians who agreed to decline gifts and marketing payments from industry, many physicians might decide that the benefits of being so identified outweigh the benefits of accepting such gifts and payments.

Particular incentives can have both positive and negative aspects. For example, when it rated medical schools on aspects of their conflict of interest policies, the American Medical Student Association used the "sunshine" of publicity in ways that were positive for the schools that it viewed as having good policies and possibly embarrassing for the schools that it viewed as having deficient policies (AMSA, 2008b). Although public reporting should enhance transparency and motivate policy change, it is also possible that it could merely promote the documentation of policies rather than meaningful oversight or change. Furthermore, public reporting could discourage relationships with industry that appropriately promote institutional missions and professional goals.

Enforcement and Sanctions

On the basis of the literature reviewed for Chapters 3 and 6, the actual imposition of penalties does not seem to figure prominently in the enforcement of conflict of interest policies, except for cases that involve offenses such as violations of anti-kickback and self-referral laws. NIH surveys and site visits have uncovered shortcomings in the content and application of PHS conflict of interest regulations for research grantees, and it appears that federal officials have penalized institutions or required quality improvement or remedial programs only rarely and only in cases in which problems have been identified in other ways (e.g., congressional or media investigations) (see Kaiser [2008]). As described in Chapter 3, NIH opposed a recommendation from the Office of the Inspector General that it require additional information from grantees about identified conflicts of interest and the means for their resolution.

Although they should be applied thoughtfully, sanctions have important roles in limiting and managing conflicts of interest. For example, at the most basic level, a process needs to be in place for institutions to determine

who has and who has not submitted the required financial disclosure forms. Usually, reminders should be sufficient for those who have not submitted forms, but penalties may also be needed, at least for blatant violations. Recent highly publicized incidents of significant underreporting of financial relationships to academic institutions call attention to the need for mechanisms to verify that the information disclosed is complete and accurate (e.g., through public reporting by industry of payments to physicians; see Recommendation 3.4). Again, sanctions may be appropriate for blatant cases of inaccurate disclosure. In addition, journal editors could take a stance more aggressive than they generally have thus far toward authors who violate their journals' disclosure and conflict of interest policies.

When noncompliance is egregious, penalties such as public censure or the suspension of individuals from certain positions (e.g., a principal investigator or department chair) may be necessary. Even accrediting agencies such as the Joint Commission (formerly the Joint Commission on the Accreditation of Healthcare Organizations) that have shifted from using more negative strategies to using more positive and cooperative strategies (e.g., acknowledging high performers and helping struggling performers improve) retain a range of sanctions for use against persistent or egregiously poor performers. Sanctions are, however, neither sufficient nor desirable as the sole instruments of accountability. They must be combined with a more ambitious and effective compliance strategy that employs collaboration, consensus building, and positive incentives.

RECOMMENDATIONS

Creating Incentives for Institutional Action

As this report has described, some institutions that carry out medical research, education, clinical care, and practice guideline development have no or inadequate conflict of interest policies. Some institutions may not even fully meet the requirements of current federal regulations, and others fail to undertake monitoring and enforcement activities. This report has also described shortcomings in adherence by individual physicians and researchers to academic medical center, journal, and other conflict of interest policies.

Ideally, physicians, scientists, and medical institutions should voluntarily adopt conflict of interest policies as a matter of professional responsibility and professional ethics. A commitment to patient well-being, valid scientific research, and evidence-based education would naturally lead professionals to voluntarily adopt strong measures to minimize the negative impact of conflicts of interest on objectivity and trust. No doubt many professionals have such an attitude and act on it. Realistically, however, the committee

is aware that behaviors are shaped not only by personal commitments but also by cultural and social forces. The environment in which health care professionals carry out research, teach, provide clinical care, and develop practice guidelines should promote and reinforce a professional's internal tendency to avoid relationships that pose an unacceptable risk of improperly influencing his or her judgment. The same is true for institutions. Their commitment to improve the content and application of conflict of interest policies is more likely to be effective if strong and consistent support from multiple independent organizations exists alongside government regulations. Thus, Recommendation 9.1 calls for an array of public and private groups (that is, supporting organizations) to create incentives to promote the widespread acceptance of policies to limit and manage conflicts of interest.

RECOMMENDATION 9.1 Accreditation and certification bodies, private health insurers, government agencies, and similar organizations should develop incentives to promote the adoption and effective implementation of conflict of interest policies by institutions engaged in medical research, medical education, clinical care, or practice guideline development. In developing the incentives, these organizations should involve the individuals and the institutions that would be affected.

A number of specific suggestions about incentives were discussed above and in the earlier chapters on medical research, education, and practice and practice guideline development. Box 9-1 summarizes these and other

BOX 9-1
Examples of Methods That Supporting Organizations Can Use to Strengthen Conflict of Interest Policies

Oversight bodies that oversee or regulate medical education and practice

- Accreditation and specialty certification bodies could set standards for the adoption of conflict of interest policies by organizations that offer undergraduate, graduate, and continuing medical education. These bodies could also collect and make public information on the educational institutions that follow those standards.
- State licensing boards could require that the continuing medical education courses required for relicensure be provided only by institutions that have adopted conflict of interest policies and other relevant recommendations presented in this report.

BOX 9-1 Continued

Membership organizations

- AAMC, PhRMA, and AdvaMed could collect and make public information on which of their member organizations have adopted their recommended conflict of interest policies or codes of conduct. (Note that the last two organizations have announced that they will post the names of companies that have pledged to follow their recently revised codes.)
- WAME could collect and make public information on which medical journals have adopted the authorship, ghostwriting, and conflict of interest policies consistent with its policy statements and those of ICMJE.
- Professional societies and associations of professional organizations could set standards for conflict of interest provisions in professional codes and membership criteria, make their policies public, and establish awards for groups that have exemplary conflict of interest policies and procedures.

Private health insurance plans

- Private health insurance plans could establish incentives for hospitals and individual physicians to adopt conflict of interest policies, as recommended in this report. For example, the adoption of such policies could be a criterion for an institution to be a center of excellence or for a physician to be a member of a preferred provider program. Alternatively, the lists of physicians in a plan could include information on whether a physician has agreed to certain conflict of interest provisions. Health insurers could also establish similar incentives for other institutions that provide health care, such as skilled nursing facilities or dialysis units.
- Business coalitions, such as the Leapfrog Group, the National Business Group on Health, and the Pacific Business Group on Health, could encourage employers who purchase health insurance to provide financial incentives for health care plans and health care providers to adopt the relevant recommendations presented in this report.

Government agencies

- NIH could collect and make public information on research institutions that have policies that are not in full compliance with 1995 PHS regulations. It could expand its recent efforts to provide more guidance to grantee institutions covered by the PHS regulations, and it could also analyze a sample of grantee conflict of interest reports to understand and evaluate how grantees eliminate or manage those conflicts of interest that are identified.
- The National Library of Medicine could identify in its online databases those journals that have adopted the authorship guidelines of ICMJE or WAME. For example, a symbol could be placed near the name of the journal when it appears in the listing of an article.
- The National Guidelines Clearinghouse could include only clinical practice guidelines that follow the recommendations presented in this report, including the provision of information about the sponsoring group's conflict of interest policies, the sources and amounts of industry funding for the guideline, the steps taken to identify participants without conflicts of interest, and the limits placed on participation in decision making by members with conflicts of interest.

examples of what supporting organizations can do. Many involve collecting and making public information about which institutions have adopted and applied the recommended policies. The committee expects that the prospect of such reporting would motivate institutions to close the gaps and loopholes in their conflict of interest policies or to provide a vigorous justification of why their policies depart from the recommendations.

If voluntary measures to deal with conflicts of interest are perceived to be weak or ineffectual, then calls for additional legislation or regulation or the more intrusive or punitive enforcement of existing laws will likely grow. The opportunity to preempt sweeping and potentially burdensome legal requirements should give a sense of urgency to voluntary efforts to establish and implement conflict of interest policies that reassure the public and those who make public policy. Government directives and prohibitions can be blunt instruments for dealing with conflict of interest problems, which often call for subtle judgments of risks and benefits and which involve many uncertainties. They also may not be as sensitive as voluntarily adopted measures to the administrative burdens of compliance or the possibility of unintended adverse consequences. This caution should not be interpreted as an endorsement of lax agency oversight or the lax application of existing conflict of interest rules.

Building the Evidence Base for Policy Improvement

As has been observed throughout this report, little systematic information about conflict of interest policies is available. This lack of information extends from basic descriptive information about policies to evaluations of the effects of different kinds of policies and implementation strategies.

RECOMMENDATION 9.2 To strengthen the evidence base for the design and application of conflict of interest policies, the U.S. Department of Health and Human Services should coordinate the development and funding of a research agenda to study the impact of conflicts of interest on the quality of medical research, education, and practice and on practice guideline development and to examine the positive and negative effects of conflict of interest policies on these outcomes.

Within the U.S. Department of Health and Human Services, NIH, the Agency for Healthcare Quality and Research, and the Food and Drug Administration should be involved in defining a research agenda that addresses questions and concerns about implementing, enforcing, and possibly refining conflict of interest policies. The research agenda not only should investigate government policies, however, but also should investigate the

policies that academic medical centers, professional societies, and other private groups have adopted.

Research on the characteristics and outcomes of conflict of interest policies would be desirable for several reasons. First, research could clarify which relationships are associated with higher or lower risks of undue influence or loss of trust, as well as the magnitudes of such associations. Second, such research may identify which conflict of interest policies and procedures are effective in achieving the desired outcomes and under what circumstances various policies are likely to be more effective. These data could then guide modifications in policies and procedures. Third, research on conflict of interest policies may identify unintended adverse consequences of well-intentioned policies and, in turn, inform corrective policy changes. Unintended negative consequences might include disproportionate administrative burdens and the inhibition of constructive collaborations between academia and industry. Strengthening the evidence base should allow institutions to improve their conflict of interest policies to better protect the integrity of their missions and to maintain the trust of the public.

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A

Study Activities

During 2006, the Institute of Medicine's (IOM's) Board on Health Sciences Policy began to discuss threats to public trust in biomedical research and medicine created by certain types of financial relationships between pharmaceutical, medical device, and biotechnology companies and researchers based in universities and federal agencies. As the discussion expanded, others expressed concerns about conflicts of interest in medical education, especially continuing medical education. The IOM was also approached about whether it would examine financial relationships and conflicts of interest as they affect the publication of research and the development of clinical practice guidelines.

In response, the IOM developed a proposal for a broad-ranging study that would examine conflicts of interest across medical research, medical education, clinical practice, and practice guideline development. It secured funding for the study from both public and private sources and appointed a 17-member committee to oversee the study. The charge to the committee was to develop a consensus report that would

- examine and describe conflicts of interest involving health care professionals and industry in different contexts, including, for example, the conduct of research, the education of health care professionals, the development of practice guidelines, the provision of patient care, and the management of academic and other institutions;
- propose principles to inform the design of policies, guidelines, and other tools to identify and manage conflicts of interest in these contexts without damaging constructive collaboration with industry; and
- consider methods to disseminate, promote, implement, and evaluate these principles and policies.

The committee met six times between November 2007 and October 2008. It held public sessions at its first four meetings to hear views from a wide range of experts and interested parties. The May 2008 meeting included a workshop on conflict of interest issues in basic research and another on conflict of interest issues in the development of clinical practice guidelines. The agendas for the public meetings are listed below. The committee also invited written statements of views from approximately 50 additional organizations; those that submitted statements are listed.

INSTITUTE OF MEDICINE
COMMITTEE ON CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Keck Center of the National Academies
November 5–6, 2007—Open Sessions

November 5

3:00 **Welcome and Introductions**
Bernard Lo, M.D., Committee Chair

3:10 **Overview of Conflicts of Interest in Medical Research, Education,** and Practice
Robert Steinbrook, M.D., National Correspondent, *New England Journal of Medicine*
Eric Campbell, Ph.D., Associate Professor, Institute for Health Policy, Massachusetts General Hospital, and Harvard University
Greg Koski, M.D., Ph.D., Senior Scientist, Institute for Health Policy, Massachusetts General Hospital, and Harvard University
Peter Lurie, M.D., M.P.H., Deputy Director, Public Citizen's Health Research Group

Discussion

5:00 **Adjourn**

November 6

8:30 **Welcome and Introductions**

8:35 **Perspectives from Industry**
Garry A. Neil, M.D., Group President, Johnson & Johnson

8:50 **Discussion with Study Sponsor**
Christine Cassel, M.D., President, American Board on Internal Medicine Foundation

9:05 **Conflict of Interest in Medical Research**
Cary P. Gross, M.D., Associate Professor of Medicine, Yale University
David Korn, M.D., Senior Vice President for Biomedical and Health Sciences Research, Association of American Medical Colleges

Discussion

10:10 **Break**

10:30 **Conceptual Issues in Conflict of Interest**
Ezekiel J. Emanuel, M.D., Ph.D., Chair, Department of Bioethics, Magnuson Clinical Center, National Institutes of Health

Discussion

11:10 **Discussion with Study Sponsor**
Elias A. Zerhouni, M.D., Director, National Institutes of Health

Noon **Adjourn**

INSTITUTE OF MEDICINE
COMMITTEE ON CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Keck Center of the National Academies
January 21, 2008—Open Session

1:00 **Welcome, Introductions, and Statement About the Meeting**
Bernard Lo, M.D., Committee Chair

1:10 **Conflict of Interest in Medical Education**
Suzanne Fletcher, M.D., M.Sc., Professor Emerita of Ambulatory Care and Prevention, Harvard Medical School
Michael Steinman, M.D. (*by conference call*), Assistant Professor of Medicine, San Francisco Veterans Affairs Medical Center and University of California, San Francisco

Discussion

2:10 **Conflict of Interest in Medical Education**
Murray Kopelow, M.D., Chief Executive, Accreditation Council for Continuing Medical Education
Ingrid Philibert, M.H.A., M.B.A., Senior Vice President, Department of Field Activities, Accreditation Council for Graduate Medical Education
F. Daniel Duffy, M.D., Senior Adviser to the President, American Board of Medical Specialties

Discussion

3:10 **Break**

3:30 **Perspectives from Industry**
Paul Citron, Ph.D., Retired, Vice President for Technology Policy and Academic Affairs, Medtronic
Cathryn Clary, M.D., Vice President, U.S. External Medical Affairs, Pfizer, Inc.

Discussion

4:15 **General Discussion**

5:00 **Adjourn**

INSTITUTE OF MEDICINE
COMMITTEE ON CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Board Room, National Academy of Sciences
March 13, 2008—Open Session

8:15 **Welcome and Chair's Statement**
Bernard Lo, M.D., Committee Chair

8:30 **Statements from Organizations**
Consumers Union
Gail Shearer, Director, Health Policy Analysis
John Santa, M.D., Consultant and Associate Professor, Oregon Health Sciences University and Portland State University

Center for Science in the Public Interest
Merrill Goozner, Director, Integrity in Science

Alpha-One
John Walsh, President

Questions and Discussion

9:25 Statements from Organizations
Pharmaceutical Research and Manufacturers Association
Alan Goldhammer, Ph.D., Deputy Vice President, Regulatory Affairs

AdvaMed (Advanced Medical Devices Association)
Kris Rapp, Vice President, Global Ethics & Compliance for Hospira, Inc.

BIO (Biotechnology Industry Organization)
Jonca Bull, M.D., Director, Clinical and Regulatory Affairs, Genentech

North American Association of Medical Education and Communication Companies
Karen M. Overstreet, Ed.D., R.Ph., Past President and President, Indicia Medical Education, LLC

Questions and Discussion

10:25 Break

10:45 Lessons Learned I: Developing and Implementing Medical School Conflict-of-Interest Policies
Philip A. Pizzo, M.D., Carl and Elizabeth Naumann Dean and Professor of Pediatrics and of Microbiology and Immunology, Stanford University School of Medicine

Joseph B. Martin, M.D., Ph.D., Edward R. and Anne G. Lefler Professor of Neurobiology, and Dean, Harvard Medical School, 1997–2007

Questions and Discussion

Follow-up Questions and Discussion for Earlier Panels

12:00 Lunch break

1:00 Statements from Organizations
American Medical Association
Mark A. Levine, M.D., Chair, Council of Ethical and Judicial Affairs

American College of Physicians
Joel S. Levine, M.D., Chair, Board of Regents and Senior Associate Dean for Clinical Affairs, University of Colorado School of Medicine

American Psychiatric Association
Carolyn B. Robinowitz, M.D., President and Clinical Professor of Psychiatry at Georgetown and George Washington Universities

American College of Cardiology
John C. Lewin, M.D., C.E.O.
Sidney C. Smith Jr., M.D., Professor of Medicine and Director, Center for Cardiovascular Science and Medicine, University of North Carolina, Chapel Hill

American Medical Student Association
Brian Palmer, M.D., M.P.H., Past President and Psychiatry Resident, Massachusetts General Hospital/McLean Hospital

Questions and Discussion

2:30 Break

3:00 Lessons Learned II: Developing and Implementing Conflict-of-Interest Policies
David Korn, M.D., Senior Vice President for Biomedical and Health Sciences Research Association of American Medical Colleges
Leo Furcht, M.D., Past President, Federation of American Societies for Experimental Biology and Allen Pardee, Professor and Head of Laboratory Medicine and Pathology, University of Minnesota School of Medicine
Harold C. Sox, M.D., International Committee of Medical Journal Editors, and Editor, *Annals of Internal Medicine*

Questions and Discussion

4:15 Continued Questions and Discussion and Public Comment

5:00 Adjourn

Organizations Submitting Written Statements
In addition to the organizations presenting statements during the March meeting, the following organizations provided written statements to the committee:

Accreditation Council for Continuing Medical Education
Alliance for Continuing Medical Education
Alzheimer's Association
American Academy of Family Physicians
American Academy of Ophthalmology
American Academy of Orthopedic Surgeons
American Academy of Pediatrics
American Board of Medical Specialties
American Society of Hematology
American Thoracic Society
Coalition for Healthcare Communication
Infectious Diseases Society of America
National Kidney Foundation
North American Spine Society
Society for Academic Continuing Medical Education

INSTITUTE OF MEDICINE
COMMITTEE ON CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE

Lecture Room, National Academy of Sciences
May 22, 2008—Open Session

Conflict of Interest in Basic and Translational Research

8:15 Welcome, Introductions, and Chair's Statement
Bernard Lo, M.D., Committee Chair

8:35 Additional Perspectives on Professional Society Policies
Kenneth Kaushansky, M.D., President, American Society of Hematology and Chair and Helen M. Ranney Professor, Department of Medicine, University of California, San Diego

9:00 **Perspectives on Financial Relationships and Conflicts of Interest in Basic and Early-Stage Translational Research: Part 1**
Leslie Z. Benet, Ph.D., Professor, Department of Biopharmaceutical Sciences, University of California, San Francisco
Gail Cassell, Ph.D., Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company
Edward Benz, M.D., (*by telephone*), President, Dana-Farber Cancer Institute

Discussion

10:10 **Break**

10:30 **Perspectives on Financial Relationships and Conflicts of Interest in Basic and Early-Stage Translational Research: Part 2**
Hamilton Moses III, M.D., Chair, The Alerion Institute
Leo Furcht, M.D., Past President, Federation of American Societies for Experimental Biology and Allen Pardee, Professor and Head of Lab Medicine and Pathology, University of Minnesota School of Medicine

Discussion

11:25 **Financial Disclosures and Trust in Health Care Professionals**
Mark Hall, J.D., Professor of Law and Public Health, Wake Forest University School of Law
Kevin Weinfurt, Ph.D., Associate Professor of Psychiatry and Behavioral Sciences, and of Psychology and Neuroscience, Duke Clinical Research Institute

Discussion

Noon **Lunch break**

Conflict of Interest in Clinical Practice Guidelines

1:00 **Welcome, Introductions, and Chair's Statement**
Bernard Lo, M.D., Committee Chair

1:15 Individual and Organizational Financial Relationships with Industry
Elizabeth Boyd, Ph.D., Assistant Vice President for Research, Compliance and Policy, University of Arizona

Discussant: Mary Nix, M.S., Health Scientist Administrator, National Guideline Clearinghouse, Agency for Healthcare Research and Quality

Discussion

2:00 Organizational Policies, Practices, and Challenges in Developing and Implementing Conflict-of-Interest and Related Policies
Dina Michels, Esq., Vice President and General Counsel, American Society of Clinical Oncology
Murray Sagsveen, J.D., General Counsel, American Academy of Neurology
Sidney C. Smith, Jr., M.D., American College of Cardiology, and Professor of Medicine and Director, Academic Center for Cardiovascular Disease
Mary Barton, M.D., M.P.P., Scientific Director, U.S. Preventive Services Task Force, and University of North Carolina

Discussants:
Fran Visco, President, National Breast Cancer Coalition
Alvin Lever, M.A., C.E.O., American College of Chest Physicians
Sandra Zelman Lewis, Ph.D., Assistant Vice President, American College of Chest Physicians
Henry Masur, M.D., Chief, Department of Critical Care Medicine, National Institutes of Health Clinical Center
John C. Ring, M.D., Director, Policy Research and Development, American Heart Association

3:00 Break

3:20 Continued Discussion of Organizational Policies and Practices

4:00 Systematic Reviews and Other Strategies to Protect Against Bias in Guidelines Development
Holger Schunemann, M.D., Ph.D., Associate Professor of Medicine, University of Buffalo, and Italian National Cancer Institute, Rome, Italy

Discussion (all participants)

5:00 Public Comments

5:30 Adjourn

B

U.S. Public Health Service Regulations: Objectivity in Research (42 CFR 50)

TITLE 42—PUBLIC HEALTH
CHAPTER I—PUBLIC HEALTH SERVICE,
DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D—GRANTS
PART 50—POLICIES OF GENERAL APPLICABILITY

Subpart F–Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought

Sec. 50.601 — Purpose.

This subpart promotes objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under PHS [Public Health Service] grants or cooperative agreements will be biased by any conflicting financial interest of an Investigator.

Sec. 50.602 — Applicability.

This subpart is applicable to each Institution that applies for PHS grants or cooperative agreements for research and, through the implementation of this subpart by each Institution, to each Investigator participating in such research (see Sec. 50.604(a)); provided that this subpart does not apply to SBIR [Small Business Innovation Research] Program Phase I applications. In those few cases where an individual, rather than an institution, is an appli-

cant for PHS grants or cooperative agreements for research, PHS Awarding Components will make case-by-case determinations on the steps to be taken to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest of the individual. [p35816]

Sec. 50.603 — Definitions.

As used in this subpart:

HHS means the United States Department of Health and Human Services, and any components of the Department to which the authority involved may be delegated.

Institution means any domestic or foreign, public or private, entity or organization (excluding a Federal agency).

Investigator means the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding. For purposes of the requirements of this subpart relating to financial interests, "Investigator" includes the Investigator's spouse and dependent children.

PHS means the Public Health Service, an operating division of the U.S. Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated.

PHS Awarding Component means the organizational unit of the PHS that funds the research that is subject to this subpart.

Public Health Service Act or PHS Act means the statute codified at 42 U.S.C. 201 et seq.

Research means a systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social-sciences research. The term encompasses basic and applied research and product development. As used in this subpart, the term includes any such activity for which research funding is available from a PHS Awarding Component through a grant or cooperative agreement, whether authorized under the PHS Act or other statutory authority.

Significant Financial Interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other own-

ership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include:

(1) Salary, royalties, or other remuneration from the applicant institution;

(2) Any ownership interests in the institution, if the institution is an applicant under the SBIR Program;

(3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;

(4) Income from service on advisory committees or review panels for public or nonprofit entities;

(5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children, meets both of the following tests: Does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or

(6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed $10,000.

Small Business Innovation Research (SBIR) Program means the extramural research program for small business that is established by the Awarding Components of the Public Health Service and certain other Federal agencies under Pub. L. 97-219, the Small Business Innovation Development Act, as amended. For purposes of this subpart, the term SBIR Program includes the Small Business Technology Transfer (STTR) Program, which was established by Pub. L. 102-564.

Sec. 50.604 — Institutional responsibility regarding conflicting interests of investigators.

Each Institution must:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with this subpart and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If the Institution carries out the PHS-funded research through subgrantees, contractors, or collaborators, the Institution must take reasonable steps to

ensure that Investigators working for such entities comply with this subpart, either by requiring those Investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with this subpart.

(b) Designate an institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in PHS-funded research.

(c)(1) Require that by the time an application is submitted to PHS each Investigator who is planning to participate in the PHS-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and those of his/her spouse and dependent children):

(i) That would reasonably appear to be affected by the research for which PHS funding is sought; and

(ii) In entities whose financial interests would reasonably appear to be affected by the research.

(2) All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with this subpart for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records of all financial disclosures and all actions taken by the Institution with respect to each conflicting interest for at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR 74.53(b) for different situations.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application for the funding to which this subpart applies, that:

(1) There is an effect at that Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests

with respect to all research projects for which funding is sought from the PHS,

(2) Prior to the Institution's expenditure of any funds under the award, the Institution will report to the PHS Awarding Component the existence of a conflicting interest (but not the nature of the interest or other details) found by the institution and assure that the interest has been managed, reduced or eliminated in accordance with this subpart; and, for any interest that the Institution identifies as conflicting subsequent to the Institution's initial report under the award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on an interim basis, within sixty days of that identification;

(3) The Institution agrees to make information available, upon request, to the HHS regarding all conflicting interests identified by the Institution and how those interests have been managed, reduced, or eliminated to protect the research from bias; and

(4) The Institution will otherwise comply with this subpart. [p35817]

Sec. 50.605 — Management of conflicting interests.

(a) The designated official(s) must: Review all financial disclosures; and determine whether a conflict of interest exists and, if so, determine what actions should be taken by the institution to manage, reduce or eliminate such conflict of interest. A conflict of interest exists when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:

(1) Public disclosure of significant financial interests;

(2) Monitoring of research by independent reviewers;

(3) Modification of the research plan;

(4) Disqualification from participation in all or a portion of the research funded by the PHS;

(5) Divestiture of significant financial interests; or

(6) Severance of relationships that create actual or potential conflicts.

(b) In addition to the types of conflicting financial interests described in this paragraph that must be managed, reduced, or eliminated, an Institution may require the management of other conflicting financial interests, as the Institution deems appropriate.

Sec. 50.606 — Remedies.

(a) If the failure of an Investigator to comply with the conflict of interest policy of the Institution has biased the design, conduct, or reporting of the PHS-funded research, the Institution must promptly notify the PHS Awarding Component of the corrective action taken or to be taken. The PHS Awarding Component will consider the situation and, as necessary, take appropriate action, or refer the matter to the Institution for further action, which may include directions to the Institution on how to maintain appropriate objectivity in the funded project.

(b) The HHS may at any time inquire into the Institutional procedures and actions regarding conflicting financial interests in PHS-funded research, including a requirement for submission of, or review on site, all records pertinent to compliance with this subpart. To the extent permitted by law, HHS will maintain the confidentiality of all records of financial interests. On the basis of its review of records and/or other information that may be available, the PHS Awarding Component may decide that a particular conflict of interest will bias the objectivity of the PHS-funded research to such an extent that further corrective action is needed or that the Institution has not managed, reduced, or eliminated the conflict of interest in accordance with this subpart. The PHS Awarding Component may determine that suspension of funding under 45 CFR 74.62 is necessary until the matter is resolved.

(c) In any case in which the HHS determines that a PHS-funded project of clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted, or reported by an Investigator with a conflicting interest that was not disclosed or managed as required by this subpart, the Institution must require the Investigator(s) involved to disclose the conflicting interest in each public presentation of the results of the research.

Sec. 50.607 — Other HHS regulations that apply.

Several other regulations and policies apply to this subpart.

