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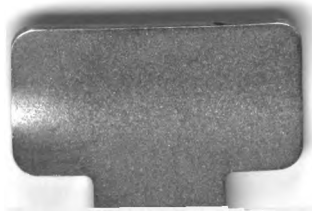
Executive Summary

ADVERSE EVENTS ASSOCIATED WITH CHILDHOOD VACCINES

Evidence Bearing on Causality

INSTITUTE OF MEDICINE



EXECUTIVE SUMMARY
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Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality

Kathleen R. Stratton, Cynthia J. Howe, and
Richard B. Johnston, Jr., *Editors*

Vaccine Safety Committee

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C. 1993

NATIONAL ACADEMY PRESS • 2101 Constitution Avenue, N.W. • WAshington, D.C. 20418

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The project was supported by funds coordinated through the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (contract no. NO1-AI-15130).

This Executive Summary is available in limited quantities from the Institute of Medicine, Division of Health Promotion and Disease Prevention, 2101 Constitution Avenue, N.W., Washington, DC 20418.

The complete volume of *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality*, from which this Executive Summary is extracted, is available for sale from the National Academy Press, 2101 Constitution Avenue, N.W., Box 285, Washington, DC, 20005. Call 800-624-6242 or 202-334-3313 (in the Washington Metropolitan Area).

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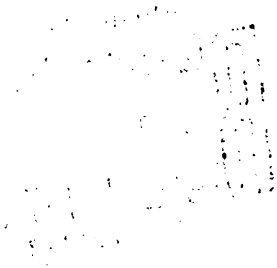
The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.



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PAUL D. STOLLEY,* Professor and Chairman, Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland

Project Staff

Michael A. Stoto, Director, Division of Health Promotion and Disease Prevention
Kathleen R. Stratton, Project Director
Cynthia J. Howe, Program Officer
Dorothy R. Majewski, Project Assistant
Michael K. Hayes, Project Editor
Tamar Lasky, Consultant
Hanaa Elhefni, Consultant

*Member, Institute of Medicine.

Preface

Few would question the profound importance of vaccines to public health. Not only have deaths from the most common childhood infections been almost eliminated, but so have the devastating morbidities of diseases like measles, paralytic polio, and congenital rubella. This revolution has occurred within the life spans of middle-aged Americans, and it has led to major savings in medical costs and gains in work productivity, as well as to reductions in death and suffering.

In the United States this success has been achieved through increased public awareness, continued support of basic and applied research, the capacity of the pharmaceutical industry, and the dedication of the public and private health care workers responsible for administration of the vaccines.

In the 1980s, however, a few concerned citizens in this country began to raise questions about the risks of vaccination. In fact, although the benefits to society were obvious, the risks to individual infants and children had not been well defined. Some parents considered not having their children immunized, and manufacturers threatened to shut down vaccine production because of an increasing number of lawsuits.

In response, the U.S. Congress passed the National Childhood Vaccine Injury Act in 1986 and the Vaccine Compensation Amendments in 1987. This legislation established a federal compensation process for persons judged to be injured by a vaccine. In addition, Section 312 of the Act mandated that the Institute of Medicine should conduct a scientific review of the possible adverse consequences of pertussis and rubella vaccines. The re-

sults of that review were published in 1991. Section 313 of the Act mandated that a second Institute of Medicine committee review possible adverse events associated with the other vaccines commonly given in childhood. This report comprises the deliberations and conclusions of that committee, the Vaccine Safety Committee.

The principal purpose of the committee's work was to describe as precisely as possible, on the basis of all available evidence, the relationships between the vaccines under review and specific adverse events. This led the committee to ask with each vaccine-adverse event pair, "Can administration of the vaccine cause the adverse event?" All available sources of information were analyzed, from epidemiologic studies to unpublished case reports. Final decisions on causality were made by consensus after group discussion of all of the available evidence. In pursuing its conclusions, the committee adopted a neutral stance and maintained that stance consistently through each step in the process, assuming neither the presence nor the absence of a causal relation between the vaccines and the adverse events until the evidence indicated otherwise.