They include, but are not necessarily limited to:

42 CFR Part 50, Subpart D–Public Health Service grant appeals procedure

45 CFR Part 16–Procedures of the Departmental Grant Appeals Board

45 CFR Part 74–Uniform Administrative Requirements for Awards and Subawards to Institutions of Higher Education, Hospitals, Other Non-Profit Organizations, and Commercial Organizations; and Certain Grants and Agreements with States, Local Governments and Indian Tribal Governments

45 CFR Part 76–Government-wide debarment and suspension (non-procurement)

45 CFR Part 79–Program Fraud Civil Remedies

45 CFR Part 92–Uniform Administrative Requirements for Grants and Cooperative Agreements to State and Local Governments

C

Conflict of Interest in Four Professions: A Comparative Analysis

Michael Davis and Josephine Johnston***

This paper presents a selective survey of the ways in which important professions other than medicine understand and regulate conflicts of interest. The professions evaluated here—law (lawyers), accountancy (certified public accountants [CPAs]), architecture, and engineering—each differ from medicine in having clients or employers rather than patients as the focus of concern. The difference is not simply one of terminology. A client or an employer is not necessarily human. Many are corporations or governments. Even the human clients differ from patients. With some exceptions (e.g., clients accused of crimes), they are typically healthy, calm, and relatively well-informed about the service to be provided; they are seldom as vulnerable as a physician's patient typically is. A client or employer simply asks that something be done (a building put up, a machine designed, a contract drawn, or a company audited). Emergencies are much rarer in these professions than they are in medicine, and time to think through a problem is more plentiful. Because of their relative sophistication and bargaining strength (compared both with patients and with the professional in question), clients or employers need not readily consent to accept the conflicts disclosed to them; they are more likely to insist that a conflict be avoided or resolved or to use the conflict to better the bargain. In other words, law, ac-

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counting, architecture, and engineering are professions in which one might expect much less concern with conflicts of interest than in medicine.

Although these are the chief differences between medicine and the professions discussed here, they are not the only ones. These other professions differ substantially in size from medicine—and from each other. Physicians outnumber architects in the United States by about 10 to 1, engineers outnumber physicians by about 3 to 1, and the numbers of individuals in the other professions fall somewhere in between. Importantly, only one profession, engineering, does much that physicians would recognize as scientific research.

The professions evaluated here were chosen because none is a close analogue of medicine. Medicine tends to be the model for adjacent professions (osteopathy, dentistry, pharmacy, nursing, and so on). The comparison of medicine with an adjacent profession would provide less contrast and therefore less understanding of conflict of interest as a general problem for professions. All of the professions discussed here have substantial experience with employment in large organizations. Two of the professions—engineering and accounting—have a long history of employment in such organizations. Only a small minority of engineers has ever been self-employed in the way that most physicians, except those in research and teaching, were until recently. Even self-employed architects, lawyers, and accountants often work for and in large organizations in a way that physicians have only recently begun to do in large numbers. Looking at how these nonmedical professions respond to the conflicts of interest that are more likely to arise in large organizations should help physicians both look critically at present arrangements and anticipate the future. Finally, these professions all recognize conflicts of interest as posing a threat to the integrity of the profession and have developed ethics rules to address the threat.

TERMINOLOGY

"Conflict of interest" is not an old term. The first court case to use it in something like the sense that is now standard occurred in 1949.[1] Federal legislation first addressed conflict of interest in the late 1950s.[2] The *Index of Legal Periodicals* had no heading for "conflict of interest" until 1967; *Black's Law Dictionary* had none until 1979. No ordinary dictionary of English seems to have had an entry for "conflict of interest" before 1971. The term also began to appear in codes of ethics in the 1970s, although related terms, such as "adverse interest," "conflicting interest," "bias,"

[1] *In re Equitable Office Bldg. Corp.*, D.C.N.Y., 83 F. Supp. 531.

[2] Staff report of the Antitrust Subcommittee (Subcommittee No. 5) of House Judiciary Committee, 85th Cong., 2d sess., Federal Conflict of Interest Legislation (Comm. Print 1958).

"prejudice," and the like appeared in codes much earlier.[3] This short history may explain, at least in part, the variation in how the term is used among professions. We are all trying to keep pace with the usage.

The term "conflict of interest" is not self-explanatory but is an idiom or term of art (a term designed to pick out a phenomenon until then lacking a suitable name). For the professions discussed here, the term groups together a range of scenarios in which the professional judgment of the individual in question risks being compromised.[4] These professions do not use explicit definitions of "conflict of interest" but instead describe in their codes a variety of situations that fall under the heading "conflict of interest" and that must either be avoided or managed in specified ways. For example, the definitions section of the American Bar Association's (ABA's) *Model Rules of Professional Conduct* includes definitions of "informed consent" and "fraud" but not "conflict of interest."[5] Instead, situations labeled conflicts of interest are described in the *Model Rules*.[6] Similarly, the American Institute of Certified Public Accountants' (AICPA's) *Code of Professional Conduct* includes a definition of some of the terms used in its conflict of interest rules, such as "immediate family" but not "conflict of interest." In fact, AICPA's Code does not use the term "conflict of interest" at all, speaking instead of various threats to "independence" and "objectivity," including the threat posed by certain financial interests.[7]

The major concern uniting the professions' use of the term is to protect the judgment of individual professionals from undue influence, whether the risk arises from gifts or kickbacks; an individual's personal (generally financial) interests; or the interests of family members, colleagues, or current and former clients. In some of the professions, a situation—for example, the representation of both plaintiff and defendant in the same legal case—is labeled a conflict of interest when it would be described as a conflict of obligations or responsibilities in the report to which this paper is an appendix (see Chapter 2) because neither obligation would be considered secondary to the other.

For all of the professions discussed in this paper, a certain sort of expert

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[3] Neil R. Luebke, "Conflict of Interest as a Moral Category," *Business and Professional Ethics Journal* 1987; 6 (Spring): 66–81.

[4] Michael Davis, "Conflict of Interest Revisited," *Business and Professional Ethics Journal* 1993; 12 (Winter): 21–41.

[5] American Bar Association, Model Rules for Professional Conduct: Rules 1.0. www.abanet.org/cpr/mrpc/rule_1_0.html.

[6] American Bar Association, Model Rules for Professional Conduct: Rules 1.7–1.10. www.abanet.org/cpr/mrpc/mrpc_toc.html.

[7] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility: Section 100—Independence, Integrity, and Objectivity. www.aicpa.org/About/code/sec100.htm.

and trustworthy judgment in individual situations (the judgment characteristic of the profession) is what makes members of the profession useful. A conflict of interest makes that judgment unreliable just when reliability is needed. A conflict of interest is therefore always considered a threat to the good that the profession seeks to achieve and is often also a threat to the profession's reputation. That is what makes having a conflict of interest a serious concern in professional ethics.

The next four sections of this paper consider in detail how the four professions on our list understand conflict of interest, respond to it, and why. The final section summarizes and compares the professions and identifies approaches from which medical research, education, and practice might learn.

LAWYERS

The main legal professions—lawyers and judges—have traditionally taken conflict of interest very seriously. Because justice is to be fairly meted out, interests that might cause a judge to be or appear to be partial are also generally prohibited. Although lawyers owe obligations to the legal system and the public, their primary obligation is to their clients; interests that might interfere with this obligation are generally to be avoided. The legal professions have some of the strictest rules about conflict of interest and have a long history of examining and enforcing those rules. In the interests of space, the focus here is on lawyers because their work, in most respects, is more like that of physicians than is the work of judges. (Judges are more like physicians serving on drug and device approval panels or as authors of review articles, whose charge is to weigh all the evidence and reach a reasoned and impartial decision.[8])

In legal practice, conflicts of interest are conceptualized in the context of the attorney-client relationship, which is protected by very strong obligations of loyalty and confidentiality. Broadly speaking, two kinds of conflict are understood to arise in that relationship: first, conflicts between the interests of two or more clients (whether they be current clients or a current client and a former client) and, second, conflicts between the interests of one or more clients and the personal interests of the attorney.

The first kind of conflict is created by the act of entering into a certain attorney-client relationship. For that reason, lawyers routinely conduct "conflicts checks" before taking on a new client or a new file from an existing client. The second kind of conflict can be created by either enter-

[8] For an example of rules of professional conduct for judges, see New York State Commission on Judicial Conduct, Rules of Conduct, at http://www.scjc.state.ny.us/Legal%20Authorities/rgjc.htm. Judicial ethics emphasizes independence.

ing into a new attorney-client relationship; taking on a new file from an existing client; or taking on a personal interest, including but not limited to a financial interest. In part, because the conflict of interest of one lawyer is, as a general principle, imputed to all lawyers working in the same firm or group practice, procedures, internal databases, and software have been developed to assist large firms in identifying possible conflicts of interest. So, for example, a lawyer who marries will immediately report that change of status to his firm along with the spouse's investments, family connections, employer, and the like. In some cases, law firms have staff dedicated to monitoring conflicts of interest, including, according to one New York City law firm partner whom we spoke with, general counsel whose risk management responsibilities include conflict of interest issues. Lawyers also use letters of engagement to carefully specify which of the firm's lawyers will be working for the client on the particular matter to avoid or make more manageable any future conflict of interest.

For the first kind of conflict, the analogy with medicine is not particularly strong: physicians are not generally constrained from taking on new patients because of their loyalty to other (current or former) patients, although analogous problems concerning confidentiality may arise when one physician serves several members of the same family. The analogy becomes somewhat stronger if one thinks of a pharmaceutical company or a device manufacturer with whom a physician has a financial relationship as one "client" and one or more patients as the other "client."

The legal profession's management of the second kind of conflict—a conflict between a lawyer's personal interests and the interests of a client—could provide more direct instruction to medicine, insofar as there is a concern that physicians' financial and other relationships with industry might lead physicians to make clinical decisions that they would not have made but for those financial or other relationships.

Furthermore, the legal profession's general attitude toward conflict of interest might be instructive for medicine. Conflicts of interest are understood to be a common feature of legal practice for which the profession has developed norms, rules, and procedures. Censure attaches not to finding oneself in a position in which agreeing to represent a client would create a conflict of interest (all lawyers are in this position from time to time, even though they try to avoid it) but to agreeing to represent that client without properly addressing the conflict of interest.

Lawyers share some similarities with physicians. Until recently, many lawyers worked alone or in small group practices. Lawyers are under a strong obligation of fidelity to their individual clients; and although some clients are large companies or sophisticated and powerful individuals, many are vulnerable individuals, including people who are in trouble with the law, are victims of physical harm or abuse, or are making major decisions

that can have a lasting impact on their lives and the lives of their families (e.g., buying or selling property, making a will, or adopting a child). However, although some lawyers represent clients with a compromised decision-making ability, lawyers do not routinely deal with clients whose decision-making ability may be medically impaired.

In the United States, as in most other common-law jurisdictions, a lawyer (often called an attorney) may conduct all aspects of litigation (including court appearances); may represent clients in negotiations; may give legal advice; and may prepare contracts, wills, and other legal documents. The specific criteria for admission to the bar are set by each state: candidates must generally hold a law degree (J.D.) from an accredited law school; pass that state's bar examination; and in all but three jurisdictions, pass the Multistate Professional Responsibility Examination, which is a 2-hour-long multiple-choice test that includes questions about conflict of interest.[9]

To be accredited, American law schools are required to provide substantial instruction to all J.D. students in the values, rules, and responsibilities of the legal profession, including instruction in the identification and management of conflicts of interest.[10] Law professors themselves are subject to any conflict of interest policies of their own institutions. In keeping with the Association of American Law Schools' 2003 *Statement of Good Practices by Law Professors in the Discharge of Their Ethical and Professional Responsibilities*, law professors are obligated in publications and presentations to "disclose the material facts relating to receipt of direct or indirect payment for, or any personal economic interest in, any covered activity that the professor undertakes in a professorial capacity."[11]

To maintain the license to practice law, 41 U.S. states require completion of a prescribed number of hours of continuing legal education (CLE), and 36 of these states mandate the inclusion of professional responsibility (also called "legal ethics"), including in some states "elimination of bias."[12] Providers of mandatory CLE, which can be law schools, law firms (which offer CLE only to lawyers in-house or to outside lawyers as well), or private companies, must individually be accredited by each state's CLE accrediting authority. Mandatory CLE can be funded in a number of ways: it may be provided for a fee or it may be offered for free by the ABA, by state bar

[9] American Bar Association, Bar Admissions Basic Overview. www.abanet.org/legaled/baradmissions/basicoverview.html.

[10] American Bar Association, 2007–2008 Standards for Approval of Law Schools, Interpretation 302-9. www.abanet.org/legaled/standards/standards.html.

[11] Association of American Law Schools, Statement of Good Practices by Law Professors in the Discharge of Their Ethical and Professional Responsibilities, 2003. www.aals.org/about_handbook_sgp_eth.php.

[12] American Bar Association, Summary of MCLE Jurisdiction Requirements. www.abanet.org/cle/mcleview.html.

associations, or by law firms. (One lawyer with whom we spoke noted that large malpractice firms sometimes sponsor CLE.) The lawyer or the lawyer's employer pays the fee. Providers are required to offer tuition assistance to unemployed attorneys, attorneys working in the public sector, and those in a financial hardship situation. Lawyers seem unconcerned about the prospect of commercial interests being involved with CLE—they even allow corporate sponsorship at CLE events. Of course, in general, commercial providers of CLE are not potential clients or adverse parties but simply the makers of the tools or the providers of the services that lawyers use in the course of their work.

As a result of these requirements, virtually all, if not all, U.S. lawyers have received instruction on the identification and management of conflicts of interest, and many continue to address this issue in their CLE. Because the legal profession has developed considerable case law, detailed rules (described below), and legal scholarship (two or three dozen articles per year) addressing lawyers' conflicts of interest, there is much for American law students and lawyers to learn.

Canons, Model Codes, and Model Rules

Although local bar associations began to appear in the United States in the late 19th century, most U.S. lawyers at the time were only informally controlled by reputation and peer pressure. The ABA was founded in 1878; and one of its first major initiatives became, in 1908, the Canons of Professional Ethics, developed in response to a perceived need to promote and vouch for the integrity (or reliability) of lawyers generally.[13] Initially there were 32 canons, and the number of canons eventually expanded to 47. The individual canons were fairly brief (the briefest is one sentence of two dozen words, whereas the longest is a few paragraphs). They were not accompanied by further guidance or detailed explanation, as is found in modern codes of legal ethics. Nevertheless, they were influential. By 1924, virtually every state and local bar association had adopted the canons.[14]

A number of the canons are relevant to conflict of interest, although it was the sixth canon (titled Adverse Influences and Conflicting Interests) that addressed the issue directly. Canon 6 consisted of three short paragraphs, and although it was fairly unsophisticated and incomplete, it captured the major conflict of interest issues that attorneys face even today. It attempted

[13] Ted Schneyer, How Things Have Changed: Contrasting the Regulatory Environment of the Canons and the Model Rules. www.abanet.org/cpr/schneyer.pdf.

[14] James M. Altman, "Considering the ABA's 1908 Canons of Ethics," *Fordham Law Review* 2003; 71: 2395–2524, at 2396, quoting Report of the Standing Committee on Professional Ethics and Grievances, *American Bar Association Report* 1924; 49: at 466, 467.

a definition of client-client conflict of interest as a conflict of obligation ("when, in behalf of one client, it is his duty to contend for that which duty to another client requires him to oppose"), identified client loyalty and confidentiality as two values threatened by conflict of interest, identified the particular problems of concurrent and subsequent representation of conflicting clients, and proposed one remedy for concurrent representation (disclosure followed by informed consent).[15] Other canons dealt with related conflict of interest issues, including a prohibition on a lawyer purchasing an interest in the subject that is a matter of litigation and a requirement that contingency fee arrangements be supervised by the court to prevent unjust charges.

Fifteen amendments to the canons (none related to Canon 6) were adopted before the ABA developed a new code, the *Model Code of Professional Responsibility*, in 1969.[16] The *Model Code* was a far more detailed document than the canons. It contained nine "canons" (described as "axiomatic norms"). These doubled as section titles. Each canon was followed by a series of Ethical Considerations and Disciplinary Rules. The Ethical Considerations were described as "aspirational in character," representing the objectives toward which all lawyers should strive. The Disciplinary Rules were, unlike the Ethical Considerations, mandatory and set "the minimum level of conduct below which no lawyer can fall without being subject to disciplinary action."

Conflict of interest was mainly addressed in Canon 5 of the *Model Code*, which states: "A Lawyer Should Exercise Independent Professional Judgment on Behalf of a Client." The first of the 24 Ethical Considerations for Canon 5 explains that

> [The] professional judgment of a lawyer should be exercised, within the bounds of the law, solely for the benefit of his client and free of compromising influences and loyalties. Neither his personal interests, the interests of other clients, nor the desires of third persons should be permitted to dilute his loyalty to his client.

The seven Disciplinary Rules describe a mix of situations in which a conflict of interest is prohibited outright and situations in which the interest is permissible only after the conflict of interest is fully disclosed to and informed consent is received from the client or clients in question.

Although the states more or less uniformly adopted the *Model Code*, it was soon abandoned.[17] In 1983, the ABA adopted a replacement. One theory about why the *Model Code* was so quickly replaced is that it mixed

[15] American Bar Association Canons of Ethics, Canon 6.

[16] American Bar Association, Model Code of Professional Responsibility, 1983. www.law.cornell.edu/ethics/aba/mcpr/MCPR.HTM.

[17] Charles W. Wolfram, *Modern Legal Ethics,* West Publishing, 1986.

minimum standards of conduct permitted under the law with ethical rules intended to set higher standards and therefore was perceived as confusing ethics with law (and, in the process, reducing ethical standards).[18] In its report to the ABA recommending the adoption of a new code of professional responsibility, the Kutak Commission on Evaluation and Professional Standards cited a steady increase in concern about professional ethics, including Supreme Court cases, statutes and regulations, opinions of the ABA's Committee on Ethics and Professional Responsibility, and reports and articles, as leading it to reconsider the *Model Code*.[19] The commission ultimately concluded that amendments would not suffice to address this increased concern, and so, just 15 years after adopting the *Model Code*, the ABA replaced it with the *Model Rules of Professional Conduct*. The states were slow to adopt the *Model Rules*, although today all states but California, Maine, and New York have professional conduct rules that follow the format of the *Model Rules*. (New York still follows the *Model Code*, and California and Maine have developed their own rules.)[20]

The *Model Rules* are fairly detailed, clustered under eight headings, and accompanied by lengthy comments. The *Model Rules* most closely related to conflict of interest fall under the heading "Client-Lawyer Relationship" and are described in the following sections.

Rule 1.7. Conflict of Interest: Current Clients

Rule 1.7[21] begins with a strong statement of general principle, followed by a description of the circumstances in which the general principle does not apply. The general principle is that a lawyer "shall not represent a client if the representation involves a concurrent conflict of interest." A concurrent conflict of interest is defined as the situation in which the representation of one client will be directly adverse to that of another client (conflict of obligation) or there is a "significant risk" that representing one client will be "materially limited" by the lawyer's responsibilities to another client, a former client, or a third party or by the personal interest of the lawyer (true conflict of interest). However, the lawyer may proceed

[18] Robert P. Lawry, "The Law and Ethics of Lawyers' Conflicts of Interest," in Thomas Murray and Josephine Johnston (eds.), *Ethical Issues in Financial Conflicts of Interest in Biomedical Research*, forthcoming.

[19] American Bar Association Commission on Evaluation of Professional Standards (Robert J. Kutak Chairman), "Model Rules of Professional Conduct: Discussion Draft," January 20, 1980. www.abanet.org/cpr/mrpc/kutak_1-80.pdf.

[20] American Bar Association website, ABA Model Rules of Professional Conduct: State Adoption of Model Rules. www.abanet.org/cpr/mrpc/model_rules.html.

[21] American Bar Association, Model Rules for Professional Conduct: Rule 1.7. www.abanet.org/cpr/mrpc/rule_1_7.html.

despite this conflict with the written informed consent of each client and provided that so proceeding (1) is not prohibited by law and (2) will not involve representing two opposing parties in litigation and (3) provided that the lawyer "reasonably believes" that he or she can provide competent and diligent representation to both clients. (The *Model Rules* define "reasonably believes" in both subjective and objective terms: the lawyer must actually believe, and the belief must be reasonable.)

Rule 1.7 is accompanied by a comment, which is 35 paragraphs long.[22] Its second paragraph describes the process that lawyers must go through under the rule: they must

> 1) clearly identify the client or clients; 2) determine whether a conflict of interest exists; 3) decide whether the representation may be undertaken despite the existence of a conflict, i.e., whether the client's consent could be an appropriate cure; and 4) if so, consult with the clients affected under paragraph (a) [any clients affected by a concurrent conflict of interest] and obtain their informed consent, confirmed in writing.

Determining whether a conflict of interest exists often involves some judgment (although the comment casts the net fairly widely to include cases both of "direct adverseness" and of "significant risk that a lawyer's ability [to act for the client] will be materially limited"). The key judgment here, however, is whether the conflict is "consentable"—bearing in mind that the presumption is that a lawyer must not represent opposing parties in litigation or where prohibited by law. The rationale for the division between consentable and nonconsentable seems to be that some conflicts of interest are too risky for the client or profession—for example, the lawyer might appear to a reasonable outsider to be taking egregious advantage of the client for the lawyer's personal benefit (even though the lawyer is not).

Paragraph 14 of the comment for Rule 1.7 begins by noting that although clients may ordinarily consent to representation notwithstanding a conflict, "some conflicts are nonconsentable, meaning that the lawyer cannot properly ask for . . . agreement or provide representation on the basis of the client's consent." Although it is long, the comment provides little additional guidance on how to determine whether a conflict is consentable other than to note at Paragraph 15 that representation is prohibited if the lawyer "cannot reasonably conclude that [he or she] will be able to provide competent and diligent representation." The next two rules provide more specific guidance.

[22] American Bar Association, Model Rules for Professional Conduct: Rule 1.7 Comment. www.abanet.org/cpr/mrpc/rule_1_7_comm.html.

Rule 1.8. Conflict of Interest: Current Clients: Specific Rules

Rule 1.8[23] adds to the general principles contained in Rule 1.7 10 classes of conflict of interest situations, some of which may be resolved with the consent of the client (and sometimes subject to other protective measures) and some of which cannot be resolved even with consent. Rule 1.8 therefore helps lawyers to determine when a conflict may be consentable.

Conflict of interest situations that are not consentable include

- soliciting or preparing an instrument to receive a substantial gift from a client unless the client is a relative,
- negotiating literary or media rights that would substantially rely on information relating to the representation,
- providing financial assistance to a client for litigation except where the client is indigent or where litigation costs will be repaid under a contingency agreement or lien, and
- having sexual relations with a client unless the sexual relationship preceded the attorney-client relationship.

Conflict of interest situations that are in principle consentable (provided that other conditions are met, such as advising the client of the desirability of seeking independent legal counsel) include

- entering into a business transaction with a client,
- knowingly acquiring an ownership or other interest that is adverse to a client,
- using information about one client to another client's disadvantage,
- accepting compensation for representing a client from a third party, and
- representing two or more clients in an aggregated settlement or agreement (for example, both parties in a friendly divorce).

In such situations, provided that full disclosure is followed by valid informed consent, a lawyer might reasonably be able to argue that an "arm's-length transaction" took place (something not possible in the nonconsentable situations), that is, that the client was fully able to look after its own interests without relying on the lawyer.

[23] American Bar Association, Model Rules for Professional Conduct: Rule 1.8. www.abanet.org/cpr/mrpc/rule_1_8.html.

Rule 1.9. Duties to Former Clients

Rule 1.9[24] provides that a lawyer should not agree to represent a person if the lawyer has previously represented a client in the same or a related matter and the interests of the new person are materially adverse to the interests of the former client, unless the lawyer has the written informed consent of the former client. (The requirement of "written" consent assures both a record, in case of a later dispute, and more formality at the time that consent is given.) The same rule applies when a lawyer knowingly takes on a new client whose interests are materially adverse to the interests of a former or a current client of that lawyer's former firm and about whom the lawyer has acquired protected information. This rule is designed to respond to lawyer mobility and to ensure that lawyers do not bring with them conflicts of interest from their previous firms without the consent of the former client.

In contrast to the first two parts of Rule 1.9, which allow the lawyer to represent the new client with the informed consent of the former client, the third part of Rule 1.9 (which concerns loyalty rather than conflict of interest) provides that information about former clients cannot be used to the disadvantage of the former client unless use of that information is otherwise allowed in the rules (that is, loyalty to the client continues after the representation ends). Like Rule 1.8, therefore, Rule 1.9 distinguishes between conflict of interest situations that are low risk enough to be resolved by informed consent and those that are nonconsentable because the risk is too high to be resolved by disclosure and consent or the problem is more serious than conflict of interest (conscious disloyalty).

Rule 1.10. Imputation of Conflicts of Interest: General Rule

Rule 1.10[25] is extremely important today when so many lawyers practice in large firms rather than as sole practitioners. Under the rule, the conflicts of interest of one lawyer in a firm are imputed to all lawyers in the firm: "a firm of lawyers is essentially one lawyer for purposes of the rules governing loyalty to the client."[26] The rule prohibits a member of a law firm from knowingly representing a client that any one of them practicing alone would be prohibited from representing under Rules 1.7 and 1.9, unless the prohibition is based on a personal interest of the lawyer and "does

[24] American Bar Association, Model Rules for Professional Conduct: Rule 1.9. www.abanet.org/cpr/mrpc/rule_1_9.html.

[25] American Bar Association, Model Rules for Professional Conduct: Rule 1.10. www.abanet.org/cpr/mrpc/rule_1_10.html.

[26] American Bar Association, Model Rules for Professional Conduct: Rule 1.10. comment, www.abanet.org/cpr/mrpc/rule_1_10_comm.html.

not present a significant risk of materially limiting the representation of the client by the remaining lawyers in the firm." Disqualification under the rule may be waived with the consent of the affected client (and subject to the prohibitions contained in Rule 1.7).

Rule 1.10 is strict and can be very burdensome for large law firms. Law firms have devised methods for "screening" lawyers within firms as a way of managing conflicts of interest (discussed in more detail below), but it is important to note that screens (which in other professions or arenas might be described as "firewalls") are not discussed in the *Model Rules*, except in limited situations involving former government lawyers.

In addition to these codes of ethics, case law has developed over several centuries to deal with lawyers' conflicts of interest (under various names). In the United States, this case law is helpfully summarized in the American Law Institute's *Restatement of the Law Governing Lawyers*.[27] Chapter 8 of that document analyzes conflicts of interest in general, including conflicts between a lawyer and a client, among current clients, between a lawyer and a former client, and because of the lawyer's obligation to a third person. This case law complicates matters for lawyers, since they must follow both the rules (explicitly or implicitly) laid down in those cases and the ABA's ethical rules. At the same time, the case law effectively addresses the malpractice liability of lawyers who fail to resolve a conflict of interest adequately and provides civil remedies for this malpractice, including damages paid to harmed clients or third parties and disqualification from continuing to represent a client in a particular matter.

The combined effect of the case law described in the restatement of the law governing lawyers and the ethical rules of each jurisdiction is that lawyers who fail to avoid conflicts of interest or to manage them adequately can be sued for malpractice, forced to pay monetary damages, disqualified by a judge from representing a client, or some combination of these. They can also lose their fee or receive only a reduced fee and face disciplinary action by the state bar (including disbarment). Although conflicts of interest are, in the first instance, to be identified by individual practitioners, local bars and the courts can become involved at later stages if those conflicts have not been properly managed. In this way, lawyers rely on self-regulation backed by the threat of professional and legal sanctions.

In fact, few lawyers are disciplined and even fewer are disbarred. A 2006 ABA survey found that of over 120,000 complaints filed against lawyers on any issue, only 3.5 percent led to formal discipline and less than 0.5

[27] Charles W Wolfram (ed.), *Restatement of the Law Third, The Law Governing Lawyers*, American Law Institute, 2000.

percent led to disbarment.[28] Although data on the numbers of allegations or findings of improper management of conflict of interest are not available at the federal level, some data are available at the state level. For example, between 2002 and 2006, sanctions for conflict of interest were imposed in only 11 percent of 530 cases, only 1 of which resulted in revocation of the license to practice (other sanctions were suspensions and reprimands).[29]

Conflict of Interest Management: Key Issues for Lawyers

Although the bar's system of conflict of interest management is well developed, it is not without its critics or its thorny issues. For example, despite the large number of cases, articles, and the detailed codes or rules, the legal profession's management of conflict of interest is still described as "abstruse," "arcane," and "intractable."[30] According to law professor Kevin McMunigal, however, the primary problem in the law's conflict of interest doctrine is a failure to recognize the regulation of conflict of interest as a kind of risk management and not prevention of direct harm. This failure leads the legal profession to use harm rules, which punish lawyers who harm clients, and risk rules, which aim to prevent harm to clients indirectly by keeping lawyers out of risky situations or by otherwise managing conflicts of interest but without engaging the all important question: How much risk is too much?

McMunigal gives the example of a lawyer in a high-profile criminal case who early on accepts a lucrative book deal to write about the case. When the prosecution offers to settle the case (an option, McMunigal adds, that would clearly be in the client's best interests), the lawyer advises her client to reject the settlement. McMunigal argues that the risky situation of the book deal (with the temptation being to take the case to trial to ensure publicity and probably help future book sales) probably led the lawyer to give bad legal advice (which would be harmful if it was followed). However, as McMunigal sees it, the legal profession uses the language of conflict of interest to describe and address both the risky situation and the harmful action. If the legal profession could more clearly separate harm rules—for example, rules against lawyers providing bad legal advice or against lawyers entering into unfair business deals with their clients—from risk rules—for example, rules prohibiting a lawyer from preparing an instrument by which

[28] American Bar Association, Survey on Lawyer Discipline Systems: 2006. www.abanet.org/cpr/discipline/sold/home.html.

[29] Michigan Attorney Discipline Board, Annual Reports 2000–2006, Appendix B (in each annual report). www.adbmich.org/ANNUALRPT.HTM.

[30] Kevin C. McMunigal, "Conflict of Interests as Risk Analysis," in Michael Davis and Andrew Stark (eds.), *Conflict of Interest in the Professions*, New York: Oxford University Press, 2001.

the lawyer will receive a gift from the client or rules against accepting book deals based on cases—then, McMunigal argues, the legal profession would also avoid confusion about the goals of and justification for each kind of rule.[31]

McMunigal suggests that conflict of interest rules should be understood as being restricted to governing risky situations, leaving rules against breaching confidentiality or against providing incompetent advice to deal with situations in which actual harm has resulted (and in which the causal chain can be proved). In the medical context, conflict of interest rules could therefore focus on identifying and governing situations in which the risk of tainted judgment is considered unacceptably high. The rules invoked to deal with actual harm to patients (other than harm to trust in their physicians and the profession in general) would allege not conflict of interest but inappropriate practice, bias, breach of confidentiality, or the like. Another consequence of sharply distinguishing between risk and actual harm would be to make unnecessary the distinction between "actual" and "potential" conflicts of interest, which McMunigal considers to be a distinction of little practical use.

In his analysis of the legal profession's management of conflicts of interest, law professor Robert Lawry focuses on a different kind of problem.[32] He sees a gradual lessening of professional standards to allow for the greater mobility of lawyers, which is at least partially justified by an appeal to the increased sophistication of some clients. One reason for this reduction in standards is, as mentioned above, the mixing over time of ethics (a guide to good professional behavior) and law (minimum standards by which to police the profession). Another reason is the reality of modern legal practice, where lawyers move from town to town and firm to firm. Yet another reason that exceptions to conflict of interest rules and methods for managing conflicts of interest have developed is to allow medium to large firms to serve many clients, some of whom will, from time to time, have both opposing interests and an interest in relying on lawyers who know them.

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[31] Consider the debate over financial conflicts of interest in biomedical research: there is some confusion about whether the goal of conflict of interest rules is to identify cases of actual harm (usually bias) or to reduce the risk of harm (Shira Lipton, Elizabeth Boyd, and Lisa Bero, "Conflicts of Interest in Academic Research: Policies, Processes, and Attitudes," *Accountability in Research* 2004; 11(2): 83–102). The parties can end talking past each another, with one side asking for proof that harm was caused in this or that case by a conflict of interest before agreeing to the rules and the other side appealing to intuitive ideas about risk or to data showing correlations between conflicts of interest and bad outcomes in aggregates to justify prohibitions or other measures.

[32] Robert P. Lawry, "The Law and Ethics of Lawyers' Conflicts of Interest," in Thomas H. Murray and Josephine Johnston (eds.), *Ethical Issues in Financial Conflicts of Interest in Biomedical Research*, Baltimore (MD): Johns Hopkins University Press, forthcoming.

Screens, Chinese Walls, and Cones of Silence

One major mechanism for managing conflicts of interest with concurrent clients is through the use of screens (also known as "firewalls," "Chinese walls," or "cones of silence"). Screens are mechanisms by which lawyers working on one matter are prohibited from certain kinds of communication with lawyers in the same firm working on a conflicting matter. The prohibition is sometimes augmented by placing the lawyers in separate locations (on different floors or in different buildings), controls on e-mail and file access, and the like. Some screens are simply matters of honor; some involve real walls. Screens cannot change a nonconsentable conflict into a consentable one. Instead, screens are used "to encourage clients to consent to a loyalty conflict."[33]

Lawry sees screens as further evidence of erosion in lawyers' conflict of interest standards. Lawyers were introduced to the idea of screens in 1975 by Formal Opinion 342 of the ABA's Standing Committee on Ethics, which argued that former government lawyers should be permitted to work for a firm doing business with the government if they are screened within the firm from files that they worked on while they were in government. Without such screens, it was argued, "good lawyers would avoid government work, to the detriment of the common good." This principle, which was developed for government lawyers and which is discussed only in the *Model Rules* (and comments) in reference to government lawyers, is now routinely extended to private lawyers. Lawry reports that 22 of 51 jurisdictions allow screening without the consent of the former client.[34] Screens have also received some recognition in the courts and are endorsed in the restatement of the law governing lawyers as a way of dealing with conflicts created by lawyers switching firms. Reasonable people will likely continue to disagree about whether screens are a sign of eroding legal ethics or evidence that legal practitioners are both committed to legal ethics and capable of creating effective management systems. Nevertheless, the debate shows that lawyers are engaging with the fundamental question of how to balance the risks of conflict of interest in such situations against the benefits of tolerating the conflict if it is properly managed.

ACCOUNTANTS

As in other professions, much work in accounting can be conducted by uncertified (or unlicensed) individuals, but some accounting functions

[33] Susan R. Martyn, "Visions of the Eternal Law Firm: The Future of Law Firm Screens," *South Carolina Law Review* 1994; 45(1): 937–959.

[34] Thomas D. Morgan and Ronald D. Rotunda, *Selected Standards on Professional Responsibility*, New York: Foundation Press, 2006.

can be carried out only by a certified accountant. Certified accountants in the United States are: (1) CPAs, who are licensed by their state to provide auditing and attestation services; (2) certified internal auditors, who mostly provide their services directly to their employers; or (3) certified management accountants and certified business accountants, who, although they deal with the public, cannot audit public companies. Each of these certifications is issued by a professional body that maintains a code of ethics and that examines applicants on the basis of that code of ethics as well as on the basis of their technical skills. Individuals may carry more than one certification, but only licensed CPAs can perform the mandatory audits of publicly traded U.S. companies. CPAs are the focus of this discussion because of their prominent public role and their recent struggles to manage conflicts of interest.

Like lawyers, CPAs have clients—the companies that hire them to prepare their financial statements—but like architects and engineers and unlike lawyers, CPAs are wary of going too far in acting in their clients' interests. Lawyers, particularly during litigation, must primarily attend to their client's interests, leaving it to opposing counsel or the judge to find the flaws in their argument or weaknesses in the client's case. CPAs, in contrast, are obliged to put the public interest first when they perform an audit or attestation; they are not allowed to withhold or ignore negative information; indeed, part of their job is to seek out such information.[35] The rationale for privileging the public interest is that shareholders and other investors rely on the work of CPAs when they make decisions about whether and how to invest their money. Thus, although a company will engage and pay a CPA (often through an accounting firm) to perform its audits, both the company and the public are the beneficiaries of the CPA's work. The public benefits from having financial information that it can rely on. The company benefits from the public's ability to trust the company's financial reports.

Unlike a physician's patients, the accountant's clients are frequently sophisticated individuals or businesses; few are physically or mentally compromised. Although the matters entrusted to the accountant are seldom trivial, they are not literally life and death.

[35] That said, they are not generally required to blow the whistle on their clients by reporting fraud to outside agencies (Leonard J. Brooks, "Conflict of Interest in the Accounting Profession," in Michael Davis and Andrew Stark (eds.), *Conflict of Interest in the Professions*, New York: Oxford University Press, 2001). They are only required by law to report fraud to the client's senior management and its audit committee, a subcommittee of the client's board of directors that itself is under strict reporting requirements (Section 10A(1)(b) of the Securities Exchange Act of 1934 and American Institute of Certified Public Accountants, Statement on Auditing Standards: No. 99, Considerations of Fraud in a Financial Audit Statement).

Licenses and Professional Membership

As in other professions, professional accounting societies were developed to ensure clients that people holding themselves out as accountants met minimal levels of education, competence, and ethical conduct.[36] Today, professional accounting societies do not license accountants—that function has been taken over by the state-designated accountancy boards—but the professional societies provide guidance on many issues, from technical accounting standards to ethics. Clients, who rely on accountants to provide specialized services and advice, may find some reassurance in the imprimatur of good standing in a professional society.

AICPA is a voluntary association. Although all CPAs must be licensed by their state boards of accountancy (or the equivalent), they are not obliged to be members of their state or national CPA organizations. Membership in good standing of the state or national CPA organization can, however, enhance the reputation of the CPA. (AICPA provides marketing tool kits to its members.)

The specific requirements for the CPA license vary somewhat from state to state, but all states require that individuals pass the Uniform Certified Public Accountant examination, which was developed and which is maintained by AICPA and which is administered by the National Association of State Boards of Accountancy. Questions about professional ethics are included in the Uniform Certified Public Accountant examination and are based on AICPA's *Code of Professional Conduct*.

Many state licensing boards require continuing professional education (CPE) that includes ethics or professional conduct. These state boards prescribe CPE course requirements, but the courses are offered to CPAs by approved companies (sometimes called "sponsors") for a fee. Some attention is paid to the independence of the CPE programs and their sponsors. In New York, for example, CPE can be offered only by sponsors that have been approved by the New York Department of Education, which requires sponsors to have a "direct interest in offering courses on a regular basis" and will not approve "programs devoted to the promotion of particular products or services" or "[i]nsurance, pension, investment, software and other offerings primarily promotional or informational in nature."[37]

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[36] Leonard J. Brooks, "Conflict of Interest in the Accounting Profession," in Michael Davis and Andrew Stark (eds.), *Conflict of Interest in the Professions*, New York: Oxford University Press, 2001.

[37] The University of New York, The State Education Department, State Board of Public Accountancy, Instructions for Completing Application for Continuing Education Sponsor Agreement. www.op.nysed.gov/cpa-mcesponsorapplication.pdf.

CPE is offered by a range of sponsors, including universities and private companies.[38]

Accountancy After Enron

In addition to understanding and following AICPA's *Code of Professional Conduct* (described in more detail below), CPAs need to be aware of and follow the rules of their state board of accountancy; the ethics standards of their state CPA organization (if they are members); any applicable state laws; and any applicable federal laws, notably, the Public Company Accounting Reform and Investor Protection Act of 2002.[39] This act, commonly known as the Sarbanes-Oxley Act, was passed in response to a number of corporate and accounting scandals in the late 1990s and early 2000s. Before passage of the act, the largest accounting firms had diversified their practices to the extent that audits were a small part of the services that they provided to their clients. Considered key to gaining insight into the client's business, audit prices steadily declined while other services increased in profitability. As a business school professor at the University of Saskatchewan puts it, "Clients became sophisticated purchasers, shopping around for the best deal and putting intense pressure on audit prices, and thus on profits . . . some companies [clients] began to resort to a practice known as 'opinion shopping.'"[40] Accounting firms were soon offering consulting services to audit clients that brought in far more than the audit fee, and therefore, "the auditors did not want to do anything to rock the boat with clients, potentially jeopardizing their chief source of income."[41]

This tension between auditing and consulting was identified and critiqued before the Enron scandal, but it was only after the collapse of Enron and WorldCom that practices and codes of conduct changed to address it. Boyd calls Enron "the 'smoking gun' evidence, indicating that the profession had reached a stage where commercial interests simply overwhelmed allegiance to professional integrity." Policy makers were not content to leave it to accounting firms or AICPA to address the issue. They chose to pass legislation—the Sarbanes-Oxley Act—to restore the reliability of the public company audit process.

Subject to certain preapprovals, Section 201 of the Sarbanes-Oxley Act prohibits auditors from providing a number of other services contemporaneous to the audit, including bookkeeping, management functions,

[38] See the registry of the National Registry of CPE Sponsors. http://registry.nasbatools.com/display_page.

[39] Sarbanes-Oxley Act of 2002. http://thomas.loc.gov/cgi-bin/query/z?c107:H.R.3763.ENR.

[40] Colin Boyd, "The Structural Origins of Conflicts of Interest in the Accounting Profession," *Business Ethics Quarterly* 2004; 14(3): 377–398.

[41] Arthur Levitt, *Take on the Street*, New York: Pantheon Books, 2002.

investment advice, investment banking services, and legal services. The act also creates the Public Company Accounting Oversight Board (PCAOB) to oversee CPA practice in relation to public companies. Under Section 103 of the act, PCAOB has established standards and rules on a variety of issues, including ethics, that apply to registered public accounting firms preparing and issuing audit reports as required by the act or the rules of the Securities and Exchange Commission.

PCAOB's conflict of interest rules are designed to preserve the independence of the accounting firm.[42] Rule 3520 states: "a registered public accounting firm and its associated persons must be independent of the firm's audit client throughout the audit and professional engagement period." Rules 3521, 3522, and 3523 describe situations in which an accounting firm cannot be considered independent, for example, if the firm provides a service or product to the audit client for a contingent fee or a commission, if the firm provides assistance in planning or tax advice on certain types of potentially abusive tax transactions to an audit client, or if the firm provides any tax services to certain persons in a financial reporting oversight role at an audit client or to immediate family members of such persons.

Violation of the PCAOB rules can lead to an investigation by PCAOB. Following a hearing, sanctions can be imposed, including (1) revoking a firm's registration; (2) barring an individual from participating in audits of public companies; (3) monetary penalties; and (4) remedial measures, such as training, the implementation of new quality control procedures, or the appointment of an independent monitor.[43] PCAOB's website reports that 3 of the 17 disciplinary proceedings before PCAOB over the past 3 years have found "independence" violations.

There has been some criticism that the post-Enron measures are too burdensome,[44] with others countering that the measures fail to do enough to end auditor-client "coziness."[45] Either way, this legislation and accompanying rules and sanctions serve as a cautionary tale. They installed the external regulation of a profession that apparently had not sufficiently regulated its own conflicts of interest. Since the Sarbanes-Oxley Act was passed, AICPA and state CPA societies have strengthened their codes of conduct, an example of a change in law forcing a tightening of ethical standards.

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[42] Public Company Accounting Oversight Board, Bylaws and Rules—Rules—Professional Standards, Section 3. www.pcaobus.org/Rules/Rules_of_the_Board/Section_3.pdf.

[43] Section 105(b)(4) of the Sarbanes-Oxley Act of 2002.

[44] Jonathan D. Glater, "Here It Comes: The Sarbanes-Oxley Backlash," *New York Times*, April 17, 2005.

[45] Richard L. Kaplan, "The Mother of All Conflicts: Auditors and Their Clients," *Iowa Journal of Corporate Law* 2004; 29: 363–383.

AICPA Code of Professional Conduct

The current version of the AICPA *Code of Professional Conduct*[46] emphasizes independence and objectivity. The AICPA *Code of Professional Conduct* is divided into principles and rules. The six principles are expressed in a sentence or two. Each principle is clarified by up to five subparagraphs. The dozen rules that follow the principles are also expressed in one or two sentences but are followed by more detailed guidance in the form of Interpretations of Rules of Conduct and Ethics Rulings (rather like the American Medical Association's [AMA's] Opinions).

AICPA's professional ethics committee adopted Interpretations of Rules of Conduct "after exposure to state societies, state boards, practice units and other interested parties." The Interpretations of Rules of Conduct are intended "to provide guidelines as to the scope and application of the Rules but are not intended to limit such scope or application." Ethics rulings are formal rulings made by AICPA's professional ethics committee applying the rules and their interpretations to a particular set of facts. AICPA members who depart from ethics rulings in similar circumstances will be "requested to justify such departures."[47]

Two of the Code's principles bear on conflict of interest. The first, titled Integrity, states that "to maintain and broaden public confidence, members should perform all professional responsibilities with the highest sense of integrity" and includes a reference to observing the principles of objectivity and independence in its final subparagraph. The other relevant principle, titled the Public Interest, requires members "to act in a way that will serve the public interest, honor the public trust, and demonstrate commitment to professionalism." Acknowledging that members may encounter conflicting pressures, this principle advises that, when resolving such conflicts, members recall that when they "fulfill their responsibility to the public, clients' and employers' interests are best served."[48]

Although these two principles clearly bear on conflict of interest, it is the fourth principle (titled Objectivity and Independence) that addresses conflict of interest most directly. It states: "A member should maintain objectivity and be free of conflicts of interest in discharging professional re-

[46] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility. www.aicpa.org/About/code/index.html.

[47] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility: Introduction, Other Guidance. www.aicpa.org/About/code/othguid.htm.

[48] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility: Section 53, Article II, The Public Interest, and Section 54, Article III, Integrity. www.aicpa.org/About/code/sec50.htm.

sponsibilities. A member in public practice should be independent in fact and appearance when providing auditing and other attestation services."[49]

The general rule, therefore, is that all CPAs should always be free of conflicts of interest. An even higher standard is set for CPAs in public practice. That is, when a CPA is performing certain services in public practice, the CPA should maintain objectivity in appearance as well as in fact. Public practice is defined as the performance for a client of accounting, tax, personal financial planning, litigation support, and other professional services for which practice standards are promulgated by AICPA. (The closest medical equivalent to a CPA's public practice is a physician's publication of research or the testimonials or other public statements that an individuals makes as a physician.)

Four subparagraphs follow this principle. The first discusses, in a fairly philosophical way, objectivity (describing it as "a state of mind" and imposing the obligation to be "impartial, intellectually honest, and free of conflicts of interest") and then independence ("precludes relationships that may appear to impair a member's objectivity in rendering attestation services"). After noting the variety of roles that an accountant might play in society, including teaching, the second subclause states: "Regardless of service or capacity, members should protect the integrity of their work, maintain objectivity, and avoid any subordination of their judgment." The principle is thus fairly strict: CPAs should at no time enter into relationships that might even appear to impair their objectivity. The third subclause focuses on accountants working in public practice, stating that to protect their independence (the appearance of objectivity), they should be continually assessing "client relationships and public responsibility" and "should be independent in fact and appearance." The effect of this subparagraph is to require constant vigilance of the possible impact of interactions with clients on the CPA's (actual and apparent) commitment to the public interest. The fourth subclause applies to members not in public practice (e.g., members employed by a company rather than acting as an external accountant or auditor). That subclass concedes that CPAs not in public practice "cannot maintain the appearance of independence" but nevertheless imposes on them "the responsibility to maintain objectivity in rendering professional services."

More detail in the form of rules, interpretations, and ethics rulings follow at Sections 101 (Independence) and 102 (Integrity and Objectivity).[50]

[49] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility: Section 55, Article IV, Objectivity and Independence. www.aicpa.org/About/code/et_55.html.

[50] The American Institute of Certified Public Accountants, AICPA Code of Professional Responsibility: Section 100, Independence, Integrity, and Objectivity. www.aicpa.org/About/code/sec100.htm.

Section 101 begins with the rule that a member in public practice shall be independent according to the standards set by state boards, state CPA institutes, the U.S. Securities and Exchange Commission, and PCAOB, among others. The interpretation for this rule then describes the circumstances under which independence will be considered impaired. Situations of impairment include the following: when the accountant, during the period of professional engagement, holds or commits to acquiring a financial interest in the client; when the accountant has a loan to or from the client or in some circumstances when the accounting firm, one of its partners, or a partner's immediate family members hold an ownership stake in the client; and when the accountant's firm or a partner or employee of the firm was simultaneously a director, officer, or employee of the client. (The last prohibition applies not simply during the period of the professional engagement but during the whole period covered by the financial statements being prepared by the accountant.) When in doubt about whether a particular circumstance might cause independence to be questioned, the section asks that members "evaluate whether that circumstance would lead a reasonable person aware of all the relevant facts to conclude that there is an unacceptable *threat* to the member's and the firm's independence" (emphasis added).

Fourteen additional interpretations follow, and that number is far too many to cover in any detail here. It will be enough to note here that the net cast is fairly wide. Section 101 captures a number of situations involving the accountant; the firm; colleagues; family members; close relatives; or current or previous financial, employment, ownership, or management relationships with the client. The interpretations also differentiate between direct financial interests (such as ownership and investment interests) and indirect financial interests, including some holdings through mutual funds. In one of the Ethics Rules accompanying Section 101, the question of the CPA's acceptance of gifts or entertainment from a client is posed. The answer is that the acceptance of gifts or entertainment from a client that the CPA is auditing will be considered to impair objectivity, unless the value is "clearly insignificant to the recipient." The ethics ruling is less restrictive when the client is not an "attest client" (i.e., one for whom the CPA performs auditing or other attestation services), although even in such cases the CPA is required to assess whether accepting the gift is reasonable, given the nature, value, timing, and frequency of the gift.

The overall aim of the independence rule and its interpretations and ethics rulings at Section 101 is to ensure that audits of companies will be carried out by accountants and accountancy firms who provide no other financial services to the company, are not investors in or directors of the company, do not and have not recently worked for the company, have no other financial or other ties to the company, and are otherwise free of any appearance suggesting to a reasonable person a loss of objectivity. Despite

its detail, this section has been criticized for failing to address one particular threat to independence (and objectivity): the significance of the client company's audit fees to the bottom line of the accountant or the firm.[51] One observer points out that Arthur Andersen's Houston, Texas, office received $1 million per week from Enron while it was auditing the company: "[The] livelihoods of several audit partners and several hundred audit firm employees depend[ed] on keeping a client happy."

Section 102 (Integrity and Objectivity) is far briefer than Section 101 and applies to all CPAs in all of their work (i.e., not simply to CPAs performing audits). It begins with the rule that "in the performance of any professional service a member shall maintain objectivity and integrity, shall be free of conflicts of interest, and shall not knowingly misrepresent facts or subordinate his or her judgment to others." Although the rule is concerned with the misrepresentation of fact as well as conflict of interest, the interpretations for the rule offer a definition of conflict of interest: "a conflict of interest may occur if a member performs a professional service for a client or employer and the member or his or her firm has a relationship with another person, entity, product, or service that could, in the member's professional judgment, be viewed by the client, employer, or other appropriate parties as impairing the member's objectivity." Note that the relationship need not be financial or familial, and it need not actually impair the CPA's objectivity—it is enough that it could, in the member's judgment, appear to impair his or her objectivity.

In contrast to Section 101, which provides no way to manage the impairments to independence that it covers, Section 102 suggests that disclosure and consent may be acceptable ways to manage conflicts of interest "if the *member* believes that the professional service can be performed with objectivity, and the relationship is disclosed to and consent is obtained from such client, employer, or other appropriate parties" (emphasis added). The interpretation explicitly states that concern about independence in certain professional engagements, such as audits and reviews, as expressed in the previous rule (Section 101), cannot be addressed by disclosure and consent. The discussion ends with an explicitly nonexhaustive list of situations that ought to raise independence concerns, including when the CPA has a significant financial interest in or is on the management of a company that is a major competitor of the client for which he or she performs management consulting services, when the CPA is asked to perform litigation services for a case filed against one of his or her clients, or when a CPA provides services for several members of the same family with opposing interests.

[51] David Cotton, "Fixing CPA Ethics Can Be an Inside Job," *Washington Post*, October 20, 2002. P. B2.

These are all situations in which the usual public reliance on the auditor's work is absent.

Enforcement of Ethics Rules

The AICPA *Code of Professional Conduct* focuses on the impact of existing and preexisting relationships (whether of the accountant, firm, colleagues, and sometimes, members of the family) on the accountant's objectivity and independence. Objectivity and independence are particularly protected when the accountant is auditing a client for the public's benefit. When offering any service except external auditing, a CPA might be able to disclose a conflict of interest to the client and proceed with the client's consent, but this option is simply not available in a public audit (or other attestation) situation. The reason for the focus on independence from clients (a matter of appearance), from the CPA's personal interests, and from the interests of the CPA's firm, colleagues, and family during audits (and other attestation services) in particular is that a CPA performing an external audit has a primary obligation to the public. Indeed, the second principle in the *Code of Professional Conduct*, titled The Public Interest, states that the public relies "on the objectivity and integrity of certified public accountants to maintain the orderly functioning of commerce."

The rules and practices of CPAs, therefore, are fairly strict when it comes to preserving independence and avoiding even the appearance of conflict of interest. It is important to note, however, that like architects and engineers but unlike lawyers, accountants are able to work for competing clients, often but not always with the knowledge and consent of both parties.[52] The rationale for this difference is that accountants are able to perform an audit of one client without disclosing (or even relying on) information about the other. It would be much harder for a lawyer to adequately represent two competing clients without using the confidential information of one against or in favor of the other.

The preamble to the AICPA *Code of Professional Conduct* neatly describes how it is enforced: "Compliance with the *Code of Professional Conduct* . . . depends primarily on members' understanding and voluntary actions, secondarily on reinforcement by peers and public opinion, and ultimately on disciplinary proceedings, when necessary, against members who fail to comply with the Rules."

Members of AICPA are on notice that they must be prepared to justify any departure that they make from the *Code of Professional Conduct*.

[52] Leonard J. Brooks, "Conflict of Interest in the Accounting Profession," in Michael Davis and Andrew Stark (eds.), *Conflict of Interest in the Professions*, New York: Oxford University Press, 2001.

AIPCA's Professional Ethics Executive Committee interprets and enforces the AICPA *Code of Professional Conduct*. The committee investigates allegations of unethical conduct by both its members and the members of almost all state CPA organizations through its Joint Ethics Enforcement Program (JEEP).[53] JEEP has existed since the 1970s and was created in recognition of the fact that the codes of many state CPA societies are identical or similar to the provisions of the AICPA *Code of Professional Conduct* and that it is common for a CPA to be a member of both AICPA and one or more state societies. JEEP therefore provides an efficient mechanism for enforcing ethics rules consistently across the United States.

Violations of the *Code of Professional Conduct* can result in a CPA being expelled, suspended for a period of 1 or 2 years from AICPA or from the local CPA society, directed to complete specified CPE courses, or directed to take other action (e.g., submit subsequent work papers for continued monitoring). All decisions to expel or suspend a CPA are made public through publication on AICPA's website. Very few of these decisions (just 4 of over 150) during the past 3 years included a finding of a breach of the rules regarding independence. AICPA can also publicly admonish a member who has violated the *Code of Professional Conduct*. AICPA's ethics committee can also conclude, upon investigation, that there is no evidence of a violation of the *Code of Professional Conduct* and therefore dismiss the case or simply close a case for lack of evidence or some other reason.[54]

The enforcement mechanisms of suspension, expulsion, and public admonishment seem designed to place the public and colleagues on notice that the CPA does not comply with the *Code of Professional Conduct* and to publicly embarrass the CPA, whereas requiring completion of CPE courses or submitting reports and work papers seems to aim to reeducate the CPA. Because a CPA does not need to be a member of AICPA or a state CPA organization, a finding of violation of AICPA's *Code of Professional Conduct* is not itself sufficient to withdraw the CPA's license to practice. Only the state licensing boards can suspend or revoke a CPA's license.

One important lesson from the recent history of public accountancy is that a failure to address conflicts of interest led to federal regulation of conflict of interest in one important aspect of CPA practice: the auditing of publicly listed companies. Investor confidence in the objectivity and independence of auditors and therefore in the truthfulness of public companies'

[53] The American Institute of Certified Public Accountants, Professional Ethics Executive Committee, Fact Sheet 2004–2005. www.aicpa.org/download/ethics/ethics-committee-fact-sheet.pdf.

[54] The American Institute of Certified Public Accountants website, Ethics Enforcement. www.aicpa.org/About/code/sec100.htm.www.aicpa.org/Professional+Resources/Professiona+Ethics+Code+of+Professional+Conduct/Professional+Ethics/Ethics+Enforcement/defin_sanction.htm.

financial statements was considered an important enough goal—given the huge financial stakes involved—to warrant federal legislation and the establishment of a federal oversight body, the PCAOB. A second important lesson is that maintaining objective and independent judgment is not easy. Accountants primarily maintain their objectivity by avoiding most situations that present a conflict of interest. They also maintain their independence by avoiding most situations that could reasonably appear to present a conflict of interest.