In reaching a conclusion that the evidence favored *rejection* of a causal relation, the committee used only epidemiologic studies (controlled observational studies and controlled clinical trials). In reaching conclusions favoring *acceptance* of a causal relation, however, the committee most commonly relied on case series and individual case reports. This required that the nature and timing of the adverse event were appropriate for causality and that there were no likely alternative explanations for the event. Biologic plausibility was weighed in the overall balance of the determination but was not in itself considered sufficient evidence to accept or reject a causal relation.

As this report describes in detail, it was possible with some of the vaccine-adverse event pairs to reach a conclusion one way or the other—either that the evidence favored rejection (category 3) or that the evidence weighed more or less heavily for acceptance (categories 4 and 5) of a causal relation (see Chapter 2 for explanations of the five categories). With the majority of vaccine-adverse event pairs the evidence was considered inadequate to accept or reject causality. In some instances, the relation has not been well studied and the data are scarce; in others, the data are abundant but the evidence, on the whole, was not conclusive. Category 2 does not distinguish between these two situations, since the conclusion is the same. It could be argued in these cases that since the body of available evidence did not support causality, a causal relation does not exist. It could also be argued that in the absence of evidence favoring rejection of causality, it is possible that the vaccine could cause the adverse event. Both of these interpretations are possible. The committee regrets that this uncertainty may not make it easier to resolve litigation centered on individual instances

of putative causality. However, the stringency of our charge precluded statements beyond what the evidence allowed. Concern about this unfortunate condition of uncertainty has led the committee to urge that more definitive research be done on possible adverse events during the development of new vaccines or vaccine combinations and to urge that efforts to sharpen current postmarketing surveillance systems be accelerated.

This report represents the product of long hard work by committee members and Institute of Medicine staff. The Acknowledgments section lists a large number of other people who contributed to the effort in an important way, including parents who had the courage to remind us that public health measures affect the lives of individual human beings. In addition, the committee has recognized that it owes a special debt to its predecessor, the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. That committee developed a logical system, on the basis of the available evidence, of classifying—and thereby communicating—the nature of the causal relations between vaccines and adverse events. The committee has also recognized that the quality of this report could not have been achieved without the work of the extraordinary staff assigned to us by the Institute of Medicine—Kathleen Stratton, Cynthia Howe, Michael Stoto, and Dorothy Majewski. In particular, Kathleen Stratton, the Project Director, with intelligence, infinite kindness, and untiring persistence, kept the committee to its proper task; and we are deeply grateful.

Whatever its commissioned intent, in the end, the work of the Vaccine Safety Committee will have succeeded if this report contributes to present worldwide efforts to protect children from preventable infections using vaccines that incur the lowest possible risk.

Richard B. Johnston, Jr.
Chairman


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Acknowledgments

The committee would like to thank the following individuals who provided us with information or assistance: Kenneth J. Bart, National Vaccine Program; W. J. Bellini, Centers for Disease Control and Prevention; Bruce Berget, University of Chicago; Else Borst-Eilers, Health Council of The Netherlands; Philip A. Brunell, Cedars-Sinai Medical Center; John Brydon, Demler Armstrong & Rowland, Long Beach, California; Christine Buhk, Sturgeon Bay, Wisconsin; Hilary Butler, Tuakau, Auckland, New Zealand; Kim Chapman, Colorado Springs, Colorado; Robert T. Chen, Centers for Disease Control and Prevention; James D. Cherry, UCLA Medical Center; Kathleen Crozier, Infectious Disease News; Colette Cogliandro, Chesapeake, Virginia; Shannon Dixon, Honolulu, Hawaii; Andrew W. Dodd, Torrance, California; Philippe Duclos, Health and Welfare Canada; Paul Dyken, University of Southern Alabama; Hanaa Elhefni, University of Maryland, Baltimore; Jan Erickson, National Vaccine Information Center; Elaine C. Esber, U.S. Food and Drug Administration; Juhani Eskola, National Public Health Institute, Finland; Geoffrey Evans, Division of Vaccine Injury Compensation; Gerald M. Fenichel, Vanderbilt University/Advisory Commission on Childhood Vaccines; Jesse Ferguson, Milwaukee, Wisconsin; Reinhard Fescharek, Behringwerke AG; Harvey V. Fineberg, Harvard School of Public Health; Barbara Loe Fisher, Dissatisfied Parents Together; Bonnie Plumeri Franz, Ogdensburg, New York; James Froeschle, Connaught Laboratories; Robert Fujinami, University of Utah; Vincent A. Fulginiti, Tulane University/National Vaccine Advisory Committee; Susan Garzonio, Brodhead, Wiscon-