ARCHITECTURE

During the decade and a half before World War I, AMA organized medicine as a modern profession. Among the milestones in that process were not only the rethinking of medical education (set forth in the 1910 Flexner Report) but also the abandonment in 1903 of AMA's mandatory *Code of Ethics* of 1847 for the "suggestive and advisory" *Principles of Medical Ethics*. That was followed in 1912 by the abandonment of the 1903 principles for another code (with the same name) binding on all physicians (and surgeons). At about that time (1909), the American Institute of Architects (AIA) adopted its first code of ethics. That code applied only to members of the organization and not to all architects, but the code (like AMA's 1847 code) was binding on all architects. The AIA kept this feature when it adopted a new code in 1977, one organized—like the ABA's 1969 code (which was to be abandoned soon after)—into canons (broad statements of principle), ethical standards (more specific goals that AIA members should aspire to), rules (mandatory standards, the violation of which would justify formal discipline, including expulsion from the AIA), and commentary (when necessary to avoid a common misinterpretation of a rule).[55]

The 1909 AIA code reached all architects, not just AIA members, through its adoption by state licensing boards as local standards of practice. That simple arrangement ended in the 1970s, when the courts declared the AIA's code to be an unreasonable restraint on trade. While the AIA was rewriting its code to avoid another lawsuit (a process that did not end until 1990), the National Council of Architecture Registration Boards (NCARB) wrote its own code.[56]

Because the states' licensure of architecture is generally similar to the states' licensure of accountants (and, in some states, lawyers), continuing education requirements are also similar. Courses must be accredited to satisfy the continuing education requirements. The AIA itself offers some online courses that satisfy continuing education credit. Some of these courses

[55] See www.aia.org/SiteObjects/files/codeofethics.pdf.
[56] See www.architects.org/emplibrary/NCARB.pdf.

are now prepared by suppliers.[57] So far, supplier-prepared courses do not seem to be a problem. One reason that they are not may be that architects' specifications (the equivalent of a physician's prescription) typically either state a generic requirement or take the form "brand *x* or its equivalent." Another reason that supplier courses are not a problem may be that they do not include a trip to some ideal location, lavish entertainment, or other gifts. The course itself must be valuable enough to repay architects for their time and for lost opportunities to take other courses.

NCARB on Conflict of Interest

Architects resemble physicians, lawyers, and accountants in not being able to practice (that is, advertise, sign drawings, or otherwise publicly present themselves as architects) without registering as one (that is, being given a state license to practice). Beginning in 1919, registration boards have maintained a nonprofit group to provide a number of services to the profession: a standardized test for admission into the profession, standards for work experiences that a new graduate of an accredited architectural program should have before licensure (Intern Development Program), self-administered continuing education courses, and so on. NCARB's code of ethics (*Rules of Conduct*) is just one of these services. Adopted in 1977 (and amended since), the *Rules of Conduct* are designed to provide hard-edged rules for discipline (once a state board adopts them). Besides the nominal "Rules"—five titles numbered with Arabic numerals—the code includes (1) actual rules under each rule (numbered with a decimal), (2) a brief commentary after most of these rules, and (3) a long introduction (40 percent of the entire 10-page code). Although the NCARB code does set a somewhat lower standard than the (shorter) AIA code, it generally does so by silence rather than by providing a formal rule significantly different from the corresponding AIA rule. The AIA issues ethics opinions much as AMA does; NCARB does not. A state registration board may, however, issue an opinion as part of disciplinary action against a particular architect.

Conflict of interest is plainly important in the practice of architecture. The second of the five major divisions in NCARB's *Rules of Conduct* is titled Conflict of Interest; the third major division, although it is titled Full Disclosure, is in part (Rule 3.1) about responding to conflict of interest. The other divisions of the code—Competence (Division 1), Compliance with Law (Division 4), and Professional Conduct (Division 5)—have no connection with conflict of interest.

The overall strategy in these provisions is clear. Conflict of interest

[57] See, for example, www.gp.com/build/paperless/education.html (a course offered by Georgia-Pacific).

should generally be avoided, but when avoidance is not possible or at least not reasonable, the conflict must be fully disclosed to all appropriate parties and their consent must be won before the architect can proceed. Interestingly, the term "conflict of interest" is not used in any of the specific rules; its definition is, in effect, the rules under that title. All of the relevant rules (including Rule 3.1) are (primarily) concerned with financial interests. There are four rules under Rule 2, Conflict of Interest.

Rule 2.1 applies to ordinary compensation for services. An architect "shall not accept compensation for services from more than one party on a project unless the circumstances are fully disclosed to and agreed to . . . by all interested parties." Both disclosure and agreement are to be "in writing." The commentary explains that architects may sometimes find it hard to avoid receiving payment from two parties—for example, when ordering a large number of windows from a supplier later produces a rebate check. The architect cannot simply accept the rebate (even if it comes as a surprise) but must first inform the client (and other interested parties) of the payment and the reason for it. The architect cannot accept the payment unless at least the client (and any other interested party) approves. The commentary explains that the "bifurcated loyalty" that such a rebate threatens is "unacceptable unless all parties have understood it and accepted it." The commentary does not limit the "parties" to the client. This is because in many architectural projects several parties may be affected by the payment, such as the engineering firm typically present at any large project, the developer (who may be the immediate client but who is, in fact, a stand-in for the ultimate owner), the ultimate owner (who may be one or more individuals or a legal entity), and even the contractor or subcontractor who must work with the rebated supplies. The commentary can even be interpreted as including the window supplier's competitors among those who must be informed of the payment and the reason for it. They are certainly "interested parties." They are at a competitive disadvantage if they are not also making such rebates.

Behind Rule 2.1 is a conception of architects as having a relatively settled loyalty to the client that everyone dealing with the client relies on. An unusual payment (such as the rebate described above) unsettles the situation. There is no question here of the supplier buying the architect's loyalty with the rebate (as there would be if the payment were a bribe or kickback). The problem is that "money talks," and even architects cannot gauge how much they will listen the next time that they place an order of that sort. Their judgment that their professional judgment will not be affected is not relevant. That, too, is now under suspicion.

Disclosure of the payment makes it possible for all interested parties to redefine their relationship to the architect to take account of this unusual feature. The client may, for example, require the architect to hand over the entire rebate (as well as ask other suppliers whether they will meet the com-

petition). However, because the architect's fee is often a percentage of the total cost of the project, this solution may not be the best. It would create a "perverse incentive." The architect would, in effect, be punished for saving the client money. The architect would have an incentive to avoid suppliers who give rebates. The client might then prefer to split the rebate with the architect, or they might work out some more complicated arrangement—of which all interested parties should be made aware to ensure that their trust in the architect's judgment is not misplaced.

Rule 2.2 concerns financial interests apart from payments, for example, stock in a potential supplier or a loan to a contractor. The architect must assess whether the interest (direct or indirect) is "substantial enough to influence his or her judgment in the performance of professional services" (whether or not it does or would in fact influence it). Architects thus have some discretion under this rule (as they do not under Rule 2.1). The rationale for allowing some discretion (concerning whether an interest is substantial enough) is that avoiding all financial interests seems too much to ask. For example, an architect with money in a large investment fund that holds a few shares of stock in one of the companies she or he is dealing with has an interest in that company. Is revealing such an interest worth the trouble? Should architects be required to avoid investing in any fund that might (on a given day) invest in a potential supplier? That seems too much to require, so long as the architect reveals any interest substantial enough to affect her or his judgment. Of course, when in doubt, the architect should reveal the interest. Rule 2.2 seems to work because it governs only interests other than payments, because architects seldom invest in suppliers and because most architects work in a small world (mostly developers or builders rather than individual clients) in which a substantial investment in a supplier would soon be known.

If the interest is enough to influence the judgment, the architect must fully disclose it in writing to the client or employer (thus creating a paper trail). If the client or employer objects to the business association or the financial interest, the architect must either terminate it or offer to give up the commission or employment. The client or employer may have good reason to accept the bifurcated loyalty that the business association or financial interest in question creates, but the decision is the client's or the employer's (or both, when an architect has both a client, the person who has hired the firm, and an employer, the architectural firm). That decision should be made only with all the relevant facts laid before the decision maker in a form that the decision maker can understand. If the architect is unwilling to make full disclosure, she or he must resign from the job. There is no middle way (no way to manage the conflict) without full disclosure and consent.

Rules 2.3 applies to any payment made in return for specifying or endorsing a supplier. Strictly speaking, this rule does not concern conflict of

interest but concerns bribes, kickbacks, and other side payments that buy the architect's judgment. Architects are simply forbidden to solicit or accept such payments. The brief commentary notes that this rule is "absolute"; that is, it admits of no exception, even when all the relevant parties would agree to the payment after full disclosure. So, for example, an architect cannot have an agreement with a supplier that she or he will recommend a certain window frame even if she or he fully informs the clients of that agreement and the clients say, "Fine." Why? Although many of the payments in question are in fact illegal, the rule is indifferent to their legality. Even legal payments for specifying or endorsing a supplier (say, lending one's name to an advertising campaign) are forbidden. What explains this striking departure from architecture's standard strategy of allowing conflict of interest when the relevant parties consent after full disclosure?

The answer seems to be this: conflict of interest threatens professional judgment. It makes it less reliable than it would otherwise be. Sometimes such threats cannot be avoided or cannot be avoided at reasonable cost. Those relying on the architect's judgment then have the right to weigh the costs and benefits and decide whether to take the risk. In contrast, an agreement to specify or endorse a product does not threaten professional judgment. It does something much more dramatic. The architect has, in this respect, signed away judgment. By the agreement, the architect gives up future judgment of the appropriateness of the product in question. The agreement with the supplier prejudges the matter. The architect cannot both claim the power of an architect in that respect (the right to use her or his judgment to decide what is appropriate in that case) and follow an agreement prejudging the case.

Side payments for endorsement are also, in one respect, unnecessary. The client or employer derives no benefit whatsoever from them, and (generally) the architect does not need them to survive or prosper. They are simply not an essential part of practicing architecture.

This explanation of Rule 2.3 treats it as something other than a rule concerned with conflict of interest. Selling one's judgment does not, in general, create a conflict of interest (that is, it does not threaten professional judgment). However, sometimes it does. For example, if Person A is paid to endorse a product as part of an advertising campaign, Person A will have a greater tendency to specify that product than he or she otherwise would. That tendency is what makes Rule 2.3 in part a rule concerned with conflict of interest. Forbidding endorsements for pay eliminates one sort of conflict of interest.

Rule 2.4 concerns the architect acting as adjudicator, that is, as the interpreter of building contract documents or the judge of contract performance. When acting in this role, an architect is to "render decisions impartially, favoring neither party in the dispute." The commentary makes clear that it is customary in the construction industry for the architect, even

though he or she is paid by the owner and owes loyalty to the owner, to settle disputes between the owner and a contractor, subcontractor, or supplier concerning whether work has been performed as the contract requires or whether the contract requires this or that. When acting in this capacity, the architect must (according to NCARB) act impartially. If the architect does not believe himself or herself to be capable of acting in that way, he or she "may appropriately decline to act in those two roles" (as the agent of the owner and as a judge between the owner and an adversary). The architect's role in such circumstances has a threat to independent judgment built into it (an interest but not a "special" interest). Both architects and those they work with are aware of that threat to independent judgment. They have traditionally tolerated it since the alternative is whatever delay is necessarily consequent on seeking a truly impartial judge far from the work site. Nonetheless, the architect must at least believe himself or herself to be able to render impartial judgment. If the threat to impartiality is significant enough that the architect doubts his or her own judgment, the architect may (and, indeed, should) decline. Interestingly, the rule is not satisfied if the architect merely believes himself or herself to be impartial; the architect must actually render an impartial decision. If the decision is obviously biased, the architect would be subject to discipline under the rule, even though the architect believed himself or herself to be impartial.

Like Rule 2.3, Rule 2.4 is an absolute rule (although the commentary does not say that explicitly). The rationale for its absoluteness is also much the same as that for Rule 2.3. The point of asking the architect to judge between the owner and those working on a site is to receive quickly (something approaching) impartial judgment (a judgment informed by the architect's knowledge of construction, the documents, and local custom). If the architect were known to be partial, his or her value as a judge would be much reduced. The rule preserves the usefulness of architects in settling such disputes (an efficiency serving everyone's interests in the long run). Like Rule 2.3, Rule 2.4 is (primarily) concerned not with conflict of interest, strictly speaking, but with something closely related, that is, the typical outcome of judgment free of conflict of interest (as well as of bias and prejudice): an impartial decision.

The last of NCARB's conflict of interest rules is Rule 3.1. It requires an architect making a "public statement on architectural questions" (that is, speaking publicly in a professional capacity) to "disclose when he or she is being compensated for making such statement or when he or she has an economic interest in the issue." So, for example, an architect paid by a developer to testify on behalf of a project would have to state that she or he is being so paid. An architect writing a journal article on behalf of a certain manufacturer's product would have to disclose ownership of even a single share of stock in that company. For public statements, the standard

of disclosure is more demanding than for statements to client, employer, or other private person. (The term "substantial enough" in Rule 2.2 has no counterpart in Rule 3.1.) The commentary explains why the standard is so demanding: to preserve "the probity which the public expects of the architectural profession," architects are "not allowed under the circumstances described in the rule to disguise the fact that they are not speaking on the particular issue as an independent professional but as a professional engaged to act on behalf of a client" or with a judgment perhaps arising from the wrong sort of interest (a private interest rather than the public interest). The public is entitled to know that the architect might have a certain bias (or even that, from the public's perspective, might seem to have a certain bias), a legitimate bias if it is disclosed but otherwise an illegitimate bias. If architects routinely made public statements in the service of clients without acknowledging that service or in the service of a private interest (however small) without acknowledging that service, their public statements would eventually lose the power that comes from their being thought to be independent. The public statements would be regarded as unreliable (as, indeed, they would be).

This rationale is as interesting for what it leaves out as for what it includes. Like most professions, architecture recognizes itself as having an obligation to serve the public interest (an obligation that may not belong in hard-edged rules but appears, for example, in Canon II of the AIA code). The NCARB commentary might therefore have appealed to this obligation in support of a rule governing public statements (protecting the public). Instead, the commentary appeals to the interest that the profession itself has in maintaining its reliability ("the probity the public expects") both to explain and support the rule.

AIA on Conflict of Interest

The NCARB rules just discussed are the hard-edged rules concerning conflict of interest that state registration boards use to decide whether to discipline a licensed architect. We turn now to the AIA's code. Like AMA, the AIA is a voluntary organization. Also like AMA, it no longer is an organization to which a majority of the profession belongs. Yet, just as no AMA member wants AMA to discipline her or him, so no AIA member wants the AIA to discipline her or him. An AIA member charged with wrongdoing will generally hire a lawyer to present her or his side at the National Ethics Council (NEC) and, if the AIA member loses there, may seek redress in the courts. At least as much as physicians, architects live by their reputations. For that reason, an NEC-appointed hearing officer collects evidence and the full NEC (minus the hearing officer) decides the case in secret. However, for any serious discipline (censure, suspension, or expulsion), the ultimate deci-

sion is made public (the architect's name disappears from the membership role, and the architect can no longer be listed as an AIA member). The NEC publishes its decision in the form of a judicial opinion, stating the facts found, the penalty, and the rationale for it, without identifying the parties. The NEC also issues interpretations of the code (Advisory Opinions).[58]

The AIA code (2007) is about half the length of NCARB's and devotes proportionally much less space to conflict of interest. Canon III (Obligations to the Client) provides the overall framework for conflict of interest. AIA members should "exercise unprejudiced and unbiased judgment when performing all professional services." Ethical Standard 3.2 (titled Conflict of Interest) simply states the general strategy for avoiding tendencies to bias and prejudice. Members should "avoid conflicts of interest in their professional practices and fully disclose all unavoidable conflicts as they arise." There are only two disciplinary rules under this ethical standard. The second rule, Rule 3.202 (render decisions impartially), merely restates NCARB's Rule 2.2 (with a briefer commentary), but the first rule, Rule 3.201, adds something new.

Rule 3.201 prohibits AIA members from rendering professional services if their "professional judgment could be affected by responsibilities to another project or person, or by [their own] interests." The only exception to this prohibition is (the usual) "unless all those who rely on the Member's judgment consent after full disclosure." Rule 3.201 understands "interest" as including more than financial interest. Any "responsibility" to another project or person that could affect a member's judgment is an interest for the purposes of this rule (as is any self-interest, even if it is not financial or familial). The commentary underscores the point. The rule is, it says, "intended to embrace the full range of situations that may present a Member with a conflict between his interests or responsibilities and the interests of others." The commentary goes on to give an equally wide reading of "all those who rely." Those entitled to disclosure "may include a client, owner, employee, contractor, or others who rely on or are affected by the Member's professional judgment." An AIA member who cannot appropriately disclose a "conflict directly to the affected person must take steps to ensure that disclosure is made by another means." (Direct disclosure may not be possible because the client is, for example, an individual who is out of town or an organization whose officers are hard to reach; sending notice is not equivalent to "appropriate disclosure.") If a member cannot make adequate disclosure of a conflict of interest (directly or indirectly), he or she cannot render the professional services in question. The member must decline or withdraw.

In addition to the rules under Rule 3.2, there are at least two rules in

[58] For either, see www.aia.org/about_ethics#nec.

Canon II (Obligations to the Public) that are (at least in part) concerned with conflict of interest. Rule 2.103 forbids an AIA member from serving in a public capacity to "accept payments or gifts which are intended to influence their judgment." This rule covers bribes (payments made in exchange for some future illegal service) but not kickbacks (a payment for a referral or some other favor already done). The rules cover more than bribes, for example, a dinner or a gift of theater tickets of whatever value given with the intention of influencing judgment. This additional coverage is what justifies discussion of this rule as concerned with conflict of interest.

This is another absolute rule. It is nonetheless unusual in one respect. It is the intention of the payer or giver, not its likely consequence or the recipient's intention, that determines whether the payment or gift is prohibited. The rationale for this approach to payments and gifts is obvious. An architect serving in a public capacity will, in the ordinary course of life, receive many payments and gifts. Prohibiting them all would be unreasonable, but some should be prohibited. For example, no one wants to forbid a gift from the architect's mother or brother-in-law that is part of the normal exchange of gifts among family members. (Such gifts would seldom be given with the intent of influencing the architect's professional judgment.) In contrast, the AIA would, presumably, want to prohibit a gift from a potential developer hoping to reduce the hostility of an architect toward a project that he or she has in mind when that architect is a member of the local planning commission.

Rule 2.301 is concerned with public statements on architectural issues. It is (almost) identical to NCARB's Rule 3.1. Although there is no commentary, its placement under the canon concerned with obligations to the public suggests that its rationale is a bit different. Architects perform a useful service whenever they inform the public of their judgments on architectural issues. They perform a useful service whether they speak disinterestedly or on behalf of a client or interest. However, the service performed is different. Rule 2.301 requires architects to make clear which service they are performing so that their audience, the public, can evaluate it using the appropriate criteria. The underlying rationale is not so much to protect independent judgment as it is not to mislead the public concerning what it may reasonably expect of the judgments offered. The public's trust in what architects say depends in part on knowing who they are working for when they say it.

ENGINEERING

Engineering and medicine have historically been very different professions. Engineers have, for example, generally worked in large organizations, beginning with the army; physicians (like architects) have, until recently,

generally worked alone or in small practices (with or without an affiliation with a nearby hospital). Those who employ engineers tend to be the rich and the powerful, not the sick or the wounded. When a work of engineering fails, the result may be hundreds or even thousands of deaths—typically of people of whom the engineers knows little—not, as in conventional medicine, just one person, a patient, known to the physician. (Of course, when physicians advise the Food and Drug Administration [FDA] or a drug manufacturer, the analogy with engineering is much closer.) For these reasons (and others), many of the conflicts of interest that engineers have thought about over the last century lack an exact analogue in medicine. They are nonetheless worth considering in detail because they illustrate how a profession can work from a basic understanding of conflict of interest to a system of detailed rules likely to be of use to practitioners in what would otherwise be situations hard to navigate. To understand the system of rules, it is important to understand something of the institutions in which they are embedded.

Background Institutions

Engineering is divided into four major disciplines (as well as many smaller ones): civil, mechanical, electrical, and chemical. These are more closely related to each other than medicine is to such other health care disciplines, such as dentistry or osteopathy. That is, they are generally taught in departments of the same school; the curricula are similar, especially in the first 2 undergraduate years; the schools have the same accreditation body (ABET, Inc.);[59] and students receive the same first degree upon graduation, a B.S. (with different majors). Nonetheless, engineering has never created the equivalent of AMA. Instead, there are five major societies. One each for the major disciplines: the American Society of Civil Engineers (ASCE), the American Society of Mechanical Engineers (ASME), the Institute of Electrical and Electronic Engineers (IEEE), and the American Institute of Chemical Engineers (AIChE). The fifth major society, the National Society of Professional Engineers (NSPE), cuts across these four. Its members are (primarily) Professional Engineers (PEs). A PE is an engineer (of any discipline) licensed by a state (in much the way that lawyers, CPAs, architects, and physicians are), but only about a fifth of all U.S. engineers are so licensed. The rest, who work in large organizations, do not need a license to practice because of what is known as "the industrial exemption." Although they are not PEs, they

[59] ABET was formerly the American Board for Engineering and Technology; the name change to ABET, Inc., reflects its expansion into new areas.

are full members of the engineering profession.[60] The five major societies (along with many of the smaller ones) frequently cooperate ad hoc as well as maintain many permanent bodies, of which ABET is among the oldest and the most important.

This complexity reappears in the codes of ethics governing engineers. Except for a brief period a half century ago, each of the five major societies has had its own code (as have many of the smaller societies); and, as if this were not enough ethical complexity for one profession, ABET (or its predecessor) has had a separate code (which has not been amended since 1977),[61] one that most engineering societies have endorsed.

Although the relationship among these codes is complex, it is not muddled. The NSPE code[62] is designed (like architecture's NCARB code) primarily for adoption by state licensing boards. Its rules are supposed to be appropriate for use in a disciplinary hearing. In contrast, the ABET code is designed to guide individual engineers. ABET has no enforcement procedure whatsoever (and does not even have a committee to issue advisory opinions) and, apparently, no interest in having its code enforced through any formal procedure. The ABET code thus functions much as the AIA's Ethical Standards do and should therefore be more demanding that the NSPE code. In fact, today it is as often less demanding than more demanding.

Until the 1980s, ABET's code was clearly the most important in engineering. Most engineering societies, including two of the major ones (ASME and ASCE), had adopted it as their own (either the 1977 version or one of its predecessors). In the last decade, however, its importance has declined dramatically. Some societies have amended their codes now and then, to the point that there are now important differences between those codes and ABET's code. Some of the differences arise from the adoption of provisions that the NSPE adopted; some arise from local innovations (which other societies may or may not have followed). In addition, some societies (most notably, the IEEE) have abandoned the ABET code altogether.

The NSPE code now seems destined to become the de facto standard of the profession (in part because the ABET code has gone so long without

[60] Because most engineers are unlicensed, most continuing education depends on employers or on individual engineers. Large employers generally have their own internal technical courses (which the employer funds). Some continuing education goes on in universities as degree programs, certificate programs, or specific technical courses. Most large employers pay for an engineer's continued technical education. Engineers may also be trained by a supplier, once the employer has contracted for some new product (such as software). Most states require PEs to take accredited continuing education courses. Accreditation of such courses is handled much as it is in accounting, architecture, and law.

[61] See http://ethics.iit.edu/codes/coe/accreditation.board.engineering.tech.a.html (Code); http://ethics.iit.edu/codes/coe/accreditation.board.engineering.tech.b.html (Guidelines).

[62] See www.nspe.org/ethics/.

amendment and the IEEE code lacks sufficient detail to provide much guidance). The NSPE code is now much more often reprinted at the back of a text in engineering ethics than any other code. Although it is distinct from ABET's code, NSPE's code resembles it in layout and language because both derive from the "unity code" of a half century ago. Only the IEEE has an independent code (2000)[63]—which some other engineering societies, including the AIChE (2002), have followed. The IEEE code is quite short (260 words) and applies to IEEE members (not to engineers), an important distinction because many IEEE members are not engineers but are computer scientists, physicists, mathematicians, or the like.

This survey confines its review of engineering's methods of dealing with conflict of interest to three codes, those of the IEEE, the NSPE, and ABET, the most important (and distinctive) in U.S. engineering. For all the small differences among these three codes, there is a fundamental agreement about how to deal with conflict of interest.

IEEE Code

The one sentence on conflict of interest in the IEEE code expresses that fundamental agreement succinctly. IEEE members are to "avoid real or perceived conflicts of interest whenever possible, and to disclose them to affected parties when they do exist." The IEEE strategy for dealing with conflict of interest (avoidance whenever possible and disclosure whenever avoidance is not possible or has failed) is similar to that identified for architects but nonetheless differs in two important respects. First, the requirement of avoidance applies not only to "real" conflicts of interest but also to "perceived" ones. Perception—that is, the appearance—of a conflict of interest is treated as being just as bad as the reality. The underlying idea seems to be that an engineer's professional judgment (or, rather, an IEEE member's professional judgment) should be above suspicion. Even perceived conflicts should therefore be avoided (whatever the underlying reality about the interests in question). The underlying reality does not matter to those who would like to rely on an engineer—until it is disclosed and the false appearance is dispelled.

The second important respect in which the IEEE strategy differs from that identified for architects is that there is no indication of what is to be done after disclosure (for example, there is no requirement of consent before continuing). The other engineering codes do provide guidance concerning this question, although the particulars vary a good deal, depending on the circumstances in question. The IEEE has a committee to prepare guidelines to supplement its code.

[63] See www.ieee.org/portal/pages/iportals/aboutus/ethics/code.html.

NSPE Code

The NSPE code is divided into three main parts: a brief, four-sentence preamble; the body of the code, which consists of Part I. Fundamental Canons, Part II. Rules of Practice, and Part III. Professional Obligations; and an addendum (which may be ignored here) that quotes a 1978 federal court decision on competitive bidding and the response of the NSPE Executive Committee. The fundamental canons (about 3 percent of the code) contains three sentences relevant to conflict of interest (in language dating from one of the first engineering codes): "Engineers, in the fulfillment of their professional duties, shall: . . . 3) Issue public statements only in an objective and truthful manner. 4) Act for each employer or client as faithful agents or trustees. 5) Avoid deceptive acts."

The Rules of Practice (which accounts for a quarter of the code's 2,400 words) has six main rules, each of which corresponds to one of the Fundamental Canons. The specific rules under a rule (designated with lowercase letters) are applications or elaborations of the prefacing rule. There are 3 rules under Rule II.3, 5 under Rule II.4, and 2 under Rule II.5, for 10 rules in all. All but two of these (Rules II.3a and II.3b) concern conflict of interest (more or less). In addition, Professional Obligations (about 40 percent of the code) contains six more rules related to conflict of interest. In all, about a fifth of the entire code is concerned with conflict of interest. Apparently, the NSPE takes conflict of interest very seriously. A detailed review of the provisions shows that they cover a surprisingly large number of specific issues.

Rules of Practice

Rule II.3c forbids engineers from issuing "statements, criticisms, or arguments on technical matters that are inspired or paid for by interested parties, unless they [the engineers] have prefaced their comments by explicitly identifying the interested parties on whose behalf they are speaking, and by revealing the existence of any interest the engineers may have in the matters." Although Rule II.3c is similar to NCARB's Rule 3.1 (and AIA Rule 2.301), Rule II.3c differs in one striking respect. The engineer must not only reveal payment for a statement, criticism, or argument but even inspiration, presumably something more than NCARB's "financial interest." Although a financial interest might "inspire" a statement, so might friendship, the urging of a relative, or some other connection unrelated to compensation or financial interest. Although the language is vague, it is obviously meant to sweep wide (something that we might not expect in a code designed for discipline rather than for personal guidance). Why is there such a demanding rule?

For an engineer, the rationale for Rule II.3c is pretty straightforward. Because the rule is under Section 3, it concerns public statements. Engineers view the public much as physicians view patients. Engineers are—as Fundamental Canon 1 puts it—to "[h]old paramount the safety, health, and welfare of the public." There is no official definition of "public"; there is even some debate about the exact boundaries of the public, for example, whether the public includes employees of one's client or employer. The most popular view, though, seems to be that the public includes all those who, owing to a lack of knowledge, power, or opportunity, are unable to protect themselves fully from what engineers do. What engineers call "the public" is (more or less) as dependent on engineering judgment as the physician's patient is dependent on the physician's judgment.

Insofar as what engineers say in public may be influenced by an interested party other than the public, the public needs to know about that influence if it is to decide the appropriate weight to give the statement. The engineer, of course, tries to speak "in an objective and truthful manner" (as Canon 3 requires). If the engineer is not trying to do that, he or she should not speak at all (or, at least, not claim to speak as an engineer). However, if an engineer is aware of an influence that might (but also might not) undermine his or her ability to speak in an objective and truthful manner, he or she must warn the public of that danger to objectivity. There is nothing wrong with issuing public statements in the service of a client or an employer (as long as the statements are objective and truthful). There is, however, something wrong with an engineer giving the impression that he or she is doing something else, that is, expressing independent professional judgment (one independent of an employer, client, or other interested party) when it is not. An engineer must not give a false impression if he or she can reasonably avoid it. Experience and common sense suggest that an engineer may easily avoid giving that false impression by explicitly stating what he or she is doing as he or she begins the public statement in question.

All the rules under the next heading (Rule II.4) are concerned with protecting the client or the employer, not the public. The strategy for dealing with conflict of interest is much the same as that expressed in Rule II.3c. Rule II.4a explicitly uses the term "conflict of interest." Engineers are supposed to "disclose all known or potential conflicts of interest that could influence or appear to influence their judgment or the quality of their services." There is no requirement to avoid those that can be avoided. The rule seems to be concerned with those conflicts that cannot be (or that perhaps just have not been) avoided. Rule II.4a makes something like the distinction between the IEEE's "real" and "perceived" conflicts of interest, that is, between conflicts of interest that "could" influence and those that merely "could appear" to influence a judgment (or the quality of service). There is, however, a new distinction, that between "known" conflicts of in-

terest and those that are merely "potential." Although the distinction seems confused (should not the contrast be between "actual" and "potential" or between "known" and "unknown"?), the intent of the language seems to be clear enough: again (as in Rule II.3c), to sweep as widely as possible. Rule II.4a bars such excuses as, "I didn't know it was a conflict of interest" and "It was only a potential conflict of interest." Lastly, there is no attempt to distinguish financial interests from other kinds of interests. The rule applies to any conflict of interest whatsoever.

Rules II.4b and II.4c are similar to NCARB's Rules 2.1 and 2.2. They make avoidance the standard response to a conflict of interest. Rule II.4b forbids engineers from accepting "compensation, financial or otherwise, from more than one party for services on the same project, or for services pertaining to the same project, unless the circumstances are fully disclosed and agreed to by all interested parties." Rule II.4c forbids engineers from soliciting or accepting "financial or other valuable consideration, directly or indirectly, from outside agents in connection with the work for which they are responsible." The only significant difference between these two rules and the corresponding NCARB rules is (again) a wider sweep. Rule II.4b concerns compensation "financial or otherwise"; Rule II.4c concerns "other valuable consideration" as well as just "financial" ("directly or indirectly" solicited or accepted). So, a dinner, help finding another job, an all-expenses-paid trip to Jamaica, and a free course in some engineering subject, although they are not strictly financial compensation for work on a project (or "pertaining to the same project"), would clearly be close enough to require disclosure under Rule II.4b if they were, for example, offered in the way of offering thanks for favors done on a project. Similarly, although such things might not count as financial considerations, they still seem to count as consideration enough to be forbidden under Rule II.4c (coming from "outside agents").

The last two rules under Rule II.4 concern possible clashes between the engineer's obligations to the public and obligations to a client or an employer. Rule II.4d forbids engineers in public service as members, advisors, or employees of a governmental or a quasigovernmental body or department to "participate in decisions with respect to services solicited or provided by them or their organizations in private or public engineering practice." Engineers in public service are to recuse themselves whenever they, their employer, or their client has an interest in a decision. The client or employer may be a private firm, but the engineer should recuse himself or herself even if the client or the employer with an interest in the decision is another governmental (or quasigovernmental) agency. The rule makes no exception in the case of "full disclosure." The idea seems to be that engineers serving in government (in whatever capacity) or in a quasigovernmental agency (such as AMTRAK or the U.S. Postal Service) are supposed

to put their independent judgment at the public's service. Disclosure of a conflict of interest to the relevant agency does not, as such, protect the public. Even the agency's informed consent does nothing to ensure protection of the public interest. The disclosure would have to be made to the public directly in a way that allows the public to take appropriate action. This can seldom happen when the engineer is advising a public agency (as it can when an engineer is speaking to the public directly). Disclosure to the relevant agency does not necessarily reach the public, and even when it does, the agency and not the public would ordinarily make the decision. So, the only way to protect the public from an engineer's conflict of interest when the engineer's judgment, though exercised in behalf of the public, works through a public agency, is to have the engineer avoid participation in the decision.

Rule II.4e adopts the same strategy with respect to soliciting or accepting "a contract from a governmental body on which a principal or officer of their organization serves as a member." (For some reason, this rule is silent concerning quasigovernmental bodies.) Again, neither mere disclosure of the conflict nor disclosure with consent is enough. The engineer must never solicit or accept such a contract. Although Rule II.4e concerns conflict of interest, it is not designed to protect the engineer's judgment (as the others are) but is designed to protect the judgment of the principal or the officer of the organization that the engineer serves. Indeed, it seems to be designed to protect the principal or the officer in question from the appearance of conflict as well as from actual conflict. There is no requirement that the principal or officer know of the contract or have anything to do with obtaining it. Protecting the principal or officer in question from the appearance of conflict of interest is part of being a faithful agent or trustee.

Rule II.5b consists of three long sentences mostly concerned with bribery, but a part of the first sentence seems designed to avoid both certain conflicts of interest and the mere appearance of them (as well as actual bribes): "Engineers shall not . . . receive, either directly or indirectly, any contribution to influence the award of a contract by public authority, or which may be reasonably construed by the public as having the effect or intent of influencing the awarding of a contract." The expression "reasonably construed" is, of course, a somewhat lower standard than "perceived," as used in Rule II.4a. "Perceived" may be interpreted to include unreasonable as well as reasonable construal. The reason for the change in terms is not obvious (or known). One explanation is that what the public might reasonably construe as taking a bribe or as being a threat to judgment is too close to dishonesty (the concern of Rule II.5) to be good for engineering's reputation. However, what might unreasonably be so construed is not. There are other ways to deal with unreasonable construal; for example, pointing

out how unreasonable it is. In this context, an engineer should be above "reasonable suspicion" but cannot avoid all suspicion.

One problem with the use of "the appearance [or perception] of conflict of interest" is its subjectivity. What appears to be is in part a matter of the psychology of the person doing the perceiving. The mad, the overly suspicious, or the profoundly cynical might see a conflict of interest where no one else would. In contrast, what might reasonably be construed as a conflict of interest, given the evidence available to the person doing the construing, is an objective matter. Even if we know that there is no conflict of interest (for example, because we know that the investments in question are in a blind trust), we can see that the public would be right to draw the opposite conclusion if all it knew was, say, that the engineer in question held the compromising investment. The public's construal of the situation is, on the basis of the evidence, reasonable.

Although the distinction between reasonable construal and unreasonable construal is important, it may not be as important to interpreting the NSPE code as it seems. All codes of ethics must be applied by using reasonable interpretive principles. One principle of reasonable interpretation is that, unless it is unavoidable, an interpretation should not lead to logical impossibility or practical absurdity. Because the avoidance of all perception or appearance of conflict of interest is probably impossible or at least unreasonable, it seems likely that even the code provisions that do not specify the "reasonableness" of the perception or appearance in fact assume it—or, at least, should be interpreted as so doing.

Professional Obligations

So far we have been examining the part of the NSPE Code of Ethics called Part II. Rules of Practice. That part explicitly provides interpretations of Fundamental Canons 1 to 5, rules designed to protect the public, client, and employer. We now turn to the next part, Part III. Professional Obligations, rules that seem to offer interpretations of the remaining Fundamental Canon, which requires engineers to "Conduct themselves honorably, responsibly, ethically, and lawfully so as to enhance the honor, reputation, and usefulness of the profession." This section has nine main rules, numbered like the Rules of Practice, but not obviously derived from the wording of either the preamble or the Fundamental Canons. Except for not overlapping much with the Rules of Practice, there is no obvious unity in the subject matter of Part III. It is, in effect, a code within a code concerned (primarily) with enhancing the honor, reputation, and usefulness of the profession rather than with protecting the public, the client, or the employer (though following its rules would often have that effect too). Part III has three rules concerning conflict of interest: Rules III.4, III.5, and III.6.

Rule III.4 protects the confidentiality of business and technical information that engineers learn while they are acting in a professional capacity. Rule III.4a is concerned with the unreliability in judgment that arises from trying to judge as one would if one did not know what one in fact knows. That rule forbids engineers "without the consent of all interested parties, [to] promote or arrange for new employment or practice in connection with a specific project for which the engineer has gained particular and specialized knowledge." The engineer must have the consent of "all interested parties," generally, the old employer and the new one (as well as clients, if any), because she or he would be in an ethically untenable position otherwise. The engineer has an obligation to maintain the confidentiality of all specific business and technical information learned at the present employer (apart from what has become the engineer's skill, experience, or general knowledge). At the new job, the engineer will have an obligation to act as a faithful agent, using her or his best engineering judgment on behalf of the new employer (or client), just as she or he did at the old employer. The engineer cannot use her or his best engineering judgment while trying to ignore some of what she or he knows (say, the specifics of a new product under development). If the engineer "bends over backward" to be fair to the previous employer, she or he will not treat her or his new employer as she or he should. The engineer will give the new employer less than her or his best. If, however, the engineer does not bend over backward to be fair, she or he cannot know that she or he has treated the old employer as she or he should. (To avoid revealing too much, the engineer needs a margin of safety, which means revealing too little.) Without guidance from the fully informed "interested parties," the engineer is likely to fail the past employer, the new employer, or both. Because much technical and business information consists of trade secrets, the engineer may even provoke a lawsuit between the past and the present employer.

The only way to avoid all of these troubles, apart from never changing jobs or never seeking new employment closely related to projects that one has worked on before, is to have the parties work out an arrangement in advance of the move from one company to another. The arrangement may be as simple as the new employer agreeing to buy a right to use the technology in question or as complicated as an agreement stating what kinds of projects the engineer can work on for a specified period (say, 2 years).

Why does Rule III.4a not simply forbid engineers to seek employment too closely related to previous work? Why does it allow the consent of interested parties to resolve the conflict of interest problem (even if it does not resolve the underlying threat to judgment)? The (primary) moral wrong that conflict of interest threatens is a betrayal of justified reliance (rather than actual biased judgment). Engineers undertake to provide a certain level of service, that is, to be a reliable source of independent professional judg-

ment concerning engineering. Conflict of interest means that an engineer can no longer safely be relied on for such judgment within a certain range of activities. If an interested party, that is, someone justified in relying on that judgment, is alerted to the problem by its disclosure and, by its (informed) consent, accepts the risk, the possibility of betrayal (in that respect) is eliminated. The profession's honor and reputation for honor are preserved. What remains is only a practical problem of protecting the various interests at stake from biased judgment (that is, protecting engineering's usefulness and its reputation for usefulness). One of those interests is the public's interest in the productive use of what the engineer knows. Forbidding engineers to move from one job to a closely related one would waste some of what the engineer has learned (a social resource as well as a personal one) and make it harder for employers to find the engineers that they need.

The rationale for Rule III.4b is similar. The rule forbids engineers, "without the consent of all interested parties, [to] participate in or represent an adversary interest in connection with a specific project or proceeding in which the engineer has gained particular specialized knowledge on behalf of a former client or employer." Engineers frequently testify in court, arbitration hearings, and similar proceedings on behalf of one side or the other. The United States does not have a system of official experts for tribunals to rely on. Representation or even participating in an adversary representation (for example, by testifying as an expert witness for one side or the other) may seem like a betrayal of trust or reliance (whether or not it is), if the engineer's expertise derives even in part from specialized knowledge gained in the course of working for the adverse party ("biting the hand that once fed him or her," so to speak). The engineer should appear as an expert in such a proceeding (or otherwise participate in it) only if all the interested parties welcome the engineer as an independent expert or at least as someone who is not going to betray their justified trust or reliance. Again, the honor and the reputation of engineering are preserved. (The number of engineers makes it unlikely that the adverse party will fail to find a qualified witness even if one party rejects the first engineer for conflict of interest.)

Rule III.5 forbids engineers to "be influenced in their professional duties by conflicting interests." The rule should not be interpreted as forbidding engineers to be influenced by conflicts of interest because, so interpreted, it would be inconsistent with all of the rules discussed so far, which permit conflicts of interest when there are full disclosure and consent (however, the interests, in fact, influence the decision). The only way to avoid being influenced by a conflict of interest is to avoid the conflict of interest or, having failed to avoid it, to recuse oneself. There is no other way to ensure that the decision in question is not influenced. (Disclosure and consent protect against betrayal of trust, not the loss of independent judgment itself.) So, Rule III.5 must instead be understood as forbidding

certain kinds of interests, those that always (or at least too often) conflict with an engineer's professional duties.

The two rules under Rule III.5 confirm this inference. Rule III.5a bars the acceptance of "financial or other considerations, including free engineering designs, from material or equipment suppliers for specifying their product." (Free engineering designs, sometimes including free software, are the engineering equivalent both of the free samples of drugs that physicians receive and of drug company-sponsored courses.) Rule III.5b also bars the acceptance of "commissions or allowances, directly or indirectly, from contractors or other parties dealing with clients or employers of the engineer in connection with work for which the engineer is responsible." There is no exception for disclosure and consent. The engineer can easily avoid such interests without failing to do anything that an engineer should do for the public, a client, or an employer. The engineer should not put his or her interests in financial gain ahead of the interests of the public, a client, or an employer in having the engineer's independent judgment.

Finally, Rule III.6 is concerned with obtaining employment. Although most of the rules under it have nothing to do with conflict of interest, one does. Rule III.6a forbids engineers to "request, propose, or accept a commission on a contingent basis under circumstances in which their judgment may be compromised." At one time, most engineering codes simply forbade engineers from working on a "contingent basis" (that is, where payment, all or just part, depends on success). One consequence of a series of antitrust cases brought against professions in the 1970s was that the rule against contingent fees was declared an unreasonable restraint of trade. The NSPE then sought to restate the rule to make clear its intent, which was not to raise the fees that engineers could charge for failure but to protect engineering judgment. Engineers might, it was thought, take chances that they should not take if their income depended even in part on "success"—success not in the sense in which engineers understand it (which takes into account the public's long-term interests) but in the sense in which a client or employer might understand it (for example, getting a product out the door by a certain date). Hence, Rule III.6a is another absolute rule. The consent neither of the client nor of the employer would permit an engineer to enter a fee contingent arrangement that might compromise her or his judgment.

That completes the survey of how the NSPE code of ethics regulates conflict of interest. That does not, however, complete the survey of NSPE's regulation of conflict of interest. In addition to the code, the NSPE maintains the Board of Ethical Review (BER), which receives inquiries from NSPE members concerning questions of ethics and issues opinions in response.[64] BER publishes between 6 and 13 opinions each year. About

[64] Many of these, including most since 1990, are available at www.niee.org/cases/.

a quarter of these are indexed under "conflict of interest" (among other categories). Space does not allow for an examination of these, but such an examination would only confirm the guiding principles sketched so far: avoid all conflicts of interest that can reasonably be avoided, whether they are actual, potential, or merely apparent. Tolerate the remainder only if full disclosure to interested parties and their informed consent give them the tools that they need to protect against less reliable judgment. Neither consent nor disclosure is enough when an affected party cannot protect itself once it is fully informed.

ABET Code

The ABET code consists of two major parts: the Code of Ethics proper, which is a short document (210 words), and the much longer Suggested Guidelines for Use with the Fundamental Canons of Ethics (2,667 words). The Code of Ethics is divided into Fundamental Principles (which have much the same content as the NSPE preamble) and Fundamental Canons (which have much the same content as NSPE's Fundamental Canons). The ABET guidelines correspond to the rest of the NSPE code (Parts II and III).

For the purposes of this paper, the only significant difference between the two codes (apart from the guidelines) is that ABET's Fundamental Canon 4 has been amended to append to the language of the NSPE code a comma and the words "and shall avoid conflicts of interest." Most engineering codes of ethics now include that amendment, the result of a scandal in the middle 1970s that ended in a $7.5 million judgment against ASME.[65] Some volunteers in one of ASME's standard-setting bodies, although faithful agents and trustees of their employer (as Fundamental Canon 4 then required), had a conflict of interest when acting as members of the committee. Because the engineers involved were members of ASME, as well as volunteers, ASME had not been their client or employer (in the ordinary sense of these terms). They had not (it seemed) violated Fundamental Canon 4 (or any other rule in effect at the time). Yet, most engineers thought that they had clearly done something that an engineer should not do. Since Fundamental Canon 4 did not seem to cover the case, although it should have, ABET revised Fundamental Canon 4 (adding the reference to conflict of interest), and most other engineering societies followed (with the notable exception of NSPE—which dealt with the problem by adding or amending rules *under* its equivalent of Fundamental Canon 4).

[65] See *ASME v. Hydrolevel Corp*., 456 U.S. 556 (1982).

ABET Guidelines

Although the ABET Guidelines were explicitly designed for use with the Fundamental Canons, they are an independent code in structure (and they were in fact the body of the code itself until 1977). The guidelines consist of seven main divisions, each of which is identical to one of the code's Fundamental Canons (and carries the same number). Under each of these are lettered sections and sometimes numbered subsections interpreting or applying the canon. Many of the sections are identical in language to provisions of the NSPE code. Some differ in ways not important here. For example, ABET Rule 3d differs from NSPE Rule III.3c in using "engineering matter" rather than "technical matter," by requiring engineers to identify themselves (as well as the party for whom they are speaking), and requiring them to describe any "pecuniary interest" that they may have in what they are about to say (rather than just any interest). In what follows, we ignore such small differences, focusing on rules that add something important to what we found in the NSPE code. There are only two such rules. They are, not surprisingly, both under Canon 4 (the canon explicitly concerned with avoiding conflict of interest).

Rule 4a of ABET's code differs from its NSPE counterpart (Rule II.4a) in requiring engineers to "avoid all known conflicts of interest" (rather than simply to disclose them) and to disclose promptly to their clients or employers the rest, what the NSPE code identified as "potential" conflicts of interest: "any business association, interests, or circumstances which *could* influence their judgment or the quality of their services" (emphasis added). This guideline makes explicit what we had found implicit in NSPE's Rule II.4a. The ABET rule may, nonetheless, be less demanding than its NSPE counterpart. If the adjective "business" applies to "interest" and "circumstance" as well as to "association" (a natural reading), then Rule 4a does not require disclosure of all conflicts of interest but only those arising from business associations, business interests, or business circumstances.

The theme of avoidance is carried through the rest of the conflict of interest provisions under Rules 4b to 4g—all of which, except for Rule 4b, are (more or less) identical to the rules in the NSPE code (and, in fact, date from some of the earliest codes of engineering ethics). The exception, Rule 4b, forbids engineers to "knowingly undertake any assignments which would knowingly create a potential conflict of interest between themselves and their clients or their employers." The two uses of "knowingly" suggests not only sloppy editing but also a great concern that engineers not be blamed for undertaking such assignments inadvertently. The requirement of knowledge is a break with the ABET code's general policy, which is to require avoidance or disclosure without providing for the excuse "I did not know." (In other words, engineering codes generally treat ethical conduct as a question of competence for which "I did not know" is an

admission of wrongdoing and not an excuse.) There is only one other use of "knowingly" in the entire code, one of which is unrelated to conflict of interest (Rule 6a, avoiding association with a disreputable business). Rule 4a's knowledge requirement (like the use of "conflict of interest") is new to the 1977 code. However, it is an innovation that some other codes have followed. For example, Rule 4b in ASME's current code (2002) is simply a cleaner version of ABET's: "Engineers shall not undertake any assignments which would knowingly create a potential conflict of interest between themselves and their clients or their employers."

Conclusions from Survey of Engineering Codes

For engineering, then, conflict of interest is a threat to the profession's usefulness (the reliability of its judgment) as well as to its honor and reputation. For most purposes, the best response to an actual or potential conflict of interest is to avoid it as soon as one learns of it. In a few cases, recusal is allowed (or required); in others, those cases in which (1) disclosure allows the public, client, and employer an adequate response and (2) the engineer cannot be replaced or cannot be replaced at reasonable cost, tolerance of a conflict of interest is allowable. However, it is only allowable. Even then, there is a risk to all who rely on the engineer's judgment that the engineer's judgment will not be as good as it should be (and would be but for the conflict of interest). Disclosure is not a cure-all.

COMPARATIVE OVERVIEW

This survey has discussed both similarities and differences in the treatment of conflicts of interest by four important professions. What can be learned from this survey of lawyers, certified public accountants, architects, and engineers? The obvious point is that all four professions take conflict of interest in professional practice very seriously. The recent history of public accountancy shows that failure to take conflicts of interest seriously enough can result in federal regulation. Engineering had a similar experience three decades ago with civil liability.[66]

With the exception of engineering, these professions do not undertake the kind of scientific research carried out by some in the medical

[66] *American Society of Mechanical Engineering, Inc. v. Hydrolevel Corp*., 456 U.S. 556 (1982), in which the U.S. Supreme Court held that ASME was strictly liable for the acts of its agent (the chairman of ASME's Boiler and Pressure Vessel Codes Committee) if those acts are in breach of antitrust laws (the chairman, an officer in the competitor of Hydrolevel, had a financial interest in his committee, finding that Hydrolevel's product did not meet ASME's code).

profession.[67] They have therefore not had to deal with controversies over conflicts of interest in research. Although each profession sets standards for providers of continuing professional education, they have, it seems, not faced any significant conflict of interest in education either.[68]

One reason for the relatively low level of attention given to conflicts of interest in research and education may be that lawyers and accountants do not act as gatekeepers for significant numbers of products and services as physicians do when they prescribe medications, use medical devices, order diagnostic tests, and the like. To the extent that architects and engineers are gatekeepers for supplies, their codes of ethics carefully regulate relationships with suppliers, gifts from suppliers, and other entanglements with suppliers that might threaten their professional judgment.

All four professions treat conflict of interest situations as risk situations; bias, breach of confidentiality, fraud, and malpractice are dealt with separately. Conflicts of interest are understood to threaten the quality of the individual professional's judgment and, as a consequence, the well-being of the client or employer in question, the profession's usefulness to the public (depending on the specific circumstance), and the reputation of the profession as a whole. The four professions express concern about conflict of interest in somewhat different ways and justify their management measures by appealing to different core values. The three most prominent values are loyalty to the client (or the employer), professional judgment, and public service. Beyond the fact that the four professions share these three most prominent values, we can draw at least 13 other conclusions:

1. Each profession has, over time, developed at least one detailed national code of professional ethics. Each of these codes is generally adopted (sometimes with amendments) by state-level professional organizations, licensing boards, or both. All these codes include general principles as well as more specific rules. A substantial part of each of these codes addresses conflicts of interest, describing what the profession understands conflict of interest to mean and how members of the profession should deal with

[67] Publishable engineering research generally goes on in (1) universities, (2) government laboratories, or (3) private laboratories (such as IBM's Watson Research Center). Most of this engineering research is scientific and is therefore subject to federal conflict of interest rules much as most medical research is. Relatively little engineering research is the equivalent of testing by the FDA. Some is, however, for example, the testing done by Underwriters Laboratories. So far, it seems, engineering's strict rules concerning conflict of interest seem to have protected it from the sorts of scandals medical research has suffered.

[68] Nevertheless, some guidance on conflict of interest in scholarship is available from the Association of American Law Schools, which requires that professors disclose any economic interest that they have in the subject matter of their scholarship. Insofar as professors are themselves members of their respective professions, they will be subject to the same conflict of interest rules and codes of conduct as their nonscholarly colleagues.

specific conflicts of interest (usually describing which conflicts will be prohibited, consentable, or allowable even without consent).

2. Compliance with each profession's codes of ethics depends—as the AICPA code of ethics says—"primarily on members' understanding and voluntary actions, secondarily on reinforcement by peers and public opinion, and ultimately on disciplinary proceedings, when necessary, against members who fail to comply with the Rules." In other words, the codes of ethics of all four professions are enforced in much the same way that the AMA enforces its code of ethics. They are not designed for use by state licensing boards.

3. Protecting against conflict of interest occurs not only at the level of the professional society and state licensing board. Some conflicts of interest constitute malpractice or breach of criminal law or civil regulation (e.g., the Sarbanes-Oxley Act and its regulations). Some failures to deal properly with conflicts of interest can have serious consequences for the professionals involved. Statutes and case law, however, generally sets a standard for conduct lower than that set by codes of ethics: law is designed to set minimum standards below which no member of the profession should fall, whereas codes of ethics are designed at least in part to set a higher standard (something closer to the best that can reasonably be expected of members of the profession). For many professions, the minimum standard with respect to conflict of interest has risen substantially over the last four decades. There is no reason to expect that trend to change anytime soon.

4. There is general agreement that professionals will find themselves in some conflict of interest situations even when all reasonable precautions have been taken to avoid them. When avoidance cannot reasonably be expected or has failed, censure attaches not so much to having a conflict of interest (except for prohibited relationships) as to a professional's failure to take proper steps to deal with it.

5. The conflicts of interest discussed in this paper can arise in at least three ways:

- The interests of two or more of a professional's current or former clients (or employers) can conflict and the professional can therefore be in a situation in which serving one client competently (for example, preserving confidential information) would mean not serving another client competently (that is, the professional is not able to use all of the information that he or she knows). This is a major concern for lawyers as well as for engineers.
- The financial, familial, or other interests or relationships of a professional can conflict with the interests of one or more clients (or employers) and thereby compromise judgment (a major concern for all four professions).

- The interests of a client (or employer) can conflict with the public interest and thereby risk compromising the quality of the professional's judgment (a major concern for CPAs, particularly when they conduct audits, but also a concern for architects working as adjudicators or making public statements and for engineers making public statements or working for or with government).

6. Each of the professions, as a general matter, understands that conflicts of interest can be created not only by financial considerations but also by other considerations, such as nonmonetary gifts, friendships, family relationships, and previous employment. The crucial question is always the known or suspected tendency of the fact in question to affect professional judgment adversely.

7. Each profession understands that conflict of interest is in part a threat to the trustworthiness (or reliability) of the profession as well as to judgments in specific cases. This is clear from the way in which the professions, each in a somewhat different way, address appearances. In general, members of these professions are supposed to avoid giving clients, employers, and the public even a plausible reason to suppose that they have an interest, relationship, or the like that might impair their objectivity (the reliability of their judgment).

8. Not all conflicts of interest are treated in the same way. We may distinguish three ways of treating them. The codes of ethics for each of the four professions begin with the instruction to avoid conflicts of interest. This general instruction is then modified or further refined by distinguishing between (1) conflicts of interest that must be avoided regardless of the specific circumstances (i.e., conflict of interest situations that are prohibited), (2) those that are permitted under certain circumstances following disclosure and, generally, that are accompanied by the informed consent of the client or other parties directly affected or some other management strategy, and (3) those conflicts of interest that are permitted because of their relative insignificance. Because clients or employers are often sophisticated individuals or businesses, they are capable of refusing consent or setting conditions for consent (once a conflict is disclosed). Modifiers such as "substantial" or "significant" as well as "direct" (in contrast to "indirect") indicate that not all conflicts of interest are of equal concern. The professions understandably attempt to focus their rules on interests that seem likely to have more than a minor impact on professional judgment or on trust in the profession.