sin; Mark Geier, medical/legal consultant, Silver Spring, Maryland; Cynthia Goldenberg, Laguna Niguel, California; Stephen R. Gordon, Vaccine Adverse Events Reporting System, Ogden BioServices Corporation; Dan M. Granoff, St. Louis Children's Hospital; Marjorie Grant, Determined Parents to Stop Hurting Our Tots; Diane Griffin, Johns Hopkins University; Stephen Hadler, Centers for Disease Control and Prevention; Caroline B. Hall, University of Rochester/American Academy of Pediatrics; Neal A. Halsey, The Johns Hopkins University; Carolyn Hardegree, U.S. Food and Drug Administration; Joanne Hatem, National Vaccine Information Center; Sandra Holmes, Centers for Disease Control and Prevention; Michael Hugo, Schlichtman, Conway, Crowley, and Hugo, Boston, Massachusetts; Terry and Kurt Johnson, Mission Viejo, California; Samuel Katz, Duke University Medical Center/ Advisory Committee on Immunization Practices; Marcel Kinsbourne, Winchester, Massachusetts; Gloria Koslofsky, Norwood, New York; Saul Krugman, New York University Medical Center; Leonard P. Kurland, Mayo Clinic; Walter Kyle, attorney, Franconia, New Hampshire; John LaMontagne, National Institute of Allergy and Infectious Diseases; Kathleen Lane, Spring City, Pennsylvania; Tamar Lasky, University of Maryland, Baltimore; Rosalyn Leiderman, National Library of Medicine; Donald Lindberg, National Library of Medicine; Noel Maclaren, University of Florida; Ruth Macrides, Naples, Florida; Frank Mahoney, Centers for Disease Control and Prevention; Susan Maloney, Rowley, Massachusetts; Andrea Martin, Woodland, California; Dale McFarlin, National Institute of Neurologic Diseases and Stroke; Ann Millan, National Vaccine Information Center; Sandy Mintz, Parents Concerned about the Safety of Vaccines, Anchorage, Alaska; J. Anthony Morris, The Bell of Atri, Inc.; Edward A. Mortimer, Jr., Case Western Reserve University School of Medicine; Robert Moxley, Gage and Moxley, Cheyenne, Wyoming; John Mullen, Centers for Disease Control and Prevention; David Nalin, Merck Research Laboratories; Neal Nathanson, University of Pennsylvania; Elena O. Nightingale, Carnegie Corporation of New York; Abner Notkins, National Institute of Dental Research; Walter A. Orenstein, Centers for Disease Control and Prevention; Mary Pearce, Philadelphia, Pennsylvania; Georges Peter, Rhode Island Hospital/American Academy of Pediatrics; Stanley A. Plotkin, Pasteur M_rieux Connaught Company; John Pollard, University of Sydney Department of Medicine, Sydney, Australia; Arthur L. Prensky, Washington University School of Medicine; Regina Rabinovich, National Institute of Allergy and Infectious Diseases; Vincent Racaniello, Columbia University; Suresh Rastogi, U.S. Food and Drug Administration; Frederick C. Robbins, Case Western Reserve University; Eugene Robin, Stanford University School of Medicine; Amy Scott, U.S. Food and Drug Administration; Martin Smith, Advisory Commission on Childhood Vaccines; William Stevens, U.S. Food and Drug Administration; Peter M. Strebel, Centers for Disease Control and Prevention; Roland Sutter,

Centers for Disease Control and Prevention; Dirk Teuwen, SmithKline Beecham; Klaus V. Toyka, Neurologische Universitatsklinik und Poliklinik im Kopfklinikum, University of Wurzburg; Claudette Varanko, Demler, Armstrong & Rowland, Long Beach, California; Burton A. Waisbren, Milwaukee, Wisconsin; Joel Ward, UCLA Center for Vaccine Research; Steven G. Wassilak, Centers for Disease Control and Prevention; Curtis Webb, Webb, Burton, Carlson, Ledersen & Webb, Twin Falls, Idaho; Robert Weibel, Division of Vaccine Injury Compensation; Susan Weinberg, Baltimore, Maryland; R. P. Wise, U.S. Food and Drug Administration; Peter F. Wright, Vanderbilt University Hospital; Arthur Zahalsky, Southern Illinois University, Edwardsville, Illinois; and Elizabeth Zell, Centers for Disease Control and Prevention. The committee also appreciates the cooperation of the following organizations or institutions: Advisory Commission on Childhood Vaccines; Bell of Atri, Inc.; Centers for Disease Control and Prevention; Determined Parents to Stop Hurting Our Tots; Dissatisfied Parents Together; National Institute of Allergy and Infectious Diseases; National Library of Medicine; National Vaccine Information Center; National Vaccine Program Office; Parents Concerned About the Safety of Vaccines; U.S. Food and Drug Administration; Vaccine Adverse Event Reporting System.