9. Because so many conflicts of interest are either prohibited outright, require disclosure and consent, or are hard to manage, avoidance is, all else being equal, the preferred technique for dealing with conflict of interest. Avoidance is facilitated by certain practices; for example, a lawyer runs a "conflicts check" inside the firm before a new file is accepted. In all four

professions, the avoidance of a conflict of interest sometimes means forgoing personal gain or gain for a client or an employer, a fact that all four professions acknowledge. Avoiding conflict of interest certainly has costs (as well as benefits).

10. When the conflict of interest has not been avoided (for whatever reason and whether intentionally or unintentionally), various options to escape from or manage the conflict exist. Recusal is one option. For example, engineers who are members, advisors, or employees of a governmental department must withdraw from decisions in which they, their employers, or their clients have an interest. The engineer must comply with this ethical rule even if governmental regulation allows for disclosure and consent as an alternative way of managing the conflict. Despite the general requirement to avoid conflicts of interest, professionals can proceed despite a conflict of interest under specified circumstances. Generally, certain precautions must then be taken: (1) disclosure of the interest to the parties concerned (who can include current and former clients, current and former employers, and third parties), (2) the informed consent of these parties (although, occasionally, disclosure alone is sufficient), and (3) the implementation of additional management measures (for instance, the use of screens in law firms). The codes try to make clear when disclosure followed by consent (or disclosure alone) will be considered sufficient to preserve both the fact and the appearance of proper judgment (independence, loyalty to client, reliability, or the like). When proper judgment cannot be ensured, the conflict must be avoided, despite the advantages (to the professional, the professional's employer or client, or any other party) of accepting it.

11. Patterns of difference between (what lawyers call) "consentable" and "nonconsentable" conflicts of interest are sometimes difficult to discern (and, indeed, may be evolving). Overall, it seems that the more dependent that the client, employer, or public is on the professional and the less ability that the client, employer, or public has to manage the conflict, the more likely that consent, even after full disclosure, will not override the general prohibition of conflict of interest. In legal practice, for example, a typical nonconsentable conflict of interest arises if a lawyer undertakes the drafting of a will granting him or her a substantial gift from a client. A typical consentable conflict of interest arises if, for example, a lawyer bought a share in a hotel owned by a client (what lawyers call an "arm's-length" business transaction).

12. Instruction in understanding, identifying, and managing conflicts of interest is included in graduate education, licensing examinations, and (often) in mandated CPE for all of the professions evaluated here.

13. CPE in law, accounting, architecture, and engineering is provided by companies that are authorized by the relevant state-designated licensing boards or a national accreditation body to provide CPE. Individual pro-

fessionals must regularly complete a set amount of CPE, often including training in conflict of interest, to maintain their professional licenses. They or their employers pay the cost of the CPE, although some CPE courses are offered for free by local or national professional organizations.

Table C-1 summarizes the responses of the four professions discussed here to conflicts of interest.

TABLE C-1 Summary of the Responses of Four Professions to Conflicts of Interest

Conflict of Interest	Lawyers	Certified Public Accountants	Architects	Engineers
Gifts or rebates	Lawyers cannot solicit or prepare instruments to receive substantial gifts.	Gifts are prohibited unless the value is "clearly insignificant to the recipient."	Gifts cannot be accepted. Rebates are permitted only with the informed consent of all relevant parties.	Engineers cannot solicit or receive gifts or other valuable consideration.
Public speaking, speaking about professional issues	Not addressed.	Public speaking is not addressed, except to the extent that audits and attestations are public statements (conflict of interest management is very strict in such cases).	Architects must disclose any personal financial interests in public statements.	Engineers are forbidden from making statements on technical matters "that are inspired or paid for by interested parties," unless the engineer prefaces the statement with disclosure of the interest.
Financial or other relationships with client	Some fair financial relationships (business transactions, real estate, etc.) with a client are possible following disclosure and informed consent. Many personal relationships are nonconsentable.	Neither a CPA nor members of a firm can have direct or many indirect financial interests or familial interests in the client being audited. Restrictions on nonaudit services are offered during the time of audit.	Disclosure and consent are required if the client is not aware.	No contingent fee under conditions that could affect professional judgment is allowed. Disclosure and consent are required if the client is not aware.

Financial or other relationships with relevant (opposing) nonclients	No representation of opposing parties in litigation is allowed. Representation following disclosure and consent of both parties at other times is allowed.	Few restrictions.	Disclosure and consent of all interested parties are required.	Such relationships are generally prohibited. Exceptions (such as testifying in court as an expert witness) are allowed with full disclosure and consent.
Sponsorship of CPE	CPE is usually paid for by the lawyer or his or her firm.	CPE is paid for by the accountant or his or her firm. CPE is not approved if it is "devoted to the promotion of particular products or services."	AIA or NCARB provides CPE. CPE is paid for by the architect or the firm when it is not provided for free.	CPE is primarily required for a PE license, generally state certified. Most engineers are not required to take CPE, but whether it is required or not, it is generally paid for by the engineer or the employer.

D

How Psychological Research Can Inform Policies for Dealing with Conflicts of Interest in Medicine

*Jason Dana**

Physicians take an altruistic pledge to consider their patient's interests ahead of their own in clinical practice. Likewise, medical researchers have a professional obligation to conduct their research ethically in their search of truth. A conflict of interest is a set of circumstances that creates a substantial risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest. Although the information in this report can be applicable to many types of conflict of interest, it focuses on financial conflicts of interest, which can occur when medical professionals interact with the pharmaceutical industry. For example, when physicians accept support for clinical research or continuing education programs, accept consultantships and appointments to industry-sponsored speakers bureaus, or have informal meetings with pharmaceutical sales representatives who buy lunch and bring drug samples, there is concern about the impact of these relationships on prescribing behaviors and professional responsibilities (Marco et al., 2006).

The purpose of this paper is to bring basic psychological research to bear on understanding financial conflicts of interest in medicine and effectively dealing with these conflicts. A particular focus will be research on self-serving biases in judgments of what is fair. This research shows that when individuals stand to gain by reaching a particular conclusion, they tend to unconsciously and unintentionally weigh evidence in a biased fashion that favors that conclusion. Furthermore, the process of weighing

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evidence can happen beneath the individual's level of awareness, such that a biased individual will sincerely claim objectivity. Application of this research to medical conflicts of interest suggests that physicians who strive to maintain objectivity and policy makers who seek to limit the negative effects of physician-industry interaction face a number of challenges. This research explains how even well-intentioned individuals can succumb to conflicts of interest and why the effects of conflicts of interest are so insidious and difficult to combat.

The section Unconscious and Unintentional Bias describes the psychological research on bias in more detail, and its relevance to financial conflicts of interest will be made clearer. The section Parallel Evidence in the Medical Literature then provides a brief review that demonstrates the correspondence between the findings from studies of conflicts of interest in the medical field and the findings from basic studies of bias in the field of psychology. The section Implications for Policies Dealing with Medical Conflict of Interest details for policy makers how approaches including educational initiatives, mandatory disclosure, penalties, and limiting the size or type of gifts can be informed by the psychological bias literature. The Methods and Limitations of the Data briefly addresses the propriety of applying psychological experiments to professionalism in medicine. Finally, a conclusions section summarizes what can be learned from the psychological literature.

UNCONSCIOUS AND UNINTENTIONAL BIAS

One intuitive view of financial conflicts of interest is that the physicians who are swayed by them are corrupt. Physicians have taken an oath to put their professional obligations first, so that if they are indeed influenced by private financial incentives, they have chosen not to uphold that oath. Although there may indeed be a minority of individuals who are fundamentally corrupt, most physicians certainly try to uphold ethical standards. This intuition is implicit in the guidelines set forth by the American Medical Association, the American College of Physicians, and the self-imposed guidelines of the Pharmaceutical Manufacturers Association, all of which stress that gifts accepted by physicians should primarily entail a benefit to patients and should not be of substantial value, suggesting that the temptation to provide or accept large or personal gifts is a concern. This view perhaps suggests that physician relationships with the pharmaceutical industry are problematic and can elicit hostility from some physicians. Understandably, most physicians see themselves as ethical people who would not place their objectivity for sale, and so they believe that they can be trusted to navigate these conflicts when dealing with industry. Compounding matters, many enticements from industry are of relatively small

financial value. This prompts responses that physicians are "above sacrificing their self-esteem for penlights" (Hume, 1990) or that if panelists on a scientific committee are influenced by receiving reimbursement for travel and expenses, someone "bought their opinions" and "they obviously come cheap" (Coyne, 2005).

This view is also compatible with an orthodox economic approach, which casts succumbing to conflicts of interest as the rational output of a cost-benefit calculation. In that case, solutions to problems of conflicts of interest would involve better monitoring and punishment, hopefully to the point at which ethical lapses would be too costly to indulge.

Evidence from psychology offers us a different view, one in which our judgments may be distorted or biased in ways of which we are unaware. Some of the most compelling evidence of bias comes in the domain of optimism about the self. There is, for example, much evidence that people engage in self-deception that enhances their views of their own abilities (Gilovich, 1991). One of the most oft cited and humorous examples of self-enhancement is found in a study that reported that 90 percent of people thought they were better drivers than the average driver (Svenson, 1981). Such biases have been dubbed "self-serving" (Miller and Ross, 1975) when they lead one to take credit for good outcomes and blame bad outcomes on external sources. Although an unrealistic optimism about the self is sometimes adaptive and healthy (Taylor and Brown, 1988), these biases can lead to judgments that are unwise or unjust in situations in which we are epistemically responsible for being correct.

Perhaps most relevant to the issue of financial conflicts of interest are well-known self-serving biases in the interpretation of what allocations are fair or just. A classic demonstration of self-serving bias in fairness comes from a study by van Avermaet (reported by Messick, 1985). Subjects were instructed to fill out questionnaires until they were told to stop. When the subjects finished, the experimenter left them with money that they could use to pay themselves and send in an envelope as pay for another subject who had already left. In four different conditions, the subject was told one of the following four different conditions: (1) the other subject had put in half as much time and had completed half as many surveys, (2) the other subject had put in half as much time but had completed twice as many surveys, (3) the other subject had put in twice as much time but had completed half as many surveys, or (4) the other subject had put in twice as much time and had completed twice as many surveys.

It is first interesting to note that almost everyone took the trouble to send the other person a share of the money, even though they were free to keep it all. It was not clear to the author that the rare cases of nonreturn were not due to a mistake or a lost envelope. Clearly, the subjects' sense of ethics served as a powerful constraint on their behavior: keeping all of the

money would be unjustifiably selfish and unfair because the other subject at least did similar work, so most subjects shared it. How they shared the money, however, provides an interesting insight into human nature. The subjects who worked twice as long and completed twice as much kept twice as much money, on average, a simple application of a merit principle to pay. The subjects kept more than half of the money, however, both under the condition in which they worked longer and completed less and under the condition in which they completed more work and did not work as long. Again, their behavior was consistent with a merit principle, but the principle chosen, on average, systematically favored the subject making the allocation. Finally, when the subjects completed only half as much work and worked only half as long, they did not, on average, give the other subject twice as much money. Instead, the subjects kept about half of the money, on average, consistent with a rule of equal division rather than merit.

What we can take away from the van Avermaet study is that most people are not unabashedly selfish; they have a sense of what is fair and tend to abide by it. Yet, that does not mean that judgments of fairness are not systematically biased to favor the self. When people are free to choose among competing principles of fair behavior, they tend to gravitate toward those principles that most favor their own interests. Other early experiments have similarly found that interpretations of fair allocations of pay are self-servingly biased (Messick and Sentis, 1979). One potential shortcoming of these experiments, however, is that they used a survey methodology. Thus, the subjects' self-interest was imagined, and they had no motivation to honestly report what they thought was fair. Thus, although it is apparent that the subjects had malleable interpretations of what was fair, it is not always clear whether these interpretations reflected a bias or, for example, a strategic effort on the part of the subjects. In that case, one wonders if the use of sufficient compensation would erase the effect.

A series of experiments by behavioral economists (Loewenstein et al., 1992; Babcock et al., 1995) addresses this problem through the use of real money incentives without deception and establishes that self-serving interpretations can arise as unwitting and unintentional biases. Simulating pretrial bargaining, Loewenstein et al. (1992) conducted bargaining experiments in which subjects were presented with case materials (depositions, police reports, etc.) from an actual law suit. The subjects were randomly assigned to the role of either the plaintiff or the defendant and were asked to negotiate a settlement in the form of a payment from the defendant to the plaintiff. At the outset, the experimenters gave the defendants a monetary endowment to finance the settlement, and the division of the endowment that the subjects agreed upon through bargaining was what they took home as pay. The longer that it took the parties to agree to a settlement, the more that both were penalized by having the endowment of money that

they were dividing shrink. If they failed to settle, the defendant's payment to the plaintiff, based on the smaller endowment size, was determined by a neutral judge who had reviewed all of the case materials. Before they negotiated, both the plaintiffs and the defendants were asked to predict how the neutral judge would rule in the case and were also paid for the accuracy of this prediction.

The subjects in this experiment had every incentive to be objective in seeking a settlement; if their demands were unreasonable, the pot of money would only shrink and ultimately the award would be determined by a neutral and informed party. If the subjects' estimates of a fair settlement were biased in a self-serving manner, however, they might be inclined to view the other party's offer as unjust and unacceptable. Indeed, the subjects were often unable to settle, to their own detriment. Direct evidence that the self-serving bias played a role in this failure to settle came in the form of the predictions of the judge's ruling. The plaintiffs' predictions of the judge's award to them were, on average, substantially higher than those of the defendants, even though the estimates were secret and had no bearing on the settlement and both parties were paid to be accurate in their estimates. Furthermore, the larger that the discrepancy between a particular plaintiff's and defendant's estimates was, the lower was their likelihood of settlement, and hence, they both left the experiment worse off in terms of payment. This evidence suggests that self-serving biases are unintentional because people are often unable to avoid being biased, even when it is in their best interest to do so.

In subsequent experiments that used the same paradigm (Babcock et al., 1995), the settlement rates were markedly improved by assigning subjects their roles only after they had read the transcripts. In this way, any motivation to interpret evidence as favorable to one side over another while the subjects were reading and evaluating the materials was removed. Without the subjects having a self-interested conclusion to reach, interpretations of fairness, as measured by predictions of the judge's ruling, looked more like those of a neutral third party than an interested party. In principle, of course, these judgments were exactly like a third party's judgment. The finding is important, however, because these subjects still had the same bargaining task as in the earlier experiments. Thus, one cannot conclude that the majority of failures to settle were due to the subjects being overly competitive or having a poor strategy. Rather, manipulations targeting the objectivity of the fair ruling judgment increased the settlement rates. This finding suggests that self-serving biases work by way of distorting the way that people seek out and weigh information when they perceive that they have a stake in the conclusion.

The motivated reasoning displayed by the subjects in the study of Loewenstein et al. (1992) confirms the general findings from social psychol-

ogy research. Gilovich (1991) describes the different evidential standards that people typically use to evaluate propositions that they wish to be true versus propositions that they wish to be false. When they evaluate an agreeable proposition, people ask, "Can I believe this?" When they evaluate a disagreeable position, people ask, "Must I believe this?" The former question implies a more permissive evidential standard because it requires the decision maker only to seek out confirmatory evidence, whereas the latter question implies that the proposition must survive a search for disconfirming evidence.

These different evidential standards are exemplified by studies that use a variant of the classic Wason card selection task (Wason, 1966). The Wason task asks subjects to test an abstract logical rule by choosing which pieces of information that they want to be revealed to them. An overwhelming majority of subjects, even those with high levels of formal education, fail to reason through this task properly. The most common mistake that they make is selecting information that could confirm the rule but that is useless for testing it while failing to select information necessary for testing the rule because it could disconfirm it.

Dawson and colleagues (2002) modified the Wason card selection task by having subjects sometimes test hypotheses that they did not want to believe, such as those that implied their own early death. Providing motivation not to believe in this manner improved the subjects' performance over that in situations in which the subjects were testing nonthreatening or agreeable hypotheses. This finding is interesting because it shows not only that people approach the problem differently when the hypothesis is agreeable or disagreeable but also that the proper motivations can lead them to solve problems that they are otherwise incapable of solving. Thus, motivated reasoning appears to operate at a preconscious level.

The "can I?" versus "must I?" distinction in the motivated evaluation of evidence could be applied to thinking in many financial conflict of interest situations. For example, a physician may evaluate evidence that a particular treatment is effective. If that physician stands to make money by prescribing that treatment, the motivation of financial gain may make his or her evaluation of the drug's effectiveness hold to a weaker evidential standard.

In further studies on the self-serving bias, Babcock et al. (1995) attempted to reduce bias by educating subjects, describing to them the behavioral regularities of bias that lead to disagreement, and testing the subjects to make sure that they understood. This intervention, on average, had little success in improving settlement rates. It did help the subjects recognize bias, but mostly in their negotiating opponents rather than in themselves. Moreover, those subjects who did concede that they might be somewhat biased tended to drastically underestimate how strong their bias was. This

finding suggests not only that bias is unconscious but also that conscious attention alone cannot be expected to remove bias.

This finding—that teaching people about bias makes them recognize it in others but not themselves—has since been confirmed and extended. Several studies of the "bias blind spot" (Pronin et al., 2002) have found that for any number of cognitive and motivational biases that the researchers can describe, subjects will, on average, see themselves as less subject to the bias than the "average American," classmates in a seminar, and fellow airport travelers. That is, the average subject repeatedly sees himself or herself as less biased than average, a logical impossibility in the aggregate that suggests that self-evaluations of bias are systematically biased. Furthermore, experiments have shown that when people rate themselves as being less biased than they rate the average person, they subsequently tend to insist that their ratings are objective (Pronin et al., 2002; Ehrlinger et al., 2005). Much like in the study of Loewenstein et al. (1992), this insistence persists even after the subjects read a description of how they could have been affected by the relevant bias. Why do people recognize less bias in themselves than in others, and why does education not make this bias go away?

Further studies of the bias blind spot (Ehrlinger et al., 2005; Pronin and Kugler, 2007) have identified a mechanism behind this behavior that they term an "introspective illusion." Being privileged to their own thoughts, people use introspection to assess bias in themselves. Because biases like the self-serving bias operate below the level of conscious awareness, they can "see" that they are not biased; at least, they have no experience of bias and so conclude that they are not biased. When they assess bias in others, however, people do not have the privilege of knowing what a person thought and must rely on inferences based on the situation. If another's behavior is consistent with a bias, people will often conclude that the other is biased. Learning about various cognitive and motivational biases can exacerbate these "I'm better-than-average" effects. People will often still hold that they are not biased because they "know" their own thoughts, but they will now know what to look for in a situation that could bias others. The bias blind spot gives us one way of understanding why such strong disagreements can take place over whether conflicts of interest are problematic.

In summary, psychological research suggests that people are prone to having optimistic biases about themselves. Judgments about what is fair or ethical are often biased in a self-serving fashion, leading even ethical people to behave poorly by objective standards. Self-serving bias is unconscious and unintentional, and people often fall prey to it even when they do not want to do so and they do not know they are doing it. The bias works by influencing the way in which information is sought and evaluated when the decision maker has a stake in the conclusion (financial or otherwise). The bias thus leads to the use of more lax evidentiary standards when the deci-

sion maker wants to believe something than when the decision maker does not. Teaching about egocentric biases like the self-serving bias does little to mitigate them because when people examine their own thinking, they do not experience themselves as being biased. People do learn to look for bias in others, however, which can lead them to conclude that others are biased while they themselves are not.

PARALLEL EVIDENCE IN THE MEDICAL LITERATURE

Medical research on conflicts of interest—such as research on attitudes about or the influences of gifts to physicians from industry—has not set out to research whether unintentional bias exists. The findings in the medical literature, however, correspond nicely with the findings from basic psychological studies of bias. This correspondence serves as support for the idea that the model of unconscious and unintentional bias can help us understand conflicts of interest in medicine.

Most prominently, although some physicians may admit to the possibility of being influenced, physicians typically deny that they are influenced by interactions with and gifts from industry, even though research suggests otherwise (Avorn et al., 1982; Lurie et al., 1990; Wateska, 1992; Caudill et al., 1996; Orlowski and Gibbons et al., 1998; Adair and Holmgren, 2005). The question is whether these denials by and large reflect a sincere belief in one's objectivity. Accumulating evidence suggests that physicians believe that other physicians are more likely to be influenced by gifts than they themselves are (McKinney et al., 1990).

A study of medical residents (Steinman et al., 2001) found that 61 percent reported that "promotions don't influence my practice," while only 16 percent believed the same about other physicians. Findings that residents in general believe that others are more likely to be influenced by interactions with industry than they are have been confirmed in a more recent review (Zipkin and Steinman, 2005). Morgan et al. (2006) found that for all of four different gifts, ranging in size from a drug sample to an offer of a well-paid consultancy based only on prescribing volume, physicians rated themselves as less likely, on average, to be influenced by their acceptance of a gift than their colleagues. Even medical students see gifts of equal value as being more problematic for other professions than their own (Palmisano and Edelstein, 1980).

There is even some direct evidence that physicians do not appreciate industry's influence on them. Orlowski and Wateska (1992) tracked the pharmacy inventory usage reports for two drugs after the companies producing the drugs sponsored 20 physicians at their institution to attend continuing medical education seminars. The rates of use of the drugs described at these seminars increased, both in time series analysis of the rate

of use of the drugs at the institution and in comparison with the national average rate of use during the same period. However, before they attended the seminars, all but one of the physicians denied that the seminars would influence their behavior. Being asked about bias should make physicians more aware of the potential of bias entering into the seminar, yet this did not prevent the seminar from apparently having an impact on the physicians' decisions.

A retrospective study (Springarn et al., 1996) tracked house staff who attended a grand rounds sponsored by a pharmaceutical company and found that they were more likely to indicate that the company's drug was the treatment of choice than were their colleagues who had not attended the session. Interestingly, these same physicians were often not even able to recall the sponsored grand rounds, so they were not consciously aware that it had any influence on their decisions.

If conflicts of interest in medicine can indeed be understood as unconscious and unintentional, how might that affect how policy makers approach dealing with them?

IMPLICATIONS FOR POLICIES DEALING WITH MEDICAL CONFLICTS OF INTEREST

Short of eliminating conflicts of interest altogether, there are several interventions that universities, professional societies, and other policy makers frequently employ to guard against the inappropriate influence of industry on medical practice and research. These interventions may be implicitly predicated on the view that succumbing to conflicts of interest is a conscious choice, however, and thus they may have limited or surprising effects if physicians are subject to unconscious bias. The psychological research reviewed here suggests that policy makers may wish to be cautious in their expectations of success for these policies, as they are not tailored to deal with unconscious bias. Policy makers may also wish to consider some possible perverse consequences that can result from using these interventions.

Education

Educational initiatives can be thought of as taking two forms: substantive education in ethics and education aimed specifically at describing and explaining institutional policies and enforcement and individual responsibilities.

Perhaps the biggest barrier to the effectiveness of teaching about bias specifically is the bias blind spot. Certainly, some value exists in teaching physicians about potential conflicts of interest when they are dealing with industry. Simply knowing about the potential for bias, however, does not

prevent one from being biased. The bias blind spot (Pronin et al., 2002) research described earlier suggests that simply teaching about biases is more likely to help physicians recognize bias in other physicians than in themselves. The blind spot suggests one reason why many physicians deny that they are personally influenced by gifts from industry, despite evidence that gifts and interactions do influence decision making (e.g., Orlowski and Wateska, 1992; Caudill et al., 1996; Wazana, 2000).

Even if people are taught about bias, they are still prone to it. Navigating relationships with industry and accepting gifts while remaining completely objective, then, is not a simple imperative that physicians can be easily trained to follow. Indeed, the research of Loewenstein et al. (1992) suggests that knowing about bias is not sufficient to prevent it even if one is determined to be objective. Thus, recommendations for physicians, such as "If nominal gifts are accepted, make certain that they do not influence your prescribing or ordering of drugs" (Marco et al., 2006), are not practical. Perhaps an effective use of education is to help physicians recognize which relationships lead to bias so that those relationships may be preemptively avoided.

There is, however, some indication that teaching specifically about the unconscious aspect of bias could help in one respect (Pronin and Kugler, 2007). That is, limited evidence suggests that such teaching reduces the gap between perceptions of bias in self and others, and thus, education could reduce the sharpness of disagreement about whether bias exists.

Education aimed at conveying institutional guidelines about the receipt of gifts has produced mixed results. On the one hand (Brett et al., 2003; Agrawal et al., 2004; Schneider et al., 2006), after successfully completing such educational initiatives, residents can identify practices that are appropriate and inappropriate consistent with institutional guidelines. On the other hand, these behaviors, which are mostly of a self-report nature on a survey, do not suggest much about how residents will behave, and several authors have raised questions about how long lasting these effects are (Agrawal et al., 2004; Schneider et al., 2006; Carroll et al., 2007). Furthermore, it seems that there are also some perverse effects from familiarizing students with how to interact with industry. Although theirs was not a study about education as such, Fitz et al. (2007) found that even though clinical and preclinical students had the same knowledge about industry, their attitudes about the appropriateness of gifts could still differ, with clinical students far more likely to believe that accepting gifts is appropriate. Hyman et al. (2007) found that although students generally believed that they were not educated enough to deal with industry, students who reported feeling better educated about the pharmaceutical industry were less skeptical about the industry and were more likely to view interactions with the

pharmaceutical industry as appropriate. We cannot tell from this sort of self-reporting what the exact nature of this education was.

When guidelines are voluntary, many physicians interact with industry without familiarizing themselves with the guidelines. Morgan et al. (2006) found that although most physicians had contact with the pharmaceutical industry—as evidenced by the fact that more than 93 percent of them had received drug samples—less than two-thirds were aware of the guidelines for interaction with the industry set forth by the college to which the physician belonged, and only one-third were familiar with the guidelines of the American Medical Association. Therefore, requiring education on the content of the guidelines might be a useful point of intervention if many physicians are unaware of them.

Penalties

Deterring bias through punishment is more likely to be effective if people are knowingly influenced by financial considerations. The psychological research reviewed above, however, suggests that bias due to conflicts of interest can often arise unconsciously and unintentionally, such that people cannot overcome bias even when it is in their best interest to do so. One concern, then, is that aligning self-interest with guidelines through punishment may not be as effective as we would wish.

Perhaps even more difficult, though, is establishing whether a case of bias exists. Research identifies statistical evidence of bias by analyzing aggregated sample information, ideally against some control sample. That is much different from establishing that an individual is biased. Law typically requires that each case be considered individually, but without adequate comparisons, it cannot be established that a physician's beliefs and practices were unduly influenced by nonproscribed relationships with industry, as opposed to being genuine and objective. The prospect of penalties can, of course, help deter cases of blatant corruption and may encourage conformance to policies requiring disclosure of financial interests. The vast majority of industry's influence on physicians, however, is likely of a more nuanced nature, the result of basically ethical individuals being subtly biased. There are thus serious barriers to effective penalties.

Disclosure

One common policy response is to require physicians with potential conflicts of interest to disclose them to those whom they advise. In this way, patients or those hearing a presentation can consider the potential for bias, and the physician may perhaps be mindful of this when he or she enters into relationships with industry. For several reasons, this policy is

problematic, and disclosure may be largely ineffective by itself and in some instances could have perverse effects.

As an example, consider a physician who advises a patient to pursue some treatment and discloses a possible financial conflict of interest. How should the patient rationally discount the physician's advice in light of the disclosure? Even if the physician has private incentives, it does not follow that the advice is not genuine. Furthermore, even if the physician is likely to be biased, that does not mean that the advice is incorrect. Often it will be the case that the patient can either take or ignore the physician's advice, and the disclosure does little to alleviate uncertainty. In addition, patients are in often a vulnerable situation with a need to trust their physicians.

Forcing the physician to disclose a possible conflict of interest may also have perverse effects. For example, now that the disclosure has taken place, the physician may expect that the patient will be skeptical and respond by making the message more forceful, a sort of strategic exaggeration (Cain et al., 2005). If patients metaphorically cover their ears, physicians who believe that they must get their message across will yell louder. Although the exaggerated advice may perhaps be discounted, it may still be followed.

Decades of psychological research on anchoring and insufficient adjustment has shown that when judgment begins from even a random anchor that people know is incorrect, judgment will not be adjusted sufficiently far from the anchor. For example, experimenters ostensibly spun a wheel of fortune that actually always landed on 65 or 10 and then asked two questions (Tversky and Kahneman, 1974): "Is the proportion of African nations in the United Nations less than or greater than (10/65)?" and "What is the proportion of African nations in the United Nations?" The median response when the wheel was spun to 10 was much lower (25) than the median response when the wheel was spun to 65 (45). Although the subjects did adjust away from the implausible anchors that they were given, they were still affected by those anchors, even though they knew that the values of the anchors were irrelevant. This effect is one of the strongest in the judgment and decision-making literature. One implication, then, is that even if advisees know that the advice is exaggerated, they will still be influenced by it.

An experimental study of the effects of disclosure has found just that (Cain et al., 2005). Experimental "advisers" were asked to give advice on the worth of a jar of coins that they could get close to and hold. Their advisees earned money by accurately guessing the value in the jar, whereas the advisers earned money by inducing higher guesses from the advisee. Perversely, when advisers had to disclose these incentives, advisees were made significantly worse off. This effect was in part due to the fact that the advisers exaggerated their advice in light of disclosure, whereas the advisees were unable to sufficiently adjust down from the inflated advice.

Limiting Gifts by Size or Use

Policies on gifts often suggest that any gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value. Certainly, small gifts are preferable to large gifts. Because bias is unintentional and not a matter of corruption, however, small gifts may still produce results and therefore should not be assumed to be benign. Katz and colleagues (2003) reviewed and synthesized a sizeable body of social science literature that suggests that small gifts induce feelings of reciprocity, get a message across by mere exposure (pens, notepads, etc.), and can be effective in changing behavior. Even the sheer ubiquity of trinkets like pens and notepads suggests that this is true. Why else would profit-minded entities who conduct market research on their practices continue to supply them if their efforts did not fetch a return?

The ethical distinction of a gift having versus not having a primary patient benefit, though intuitively appealing, may also be meaningless. The distinction may reveal a lack of appreciation of the fungibility of money, as first pointed out in Thaler's treatise on mental accounting (1980). For example, if a physician receives a $100 anatomical model, then he or she does not have to buy it, and that frees up $100 to buy something else for themselves, such as a golf bag or a nice dinner. This situation is consequentially equivalent to the company giving the physician an inappropriate monetary gift, even though our intuitions may tell us that the latter is much worse because we place it in the "extravagance" account rather than the "patient care" account. The research evidence cannot tell us what is ethical, but the policy maker should keep in mind that any gift is still a gift, because the economic value is exchangeable whether it is received in the "extravagance" account or the "patient care" account.

Even gifts with clear patient benefit—like the ubiquitous drug sample—have been associated with problems. Physicians and their staff frequently end up using the samples that are intended for patients (Westfall et al., 1997), which can also provide a covert means for pharmaceutical representatives to supply physicians with free medications for personal or family use. Furthermore, there is evidence that physicians with access to drug samples will end up prescribing more advertised, expensive drugs in the future (Adair and Holmgren, 2005), so that these gifts can also drive up health care costs.

Limitations on the size and use of gifts may not be a bad policy in terms of limiting corruption, but there may still be influence associated with gifts that are permitted under many current policies.

METHODS AND LIMITATIONS OF THE DATA

A common problem with data from psychology experiments is that they overly rely on college undergraduates as a sample of convenience. This problem is perhaps serious in that it raises questions about the generality of the results. Whereas care should be used in extrapolating the findings of experiments conducted with populations composed entirely of college students, there are reasons to take the findings on unconscious bias seriously. First, the phenomenon in question is less likely to suffer from a lack of generality because it is proposed to be a function of the human brain and is not dependent much on context or experience. Because the brain development of college students has mostly been completed, these findings should hypothetically generalize to older adults. Second, absent a theory of how physicians differ from other college students, there is no reason to suspect that they will not be subject to unconscious bias. As support for this idea, the applicability of the psychological research to other professionals (auditors) was also drawn into question when findings of unconscious bias were suggested as a cause for financial malfeasance. Yet, when a study was done with a sample of actual auditors (Moore et al., 2006), the findings of bias were much as what would be expected in the laboratory with college students.

Perhaps more importantly, the types of decisions and incentives studied in psychological experiments are considerably different in quality from the treatment decisions made by physicians who have relationships with industry. The intention of this paper is not to overstate the similarity between the two. That does not mean, however, that the concept of unconscious bias does not raise valid concerns over how to deal with conflicts of interest. Indeed, the fact that the findings from research on bias in medicine (and other professions) mirror the findings from the psychological research on bias suggests that the concept of unconscious bias is a good tool to be used to obtain an understanding of conflicts of interest in medicine.

CONCLUSIONS

Psychological research tells us that people are prone to having optimistic biases regarding themselves, including judgments about whether their own behavior is objective. A large body of literature has shown that these biases are unconscious and unintentional: people fall prey to them even when they do not want to or think that they do. Although it may seem to be intuitively and easily recognized that people are biased in assessing themselves, the fact that these biases are often unconscious and unintentional is not intuitive and is largely underappreciated. The findings of research on the influence of industry on medical practice corresponds closely to the

findings of psychological research, suggesting that we might view the biasing effect of conflicts of interest in medicine to result from an unconscious and unintended bias.

Although this view is kind to physicians, in that it allows the biased individual to be understood as basically being well intended, it is also a cause for concern, in that research suggests that such unconscious biases are quite difficult to combat on the large scale. For example, teaching about egocentric biases does not mitigate them because when we examine ourselves, we do not experience ourselves as being biased. This distinction is not merely an academic argument about human nature; several policies that we expect to combat the effects of conflict of interest may not be effective if unconscious bias is an important factor, and the effects of these policies could even be perversely counterproductive. Policy makers may benefit from recognizing and accommodating a more psychologically nuanced view of conflicts of interest in their interventions.

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E

The Pathway from Idea to Regulatory Approval: Examples for Drug Development

*Peter Corr and David Williams**

IN BRIEF: FROM IDEA TO MARKET AND CLINICAL PRACTICE

For small-molecule drugs, the path to a marketed drug involves a long and exhaustive journey through basic research, discovery of the medicine, preclinical development tests, increasingly complicated clinical trials with humans, and regulatory approval by the Food and Drug Administration (FDA). Several years—usually 10 to 15—and hundreds of millions of dollars later, under the best of circumstances, a new drug will be approved for marketing. Because of its complexity, drug discovery and development is widely recognized as one of the most financially risky endeavors in all of science and a major challenge for the biomedical industry. Much of this cost comes from failures, which account for 75 percent of the total research and development costs. Although these failures are disappointing and costly, they still contribute to the body of knowledge on disease processes. Academic health centers and research institutions play major roles in defining the targets applicable for small molecules and carrying out the clinical trials that are needed. The discovery and development process for therapeutic proteins or biologics is similarly long and difficult, and success is far from certain. Biologics are derived from living sources, including humans, other animals, bacteria, and viruses. From these sources come products such as vaccines and monoclonal antibodies, which also are regulated by the FDA. Academic health centers and research institutions have led the development of many biological agents, many of which have been successfully codeveloped with pharmaceutical and biotechnology companies.

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Medical devices include a range of technologies, from surgical gloves, syringes, and thermometers to sophisticated prosthetics, imaging equipment, artificial heart valves, and electronic neurostimulators. Reflecting this diversity, the path from idea to product development for medical devices can be quite variable and quite different from that for drugs and biologics. The same is true for the extent of collaboration among academic, industry, and government researchers. Before they can market complex devices, device manufacturers must seek either premarket clearance (which is most common and which generally does not require clinical data) or premarket approval (which is required for only a small number of devices—often implanted devices—and which does require clinical data) from the FDA. As is the case for drugs, obtaining premarket approval is a complicated process that can take many years. For complex medical devices, the research team may include physicists, materials scientists, engineers, and mathematicians, as well as biologists and physiologists. Physicians often play a critical role in defining the needs for devices and the initial testing of prototypes in human clinical trials. In some cases, the basic idea for important medical devices can come from individuals who are not involved in basic or clinical research. For example, the idea (and crude first model) for a device to drain the buildup of cerebrospinal fluid in individuals with hydrocephalus came from a self-described mechanic who was the parent of an affected infant (Baru et al., 2001).

The following sections briefly describe the sequence of events for small-molecule drugs from concept to a marketed product. Figure E-1 (developed by the authors) depicts the process in graphic form for each of the following seven sections. (A more thorough review of the research and development process for small molecules, therapeutic proteins, vaccines, medical devices, and diagnostics can be found at www.rdguide.org.)

BASIC RESEARCH: THE IDEA

Long before a new drug can even be imagined, scientists are working to gain a basic understanding of a disease or of specific normal chemical pathways that are subverted in an abnormal cell. This research might be conducted in academic laboratories and research institutes around the world, and some of it is paid for by industry. Industry also plays a large role in the development of novel technologies, such as new approaches to sequencing of the human genome.

Along the road toward developing new medications, researchers have to acquire a basic understanding of bacterial, animal, and human genomes. They study which genes are involved in specific diseases. They also look at how gene products—or proteins—contribute to the derailments in cellular processes that result in the initiation or maintenance of a disease.

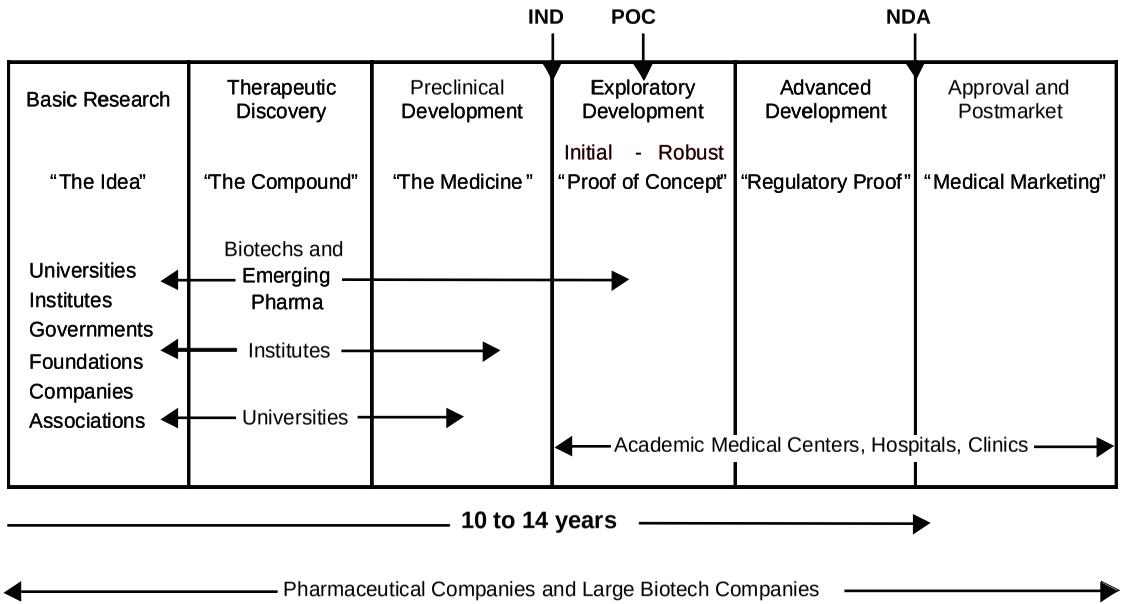

FIGURE E-1 Defining biomedical research from idea to market. IND = Investigational New Drug application; POC = proof of concept; NDA = New Drug Application; Pharma = pharmaceutical companies. SOURCE: Adapted from Corr, 2008.

In a kind of medical reconnaissance mission, biologists seek out and identify targets that might be attacked with a new drug. These targets are proteins, as well as the genes that define how those proteins are structured. Either may play a role in the onset or progression of a particular disease.

Until recently, researchers were limited to studying the biology (the function or the structure of molecules and cells) of only about 500 target proteins or genes. Now, with scientific advances, such as knowledge of the sequence of the human genome, the number of available biological targets has soared. Despite these gains, however, researchers still know very little about the role that many of these new targets play in causing or maintaining diseases.

Once researchers have identified a target, they then validate them by determining whether the target is relevant to the disease that they are studying. They must then determine if a drug could affect the target enough to alter the course of the disease. To do this, they use biochemical, cellular, or animal models to validate the biological mechanism of the target gene or protein.

Box E-1 summarizes an example of successful, extended, and complex collaboration that involved scientists from the National Institutes of Health as well as academic and industry scientists. Chapter 4 of the committee report cites additional examples.

Searching for Compounds

When a potentially relevant target for an identified disease is validated, chemists then mount a massive search for chemicals that might modify the target or targets. They screen vast compound libraries to develop a list of potential chemicals that might some day become a new medicine. This sophisticated process can be divided into three distinct steps: (1) development and maintenance of large compound libraries, (2) specific assay development, and (3) high-throughput screening.

Assays are analyses that quantify the interaction of the biological target and the compound that the researchers are investigating. They also might measure how the presence of the compound changes the way in which the biological target behaves.

The chemical compounds tested in these assays are maintained in large compound libraries, some of which contain more than 5 million chemicals. Products from natural sources like plants, fungi, bacteria, and sea organisms can be integrated within compound libraries. Most compounds, though, are derived through the use of chemical synthesis techniques, in which researchers create chemical compounds by manipulating chemicals. They might also use combinatorial chemistry, in which researchers create

BOX E-1
Case Example of Successful Collaboration in Drug Discovery and Development

In 2002, the biotechnology company Sugen and the Salk Institute published the human kinome, a subset of the human genome (Manning et al., 2002). Kinases regulate proteins and, in turn, have multiple functions in cells in both the normal and the disease states. On the basis of that work, scientists now know that there are 518 kinases in humans. These findings have revolutionized the approach to the inhibition of these kinases by drugs used to treat cancer and other diseases and that are currently on the market.

Elsewhere, researchers knowledgeable about patients with severe combined immunodeficiency disease (popularly referred to as the "bubble boy syndrome") had identified these patients as having mutations within the JAK-3 kinase, which suggested that a possible mechanism for affecting the deficiency of the immune system could be achieved through a JAK-3 inhibitor (Russell et al., 1995). This research was done at the National Institutes of Health.

Industry scientists at Pfizer spent several years discovering a compound that is active against JAK-3. The goal was to find a compound that would not block JAK-1 or JAK-2 kinase but that would be effective as an immunosuppressant by specifically and partially blocking JAK-3 without causing severe side effects.

Pfizer focused first on the drug's role as a potential antirejection drug for patients who have received an organ transplant. It collaborated with the transplant center at Stanford University to conduct studies with primates, with promising results (see, e.g., Borie et al. [2004]). The drug is being tested with human transplant recipients. It is also being investigated as a treatment for rheumatoid arthritis (see, e.g., Changelian et al. [2008] and Stanczyk et al. [2008]).

new chemical compounds in large masses and test them rapidly for desirable properties.

Testing of the expanding number of available biological targets against millions of chemical entities requires some highly sophisticated screening methods. Researchers use robotics, for example, to simultaneously test thousands of distinct chemical compounds in functional and binding assays. Many times, academic researchers with expert knowledge of specific pathways may guide the development of assays in collaboration with industry.

The chemical compounds identified through this kind of screening can provide powerful research tools that help provide a better understanding of biological processes. This, in turn, may lead to new targets for potential drug discoveries.

The purpose of this chemistry stage is to refine the compound. Hundreds and possibly thousands of related compounds may be tested to determine if they have greater effectiveness, less toxicity, or improved pharmacological behavior, such as better absorption after a patient takes the drug orally.

To optimize the molecules being investigated, scientists use computers to model the structure of the lead compounds and how they link to the target protein. This approach to structure-based design is known as in silico modeling (the word "silico" refers to the silicon technology that powers computers). This kind of structural information gives chemists a chance to modify the molecules or compounds selected in a more rational way. Lead optimization produces a drug candidate that has promising biological and chemical properties for the treatment of a disease.

The drug candidate is then tested for its pharmacokinetic behavior in animals, including its gastrointestinal absorption, body distribution, metabolism, and excretion. It is also tested for its pharmacodynamics, which refers to the relative effectiveness of the molecule.

Preclinical Studies: The Medicine

Once a single compound is selected, preclinical studies are performed to evaluate a drug's safety, efficacy, and potential toxicity in animal models. These studies are also designed to prove that a drug is not carcinogenic (i.e., it does not cause cancer when it is used at therapeutic doses, even over long treatment intervals), mutagenic (i.e., it does not cause genetic alterations), or teratogenic (i.e., it does not cause fetal malformations). Because a patient's ability to excrete a drug can be just as important as the patient's ability to absorb the drug, both of these factors are studied in detail at this stage of preclinical development.

Preclinical studies also help researchers design proposed Phase I studies to be conducted with human. For example, preclinical studies with animals help determine the initial dose to be evaluated in the clinical trial and help identify safety evaluation criteria. The latter include factors such as patient signs and symptoms that should be monitored closely during clinical trials.

The result of work at this stage is a pharmacological profile of the drug that will be beneficial long into the drug's future. Researchers can use the profile to develop the initial manufacturing process and pharmaceutical formulation to be used for testing with humans. Industry has particular strengths in these areas, and most development efforts at this stage are based in biotechnology or pharmaceutical companies. They can also use specifications assigned in this stage to evaluate the chemical quality and purity of the drug, its stability, and the reproducibility of the quality and

purity during repeat manufacturing procedures. At this stage, and before testing with humans begins, an Investigational New Drug (IND) application is filed with the FDA. If the IND application is approved, then clinical trials can begin.

Phase I Clinical Trials: Safety

Phase I trials are the first time that a drug is tested in humans. These trials may involve small numbers (20 to 100) of healthy volunteers, or they may include patients with specific conditions for which targeted pathways have been identified as potentially relevant to the disease under study. A Phase I study may last for several months. The focus of a Phase I study is the evaluation of a new drug's safety, the determination of a safe dosage range, the identification of side effects, and the detection of early evidence of effectiveness if the drug is studied in patients with disease, for example in patients with cancer. From Phase I clinical trials, researchers gain important information about

- the drug's effect when it is administered with another drug (the effect is often unpredictable and sometimes results in an increase in the action of either substance or creates an entirely new adverse effect not usually associated with either drug when it is used alone);
- the drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) to better understand a drug's actions in the body;
- the acceptability of the drug's balance of potency, pharmacokinetic properties, and toxicity or the ability of the drug to zero in on its target and not another biological process; and
- the tolerated dose range of the drug to minimize its possible side effects.

Phase II Clinical Trials: Proof of Concept

In Phase II clinical trials, the study drug is tested for the first time for its efficacy in patients with the disease or the condition targeted by the medication. These studies may have up to several hundred patients and may last from several months to a few years. They help determine the correct dosage, common short-term side effects and the best regimen to be used in larger clinical trials. This usually begins with Phase IIa clinical trials, in which the goal is to obtain an initial proof of concept (POC). The POC demonstrates that the drug did what it was intended to do, that is, interacted correctly with its molecular target and, in turn, altered the disease. Phases I and IIa are sometimes referred to as "exploratory development." The Phase IIb

trials are larger and may use comparator agents and broader dosages to obtain a much more robust POC.

Phase III Clinical Trials: Regulatory Proof

Phase III clinical trials are designed to prove the candidate drug's benefit in a large targeted patient population with the disease. These trials confirm efficacy, monitor side effects, and sometimes compare the drug candidate to commonly used treatments. Researchers also use these clinical trials to collect additional information on the overall risk-benefit relationship of the drug and to provide an adequate basis for labeling after successful approval of the drug.

Phase III studies are conducted with large populations consisting of several hundred to several thousand patients with the disease or the condition of interest. They typically take place over several years and at multiple clinical centers around the world. These studies provide the proof needed to satisfy regulators that the medicine meets the legal requirements needed to be approved for marketing. The study drug may be compared with existing treatments or a placebo. Phase III trials are, ideally, double blinded; that is, neither the patient nor the researcher knows which patients are receiving the drug and which patients are receiving placebos during the course of the trial. Phase III trials are usually required for FDA approval of the drug. If the trials are successful, then a New Drug Application is submitted to the FDA. The process of review usually takes 10 to 12 months and may include an advisory committee review, but such a review is at the discretion of the FDA.

Phase IV Clinical Trials: Marketing and Safety Monitoring

Phase IV trials are studies conducted after a drug receives regulatory approval from the FDA. They may be used primarily for medical marketing. In some cases, the FDA may require or companies may voluntarily undertake postapproval studies to generate additional information about a drug's long-term safety and efficacy, including its risks, benefits, and optimal use. These studies may take a variety of forms, including studies that use data from the administrative databases of health plans as well as observational studies and additional clinical trials.

Postapproval trials may also be designed to test the drug with additional patient populations (e.g., with children), in new delivery modes (e.g., as a timed-release capsule), or for new uses or indications (i.e., for the treatment of a different medical condition). Because these postapproval trials are intended to provide the basis for FDA approval of further uses or

delivery modes, they must meet the same standards as the Phase III trials conducted for initial approval.

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F

Model for Broader Disclosure

This appendix has two parts. The first is a proposal by three committee members for a model for broader disclosure of financial relationships and conflicts of interest than is presented in the committee report. The second is a response by the other committee members.

I. A PROPOSED MODEL FOR BROADER DISCLOSURE

Lisa A. Bero, Robert M. Krughoff, and George Loewenstein

We believe that the recommendations in Chapter 3 regarding disclosure of financial relationships or conflicts of interest would be greatly improved if they explicitly called for more extensive and standardized public disclosure by researchers, physicians, and senior officials of institutions. We believe that—with the help of interpretation by the press, public-interest groups, researchers, health care consultants, patient representatives, and other information intermediaries—expanded disclosure would provide important information for physicians, patients, researchers, health plans, regulators, policy makers, financial donors, and others who rely on research, practice guidelines, educational programs, and the quality and efficiency of medical care.

We believe that the recommendations should be extended to a "broader-disclosure model" in which

- The consensus-development process described in Recommendation 3.3 would not only set out the standardized content, formats, and procedures for disclosure to institutions but also design a secure national

online database system that could be used to report the same information to appropriate institutions and to the public.

- The consensus-development process would set out minimum standards as to the data elements that must be reported by people in specific roles (such as physician researchers and hospital administrators) to their institutions and would allow institutions to have higher standards if they so choose.
- Each institution would require that any information on financial relationships or conflicts of interest that must be reported to it—or at least all information included in the consensus-defined minimum standards—also be made available to the public through the online system.

We envision the broader-disclosure model working as follows:

- The first time that a person was required to report information on financial relationships or conflicts of interest to an institution, he or she would register on the secure national online database system; create a profile with name, location, and other nonconfidential information; select a permanent ID; and get a confidential password. The system would have procedures for verifying the person's identity. The person's profile associated with the ID would be sufficient to identify the person to public users of the database. (In the case of physicians, the profile might include a field for the National Provider Identifier number.)
- The person would enter, in a standardized format dictated by the database system, at least the minimum standard information on all financial relationships or conflicts of interest that he or she was required to report to an institution. Depending on the person's role in each institution with which he or she had a relationship, more or less information might be required.
- When the person instructed the database to make any information available to any institution, the same information would automatically become available to the public. (Provisions might be made to protect some details of intellectual property, for example, of a drug formula until patent registration.)
- The person-reported information in the database designed by the consensus-development process would ideally be linked to industry-reported information called for in Recommendation 3.4. One objective of the consensus-development process would be to make it convenient to find—in one place, in one format, for any person—any information reported by the person (to an institution) or by industry. Each database could be used to check the completeness of reporting in the other.

We stress the following elements of the model:

- The model would require public reporting only by persons already required to report to institutions and would not add any reporting burden—just "one more press of the button." In fact, the model would probably reduce the overall burden on people by eliminating the need to re-enter information for reporting to multiple institutions.
- The model would make it easier to report correctly by providing explicit standards and instructions.
- The vast majority of practicing physicians do not have to report relationships or conflicts to institutions, so they would not be required to report to the public.
- The information that people would have to report would be limited to financial relationships and conflicts of interests related to drug, medical-device, or biotechnology companies, not other financial or personal information.
- The person-reported information available to the public would add to what would be reported by industry according to Recommendation 3.4 in that it would include information on equity ownership in companies and testing facilities, patent rights, and other types of interests (see list in Table 3-3), not just payments from industry.
- The system of person-reported information would allow people to incorporate more explanatory material about payments received (for example, reasons for payments for consulting) than would probably be reported by industry.
- The centralized nature of the system would make it easier to update reporting requirements for everyone involved if future consensus-development processes deemed it important to include different types of information in standard reports.
- The model would allow persons who might rely on information on financial relationships or conflicts of interest to obtain it when they want it—for example, before enrolling in a continuing medical education program or long after participating in one, or when meeting with family and friends before or after meeting with a surgeon rather than in the brief time with the surgeon.

We believe this model would be a strong and flexible tool for managing conflicts of interest. In key areas of health care, including those in the conflict of interest charge as the committee has defined it for purposes of this report, we are troubled by the possible harms that might arise from conflicts between commercial interests and patient and public interests. This is true in research, in education, and in the development of practice guidelines. But we believe that in each of these areas, totally eliminating all

conflicts—for instance, removing all industry roles in translational research or barring all educational organizations from having any direct or indirect support from industry (even for research or for an endowed chair)—might involve more change than could be justified in light of how research, education, and medical-care systems have evolved. We conclude that greatly expanded requirements for public disclosure would create incentives and monitoring tools that would reduce the risk posed by some of the conflicts that it might not be practical to eliminate.

As documented throughout this report, there are serious limitations in the accuracy, completeness, comparability, and timeliness of conflict of interest information reported to institutions and to the public—for example, as conflicts are shown in National Guideline Clearinghouse documentation of practice guidelines or as conflicts are reported by speakers in continuing medical education programs. These limitations make it difficult for patients, students, clinicians, and others who might be affected by conflicts to make timely assessments of their presence or severity. These limitations also make it difficult for researchers, the press, policy makers, and others to assess the extent of conflicts and the effectiveness of efforts to manage them. We believe that the broader-disclosure model would help to overcome the limitations of currently available information and that the information made available by the model would encourage and facilitate expanded efforts by researchers, the press, public-interest groups, and other information intermediaries to assess and compare conflict of interest policies and practices of all relevant parties.

Even if information on financial relationships or conflicts of interest were rarely used by patients, physicians, or others to make decisions, the fact of public reporting would probably motivate some researchers, physicians, and senior officials to eliminate unproductive conflicts. The model would also create incentives for people to report to institutions completely and accurately to avoid the risk of being identified as having failed to do so.

We recognize the challenges of reaching broad agreement on standard content, formats, and procedures for reporting in an online system—even if the information would be reported only to institutions and not the public. But we believe, on the basis of academic research and experiences in our own organizations, that the cost of maintaining such a system would be minor. Knowing that the information would be public would encourage organizations to participate in planning and designing the system.

We are aware that proposals for public disclosure often elicit concerns about compromising personal privacy. But most people would not have information on financial relationships or conflicts of interest to report and so would have nothing to report publicly. Most mutual-fund shares, stocks, bonds, bank accounts, salaries from institutions, income from medical

practice, and other forms of assets and income would ordinarily not be reported. We assume that even among people who would have relevant financial interests or conflicts of interest to report, the financial interests involved would usually constitute a relatively minor part of their financial affairs and not be a meaningful indicator of individual or family income or wealth; if this assumption is not accurate, public reporting of the information would be all the more important.

There are numerous examples of public reporting of financial information currently in effect that have not been shown to have substantial adverse consequences or to discourage people from participating in the institutions or programs that require reporting—for example, the required public disclosure of salaries of government employees, the public disclosure of individual contributions to political candidates, the public disclosure (on Internal Revenue Service Form 990) of salaries of higher-paid employees of most tax-exempt nonprofit organizations, and, most pertinent, the currently required public accessibility, under state freedom of information laws, of financial relationships or conflicts of interest reported to state universities and health care systems.

We are not persuaded by arguments that the model would create an unfair imbalance in reporting requirements between physicians who work for institutions and physicians who work only in private practice. We note that physicians who have relationships with universities and other institutions already have reporting requirements (to the institutions and subject to public release in the case of public institutions) that other physicians do not have. And we believe that the distinction between institution-affiliated physicians and other physicians is logical: physicians affiliated with institutions are more likely than other physicians to have equity interests, intellectual-property interests, and other interests that may represent conflicts, whereas reporting by every practicing physician would create a large and burdensome system that would not contribute much public information beyond that expected to be included in the industry disclosures under Recommendation 3.4.

We are aware that there might be concerns about misinterpretation of the disclosed information. In a society with freedom of speech and press, any type of information can be misinterpreted or overemphasized. But we believe that the very discipline of free speech, armed with widely available information, would lead generally to better decisions than would result from less complete information.

II. THE RESPONSE OF THE COMMITTEE MAJORITY TO THE PROPOSED MODEL FOR BROADER DISCLOSURE

Wendy Baldwin, Lisa Bellini, Eric G. Campbell, James F. Childress, Peter B. Corr, Todd Dorman, Deborah Grady, Timothy S. Jost, Robert P. Kelch, Bernard Lo, Joel Perlmutter, Neil R. Powe, Dennis F. Thompson, and David A. Williams

As described in Chapter 3 of the report, the full committee supports the development of a public database for company reporting of payments and generally favors making more information on financial relationships and conflicts of interest public. We do not, however, endorse the proposed broader-disclosure model, which calls for institutions that require disclosure from physicians and researchers to require that those individuals also make their disclosures public each time that they report a financial relationship or conflict of interest to those or any other institutions. (That is, the institution would impose the requirement, but the individual would transmit the information.)

We do not endorse the proposed broader-disclosure model for several reasons. First, most members were not convinced of the value that would be added by the suggested expansion of institutional requirements if the other recommendations made in this report were adopted. According to Recommendation 3.4, pharmaceutical, medical-device, and biotechnology companies would be required to report their payments to various individuals and institutions, and that information would be available in a public searchable database. Depending on how many institutions adopted the additional public-disclosure requirements, the proposed expansion might yield some additional information about relationships or interests, such as holdings in publicly traded stock and possibly some expert-witness fees. Such relationships might already be public in specific contexts, for example, in connection with a journal article or educational presentation. In contrast, congressional action on the Medicare Payment Advisory Commission (MedPAC) proposal for the disclosure of physician-ownership interests in health care facilities would provide information about conflicts of interest that are more likely to influence physician decisions about patient care.

A second concern of the committee majority involved intrusions on privacy if physicians and researchers were required to make public the additional information that they disclose to academic medical centers and other institutions. It is likely that many people will not want further exposure to the risks of identify theft, mischaracterization by the mass media, or other kinds of harm, particularly if the database of expanded disclosures is privately managed. The privacy of family members is also at stake because some institutions require the disclosure of the financial relationships of

spouses or domestic partners and children for some purposes. Managing a secure and up-to-date website with personal information requires resources and expertise to protect against errors in disclosure, to offer ways to correct errors, and to clarify disclosures with supplementary information. If the information becomes public without such safeguards, there could be allegations of intentional deception when honest mistakes occur or when a person discloses information to other institutions that have different requirements or formats for disclosure. A system would also need to protect against the malicious entry of erroneous information. We believe the committee did not have the expertise to investigate many matters like these.

A third concern was the additional cost of expanded public disclosure. For example, the proposed unified database would require that the additional disclosures be approved for integration into a federally mandated and overseen database of company-reported payments, or, alternatively, some party would have to create and manage an integrated, secure private database. Either would involve additional costs for creating, maintaining, updating, and correcting the integrated database and maintaining security. In an era of increasing cost pressures on medical institutions and governments, the committee is not convinced that spending for additional, marginal public disclosures can be justified over such alternatives as spending for electronic medical records. In addition, in the committee's experience, estimates of costs for information systems, even seemingly straightforward ones, often fall short of actual costs.

Fourth, we were concerned about setting up a disparity, in particular, between university faculty and private practitioners and between medical institutions that require additional disclosure and ones that do not. Although it is not clear how many institutions would choose to require physicians and researchers to make public their disclosures to all institutions, the institutions that did so would place an extra burden on people who, for the most part, are faculty members whose relationships and conflicts of interest are already overseen by their academic institutions. In contrast, many physicians in private practice have no reporting requirements and no oversight. Thus, the expansion of disclosure is not targeted to higher-risk situations. Furthermore, unless the additional public reporting of institutional disclosure was mandated by the U.S. Congress, there could be perverse consequences for academic or other institutions that required people to make public the information that they disclose both to those institutions and to other institutions. Some physicians and researchers might be attracted by such transparency; but we believe that others would prefer to work at institutions that kept their disclosures confidential, except when disclosure is required for specific purposes, such as publication of a journal article or participation in the development of a clinical-practice guideline.

Finally, we are concerned about other risks and unintended adverse

consequences of requiring additional public disclosure beyond company-reported payments. For example, the requirement would add to the risk that information from different sources might fail to match exactly because of technical errors or differences in reporting requirements, procedures, or periods.[1] Some might seize on the lack of an exact match as evidence of misbehavior—that is, a deliberately incomplete or inaccurate disclosure—on the part of institutions or individuals, who then might have to respond to public accusations; this would distract from their primary responsibilities for research, education, or clinical care. Misinterpretation already may occur with the reporting of payments by companies to physicians; for example, reporters may treat scientific and promotional consulting as equivalent and deserving of the same criticism.

Overall, the majority of committee members thought that making public the information that physicians and researchers report to institutions was not supported by the principle of proportionality and that responses to conflicts of interest should be based on assessment of their severity. The likely burdens on individuals and institutions of an expanded public-disclosure system beyond that proposed in Recommendation 3.4 or already in place in accordance with other public or private policies are disproportionate to any benefits from the marginal amount of additional information that would be provided.

[1]According to Recommendation 3.3, consistency in institutional disclosure requirements and formats would increase and reporting burdens would decrease for people who must make disclosures to multiple institutions.

G

Committee Biographies

Bernard Lo, M.D. (*Chair*) is professor of medicine and director of the Program in Medical Ethics at the University of California, San Francisco (UCSF). At UCSF, he directs the Research Ethics Component of the Clinical and Translational Sciences Institute, which is funded by the National Institutes of Health (NIH), and he codirects the Policy and Ethics Core, Center for AIDS Prevention Studies. He is national program director of the Greenwall Faculty Scholars Program in Bioethics. He is a member of the Institute of Medicine (IOM), serves on the IOM Council, and has served as chair of the Board on Health Sciences Policy and as chair or member of several IOM committees. He cochairs the Scientific and Medical Accountability Standards Working Group of the California Institute for Regenerative Medicine and serves on the Medicare Evidence Development and Coverage Advisory Committee at the Centers for Medicare and Medicaid Services, the Medical Advisory Panel for the Blue Cross Blue Shield Association Technology Evaluation Center, the Ethics Advisory Committee (uncompensated) for Affymetrix (which develops and supplies genetic research products), and two Data and Safety Monitoring Committees at NIH. In the past he served on the National Bioethics Advisory Committee, the Ethics Working Group of the NIH-sponsored HIV Prevention Trials Network, and the Ethics Committee of the American College of Physicians. Dr. Lo is the author of numerous publications, including *Resolving Ethical Dilemmas: A Guide for Clinicians*. He is board certified in internal medicine and currently teaches courses on clinical ethics and the responsible conduct of research.

Wendy Baldwin, Ph.D., is director of the Population Council's Poverty, Gender, and Youth program. Before coming to the council, she served as executive vice president for research (EVPR) at the University of Kentucky,

Lexington. The EVPR is responsible for grant and contract oversight, including technology transfer and evaluation of conflicts of interest. She also spent three decades at the National Institutes of Health (NIH), completing her service as the deputy director for extramural research, a program that represents more than 80 percent of the NIH budget and that applies conflict of interest policies for researchers who receive NIH funds. Dr. Baldwin, who is a social demographer, has served on the National Research Council Committees on Assessing Behavioral and Social Science Research on Aging and Assessing Interactions Among Social, Behavioral, and Genetic Factors in Health.

Lisa Bellini, M.D., is associate dean for graduate medical education and is also vice chair for education in the Department of Medicine, University of Pennsylvania. Her primary responsibilities revolve around directing educational programs for residents and fellows. She is the program director of the Internal Medicine Residency program, which has 150 residents. In her role as vice chair, she is also responsible for overseeing all of the subspecialty fellowship programs. She spends a large portion of her time teaching trainees at all levels. Given the concentration of her teaching experiences on inpatient services, Dr. Bellini is responsible for the organization and maintenance of inpatient medicine services for over 220 beds and 15,000 admissions per year. In 2005, she assumed responsibility for all of the graduate medical education for the health system. As associate dean, she oversees the education and training of over 850 residents across 61 different programs. Her primary research interests involve the design, implementation, and evaluation of new educational initiatives. Current interests involve issues related to quality of life for the house staff, including sleep deprivation, depression, burnout, and empathy. Her clinical interests include general pulmonary medicine, particularly advanced lung disease.

Lisa A. Bero, Ph.D., is a professor in the Department of Clinical Pharmacy, School of Pharmacy and Institute for Health Policy Studies, School of Medicine, University of California, San Francisco (UCSF). She is vice chair in the Department of Clinical Pharmacy and chair of the UCSF Conflict of Interest Committee. She is also a member of the UCSF Academic Senate Vendor Relations Task Force and has served on numerous institutional and international committees related to conflicts of interest. In addition, Dr. Bero is a member of the World Health Organization (WHO) Essential Medicines Committee and has participated in advising on guidelines related to conflict of interest disclosure for the WHO guidelines development process. She is codirector of the San Francisco Branch of the U.S. Cochrane Center; a member of the Steering Group of the Cochrane Collaboration; and editor for the Cochrane Effective Practice and Organization of Care Group, which

is conducting a meta-analysis of the literature on interventions that are used to change the behavior of health care professionals. She was involved in drafting and incorporating international commentary on the Cochrane Collaboration's Commercial Sponsorship Policy and is currently the funding arbiter for the Cochrane Collaboration. Dr. Bero is a consultant to the *British Medical Journal*. She is a pharmacologist with primary interests in how clinical and basic sciences are translated into clinical practice and health care policy. Her program of research includes examination of the influences on the design and conduct of clinical research and publication of research findings. She also conducts research on university-industry relationships and university conflict of interest policies.

Eric G. Campbell, Ph.D., is an associate professor at the Institute for Health Policy and the Department of Medicine at Massachusetts General Hospital and Harvard Medical School. His main research interests lie in understanding the effects of academic-industry relationships on the processes and outcomes of biomedical research, investigating the effects of local health care market competition on the activities and attitudes of medical school faculty, and understanding the impact of data sharing and withholding on academic science. In addition, he is researching the role of organizational culture in promoting patient safety, and he is participating in a national evaluation of the use of health information technology for the Office of the National Coordinator of Health Information Technology. Dr. Campbell has published numerous articles in professional journals and has delivered numerous presentations at local, national, and international conferences on health care policy, medical education, and science policy. He served on the Institute of Medicine Committee on Alternative Funding Strategies for the U.S. Department of Defense's Biomedical Research Program.

James F. Childress, Ph.D., is the John Allen Hollingsworth Professor of Ethics at the University of Virginia, where he teaches in the Department of Religious Studies and directs the Institute for Practical Ethics and Public Life. He has served as chair of the University's Department of Religious Studies and as codirector of the Virginia Health Policy Center. He is the coauthor of the widely used and cited textbook *Principles of Biomedical Ethics*. Dr. Childress was vice chair of the national Task Force on Organ Transplantation and was a member of the presidentially appointed National Bioethics Advisory Commission (1996 to 2001). He has also served on the board of directors of the nonprofit United Network for Organ Sharing (UNOS), the UNOS Ethics Committee, the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH), the Human Gene Therapy Subcommittee of that committee, and several Data and Safety Monitoring Boards for NIH clinical trials. He is a member of ethics advisory panels for

Roche (on tissue banking and clinical research) and Johnson & Johnson (on stem cell research). He chaired the Institute of Medicine (IOM) Committee on Increasing Rates of Organ Donation, cochaired the National Research Council Subcommittee on Use of Third Party Toxicity Research with Human Test Subjects, and served as a member of IOM committees on assessing genetic risks and establishing a national cord blood stem cell bank program. Dr. Childress is a member of the IOM.

Peter B. Corr, Ph.D., is founder and general partner of Celtic Therapeutics L.L.L.P., a private equity firm focused on the development of innovative therapeutics, the development of alliances that advance solutions for diseases of the developing world, and global advocacy for biomedical innovation. Dr. Corr retired from Pfizer Inc. at the end of 2006, where he served as senior vice president for science and technology. Before that, he served as executive vice president of Pfizer Global Research and Development and president of Worldwide Development. Before joining Pfizer in 2000, Dr. Corr was president of pharmaceutical research and development at Warner Lambert/Parke Davis (until the merger with Pfizer), and he previously served as senior vice president of discovery research at Monsanto/Searle. Dr. Corr also spent 18 years as a researcher in molecular biology and pharmacology at Washington University in St. Louis, Missouri, where he was a professor of medicine (cardiology) and a professor of pharmacology and molecular biology. Dr. Corr owns stock and retains stock options in Pfizer Inc. from his employment at the company, and he sits on the Boards of Directors of CBio, an Australian biotechnology company, and Cibus, an agricultural biotechnology firm headquartered in San Diego, California. His research has been published in more than 160 scientific manuscripts. Dr. Corr serves on the Board of Governors of the New York Academy of Sciences, the Board of Regents of Georgetown University, and several other nonprofit and for-profit boards. He is also a member of the Institute of Medicine's Forum on Drug Discovery, Development, and Translation.

Todd Dorman, M.D., is associate dean and director of continuing medical education as well as a professor of anesthesiology and critical care medicine at the Johns Hopkins Medical Center (JHMC). Among other posts, he is the vice chair for critical care services. Dr. Dorman's research interests include informatics applications in the intensive care unit (ICU), such as remote monitoring of critically ill patients; leadership strategies in the ICU; the creation of a culture of safety; and the application of pharmacokinetic models to drug administration in critically ill patients. He has participated in the development and application of conflict of interest policies in a number of areas within and outside JHMC, including continuing medical education, medical center relationships with commercial entities, guidelines develop-

ment, and scientific journal publication. He served as a co-principal investigator on the project on the effectiveness of continuing medical education funded by the Agency for Healthcare Research and Quality. Dr. Dorman is president of the American Society of Anesthesiologists and vice president of the Society for Academic CME.

Deborah Grady, M.D., M.P.H., is a professor of medicine, associate dean for clinical and translational research, and director of the Women's Health Clinical Research Center at the University of California, San Francisco (UCSF). She is a general internist who provides clinical care for adult women and is an expert on the risks and benefits of postmenopausal hormone therapy. Dr. Grady has received funding for independent research from the National Institutes of Health (NIH) and nonprofit and commercial sources and has led several large, long-term clinical studies. In addition to six current NIH-funded activities, she is currently investigator for one study of the treatment for metastatic breast cancer and two studies of treatments for menopause symptoms that are supported by Bionovo through awards to UCSF under university policies that provide for university ownership of the research data, information, and reports resulting from the research and for independence in the publication of research findings. University policies also state that faculty conducting research that is privately sponsored shall not receive honoraria, consulting fees, or other compensation from the sponsor or serve on any board or in other decision-making capacity for the sponsor during the course of the research. She is one of the directors of the UCSF Clinical and Translational Science Institute and coedited *Designing Clinical Research*, a textbook on clinical research methods. Dr. Grady is also a member of the Executive Committee of the San Francisco Coordinating Center, which provides coordination services for multicenter studies in women's health, aging, and related areas. She has participated in the development of practice guidelines and evidence reviews in a number of areas of women's health and served on the Institute of Medicine committee that assessed the need for clinical trials of testosterone replacement therapy.

Timothy S. Jost, J.D., is the Robert L. Willett Family Professor of Law at the Washington and Lee University School of Law. He is a coauthor of the widely used teaching book, *Health Law*, now in its sixth edition, and is the author of *Readings in Comparative Health Law and Bioethics*, *Health Care at Risk: A Critique of the Consumer-Driven Movement, and Disentitlement*, and the editor of *Health Care Coverage Determinations: An International Comparative Study and Regulation of the Healthcare Professions*. He has written numerous articles and book chapters on health care regulation and comparative health law and policy. Professor Jost was a member of the Institute of Medicine (IOM) committee that assessed and recommended

improvements in the U.S. system for protecting human research participants and was a scholar in residence at the IOM in 2005.

Robert P. Kelch, M.D., is executive vice president for medical affairs at the University of Michigan, Ann Arbor, and chief executive officer of the University of Michigan Health System. He oversees the University of Michigan Hospitals and Health Centers and the University of Michigan Medical School, including their policies governing conflicts of interest in research, education, patient care, and other areas. Earlier, Dr. Kelch served as vice president of the University of Iowa Health System and was previously chair of the Department of Pediatrics at the University of Michigan and physician-in-chief of C. S. Mott Children's Hospital. He has been president of the Society for Pediatric Research and chairman of the American Board of Pediatrics. Dr. Kelch has also served on the American Association of Medical Colleges task force on conflicts of interest as well as numerous other association committees. He is a member of the U.S. Department of Veterans Affairs National Research Advisory Council. His research has focused on pediatric endocrinology. Dr. Kelch is a member of the Institute of Medicine.

Robert M. Krughoff, J.D., is founder and president of Consumers' CHECKBOOK/Center for the Study of Services, an independent, nonprofit consumer organization founded in 1974. The organization publishes local versions of *Consumers' CHECKBOOK* magazine in seven major metropolitan areas (Boston, Massachusetts; Chicago, Illinois; Minneapolis/St. Paul, Minnesota; Philadelphia, Pennsylvania; San Francisco/Oakland/San Jose, California; Seattle/Tacoma, Washington; and Washington, D.C.). The magazine evaluates local service firms such as hospitals, auto repair shops, and banks. The center also has developed the *Consumers' Guide to Hospitals*, *Guide to Health Plans for Federal Employees*, and other materials and services for consumers. Before founding the Center for the Study of Services, Mr. Krughoff served in the U.S. Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services) as director of the Office of Research and Evaluation Planning and as special assistant to the Assistant Secretary for Planning and Evaluation. He currently serves on the board of directors of the Consumer Federation of America (1984 to the present) and has served on the board of directors of Consumers Union, publisher of *Consumer Reports* magazine. He chairs the Technology Assessment Advisory Committee for the ECRI Institute. Mr. Krughoff is a member of the New York Bar and District of Columbia Bar.

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Lawrence Solomon Columnist

THE BLOG

Merck Has Some Explaining To Do Over Its MMR Vaccine Claims

09/25/2014 05:29 EDT | **Updated** 11/27/2014 05:59 EST

Merck, the pharmaceutical giant, is facing a slew of controversies over its Measles-Mumps-Rubella (MMR) vaccine following numerous allegations of wrongdoing from different parties in the medical field, including two former Merck scientists-turned-whistleblowers. A third whistleblower, this one a scientist at the Centers for Disease Control, also promises to bring Merck grief following his confession of misconduct involving the same MMR vaccine.

The controversies will find Merck defending itself and its vaccine in at least two federal court cases after a U.S. District judge earlier this month threw out Merck's attempts at dismissal. Merck now faces federal charges of fraud from the whistleblowers, a vaccine competitor and doctors in New Jersey and New York. Merck could also need to defend itself in Congress: The staff of representative Bill Posey (R-Fla) -- a longstanding critic of the CDC interested in an alleged link between vaccines and autism -- is now reviewing some 1,000 documents that the CDC whistleblower turned over to them.

The first court case, United States v. Merck & Co., stems from claims by two former Merck scientists that Merck "fraudulently misled the government and omitted, concealed, and adulterated material information regarding the efficacy of its mumps vaccine in violation of the FCA [False Claims Act]."

According to the whistleblowers' court documents, Merck's misconduct was far-ranging: It "failed to disclose that its mumps vaccine was not as effective as Merck represented, (ii) used improper testing techniques, (iii) manipulated testing methodology, (iv) abandoned undesirable test results, (v) falsified test data, (vi) failed to adequately investigate and report the diminished efficacy of its mumps vaccine, (vii) falsely verified that each manufacturing lot of mumps vaccine would be as effective as identified in the labeling, (viii) falsely certified the accuracy of applications filed with the FDA, (ix) falsely certified compliance with the terms of the CDC purchase contract, (x) engaged in the fraud and concealment describe herein for the purpose of illegally monopolizing the U.S. market for mumps vaccine, (xi) mislabeled, misbranded, and falsely certified its mumps vaccine, and (xii) engaged in the other acts described herein to conceal the diminished efficacy of the vaccine the government was purchasing."

These fraudulent activities, say the whistleblowers, were designed to produce test results that would meet the FDA's requirement that the mumps vaccine was 95 per cent effective. To the whistleblowers' delight, the judge dismissed Merck's objections to the case

proceeding, finding the whistleblowers had plausible grounds on all of the claims lodged against Merck.

If the whistleblowers win, it would represent more than a moral victory (they repeatedly tried to stop Merck while still in its employ). Under the False Claims Act, the whistleblowers would receive a share -- likely 25 per cent to 30 per cent -- of the amount the government recovers. Previous settlements involving extensive fraud by pharmaceutical companies under the False Claims Act have run into the hundreds of millions of dollars, and in some cases such as against GlaxoSmithKline and Pfizer, into the billions.

The second court case, Chatom Primary Care v. Merck & Co. relies on the same whistleblower evidence. This class action suit claims damages because Merck had fraudulently monopolized the mumps market. Doctors and medical practices in the suit would be able to obtain compensation for having been sold an overpriced monopolized product, and a defective one to boot, in that the mumps vaccine wasn't effective (indeed, the suit alleged that Merck expected outbreaks to occur and, as predicted, they did -- mumps epidemics occurred in 2006 in a highly vaccinated population and again in 2009-2010).

"Plaintiffs have argued sufficient facts to sustain a claim for proximate causation, detailing the significant barriers that other companies would face to enter the mumps vaccine market," the court ruled.

The third whistleblower -- a senior CDC scientist named William Thompson -- only indirectly blew the whistle on Merck. He more blew it on himself and colleagues at the CDC who participated in a 2004 study involving the MMR vaccine. Here, the allegations involve a cover-up of data pointing to high rates of autism in African-American boys after they were vaccinated with MMR. In what could be high-profile House hearings before Congressman Posey's Science Committee -- hearings made all the more explosive given the introduction of race into the mix -- Merck could find itself under unprecedented scrutiny. The CDC still stands by its study although Frank DeStefano, the CDC's Director of Immunization Safety and a co-author in the CDC study, also stated that he plans to review his notes with an eye to reanalyzing the data.

Some say all publicity is good. In Merck's case, regardless of the ultimate merits, the publicity will be all bad.

MORE ON HUFFPOST:

BUSINESS DAY

Glaxo Agrees to Pay $3 Billion in Fraud Settlement

By KATIE THOMAS and MICHAEL S. SCHMIDT JULY 2, 2012

In the largest settlement involving a pharmaceutical company, the British drugmaker GlaxoSmithKline agreed to plead guilty to criminal charges and pay $3 billion in fines for promoting its best-selling antidepressants for unapproved uses and failing to report safety data about a top diabetes drug, federal prosecutors announced Monday. The agreement also includes civil penalties for improper marketing of a half-dozen other drugs.

The fine against GlaxoSmithKline over Paxil, Wellbutrin, Avandia and the other drugs makes this year a record for money recovered by the federal government under its so-called whistle-blower law, according to a group that tracks such numbers.

In May, Abbott Laboratories settled for $1.6 billion over its marketing of the antiseizure drug Depakote. And an agreement with Johnson & Johnson that could result in a fine of as much as $2 billion is said to be imminent over its off-label promotion of an antipsychotic drug, Risperdal.

No individuals have been charged in any of the cases. Even so, the Justice Department contends the prosecutions are well worth the effort — reaping more than $15 in recoveries for every $1 it spends, by one estimate.

But critics argue that even large fines are not enough to deter drug companies from unlawful behavior. Only when prosecutors single out individual executives for punishment, they say, will practices begin to change.

"What we're learning is that money doesn't deter corporate malfeasance," said Eliot Spitzer, who, as New York's attorney general, sued GlaxoSmithKline in 2004 over similar accusations involving Paxil. "The only thing that will work in my view is C.E.O.'s and officials being forced to resign and individual culpability being enforced."

The federal whistle-blower law, officially the False Claims Act, dates to 1863 and was originally envisioned as a check on war profiteering after the Civil War.

Whistle-blowers get a share of any money recovered by the federal government. So far, according to Patrick Burns, spokesman for the whistle-blower advocacy group Taxpayers Against Fraud, at least $10 billion has been agreed to in settlements this fiscal year, which ends in September.

The settlement, which requires court approval, stems from claims made by four employees of GlaxoSmithKline, including a former senior marketing development manager for the company and a regional vice president, who tipped off the government about a range of improper practices from the late 1990s to the mid-2000s.

Prosecutors said the company had tried to win over doctors by paying for trips to Jamaica and Bermuda, as well as spa treatments and hunting excursions. In the case of Paxil, prosecutors claim GlaxoSmithKline employed several tactics aimed at promoting the use of the drug in children, including helping to publish a medical journal article that misreported data from a clinical trial.

A warning was later added to the drug that Paxil, like other antidepressants, might increase the risk of suicidal thoughts in teenagers. Prosecutors said the company had marketed Wellbutrin for conditions like weight loss and sexual dysfunction when it was approved only to treat major depressive disorder.

They said that in the case of Avandia, whose use was severely restricted in 2010 after it was linked to heart risks, the company had failed to report data from studies detailing the safety risks to the F.D.A.

“Today’s multibillion-dollar settlement is unprecedented in both size and scope,” said James M. Cole, the deputy attorney general. “It underscores the administration’s firm commitment to protecting the American people and holding accountable those who commit health care fraud.”

The initial terms of the settlement were announced in November, and Glaxo had already set aside cash for the settlement. In a statement Monday, the company said it has since changed many of its policies, including no longer rewarding sales representatives for the number of drug prescriptions sold.

Andrew Witty, the chief executive, sought to portray the illegal actions as part of the company’s past.

“Whilst these originate in a different era for the company, they cannot and will not be ignored,” he said in the statement. “On behalf of GSK, I want to express our regret and reiterate that we have learned from the mistakes that were made.”

The three criminal charges involved Paxil, Wellbutrin and Avandia and included a criminal fine of $1 billion. The remaining $2 billion involves fines in connection with a civil settlement over the sales and marketing practices of the blockbuster asthma drug Advair and several other drugs.

Part of the civil settlement also includes claims that the company overcharged the government for drugs. Glaxo did not admit any wrongdoing in the civil settlement.

Despite the large amount, $3 billion represents only a portion of what Glaxo made on the drugs. Avandia, for example, racked up $10.4 billion in sales, Paxil brought in $11.6 billion, and Wellbutrin sales were $5.9 billion during the years covered by the settlement, according to IMS Health, a data group that consults for drugmakers.

“So a $3 billion settlement for half a dozen drugs over 10 years can be rationalized as the cost of doing business,” Mr. Burns said.

Mr. Burns and others have said that to institute real change, executives must be prosecuted criminally or barred from participating in the Medicare and Medicaid programs, an action known as “exclusion.”

This has occurred in only a handful of cases, and rarely in a case involving a major pharmaceutical company. In 2011, four executives of the medical device company Synthes were sentenced to less than a year in prison for conducting clinical trials that were not authorized by the Food and Drug Administration.

That same year, the former chief executive of K.V. Pharmaceutical was sentenced to 30 days in jail and fined $1 million for selling misbranded morphine tablets. The previous year, the Department of Health and Human Services excluded him from doing business with the federal government.

Those in the pharmaceutical industry have stressed that the activities revealed in the recent settlements occurred many years ago, and practices have changed radically since then. The Glaxo settlement includes an agreement by the company to withdraw bonuses from top executives if they engaged in or supervised illegal behavior, believed to be a first.

“That creates pressure and it creates an element of responsibility,” said Erika Kelton, who represented two of the four whistle-blowers in the Glaxo case. “I think it’s a good step in the right direction.”

Correction: July 6, 2012

An article on Tuesday about a fine levied on the British drug maker GlaxoSmithKline for illegal marketing of some of its drugs misstated the use of Depakote, an Abbott Laboratories drug involved in a similar case. It is an antiseizure drug, not an antipsychotic.

A version of this article appears in print on July 3, 2012, on Page A1 of the New York edition with the headline: Drug Firm Guilty In Criminal Case.