The committee would also like to thank the Institute of Medicine (IOM) staff members whose work supported its deliberations, principally Kathleen R. Stratton, Study Director; Cynthia J. Howe, Program Officer; Dorothy R. Majewski, Project Assistant; and Michael A. Stoto, Director, Division of Health Promotion and Disease Prevention. Others within the IOM and the National Academy of Sciences who were instrumental in seeing the project to completion were Kenneth I. Shine, President of the IOM; Enriqueta C. Bond, Executive Officer; Gary B. Ellis, Former Director, Division of Health Promotion and Disease Prevention; Christopher P. Howson, Deputy Director, Division of International Health; Linda DePugh, Administrative Assistant; Jennifer Holliday, Project Assistant; Jana Katz, intern; Marcia Lewis, Administrative Assistant; Scott Jones and Robert Albritton, computer analysts; Claudia Carl, Michael Edington, and Betsy Turvene, Reports and Information Office; Sally Stanfield, Estelle Miller, and Francesca Moghari, National Academy Press; and Susan Turner-Lowe, Office of News and Public Information. We greatly appreciate the editorial assistance of Michael Hayes. Finally, special thanks are due for the expert assistance of research librarian Laura Baird and library assistants Yauthary Keo, Eileen Moynihan, and Rhashida Beynum.


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Executive Summary

"Our aim, therefore, must be to study these [complications] as fully as possible in the confident expectation that, as in other branches of science, knowledge will bring enlightenment" (Wilson, 1967).

Childhood immunization has been one of the foremost public health measures of the twentieth century. It has allowed control and prevention of many diseases from which morbidity and mortality can be staggering. Medical personnel in the United States currently rarely see a case of the infectious diseases against which the vaccines are directed. Yet, recent measles epidemics on college campuses and in inner cities suggest that vaccine-preventable disease is not to be ignored. The first health initiative of the new presidential administration was to increase funding for childhood immunization programs to boost vaccination rates in the United States, particularly for children under age 2 years.

BACKGROUND AND HISTORY

The public policy debate regarding immunization stretches beyond the question of how to meet the goals of universal immunization. Concern over the safety of pertussis vaccine was long-standing in Great Britain by the time of the 1982 airing in the United States of a documentary entitled "DPT: Vaccine Roulette" (WRC-TV, 1982) and the 1985 publication of *DPT: A Shot in the Dark* (Coulter and Fisher, 1985). Concern has stretched to other vaccines and has spawned the formation of groups of interested citizens throughout the United States, for example, National Vaccine Information Center/Dissatisfied Parents Together, Determined Parents to Stop Hurting Our Tots, Concerned Health Professionals and Others, and Parents

Concerned About the Safety of Vaccines. More articles and books have been published (e.g., Coulter, 1990; Miller, 1992) to alert the public to the potential risks of vaccination.

In 1986, the U.S. Congress passed the National Childhood Vaccine Injury Act (NCVIA; P.L. 99-660) in response to worries about the safety of currently licensed childhood vaccines and in response to the economic pressures that were threatening the integrity of childhood immunization programs. The litigation costs associated with claims of damage from vaccines had forced several companies to end their vaccine research and development programs as well as to stop producing already licensed vaccines. The NCVIA was an attempt to encourage and ensure vaccine production by creating a no-fault compensation program (the National Vaccine Injury Compensation Program) as a required first resort for those who believed that they or their children had been injured by certain vaccines. The need for a compensation program had long been recognized, and several groups had proposed possible mechanisms for compensating people believed to be injured by vaccination (Institute of Medicine, 1985; Office of Technology Assessment, 1980). This program was envisioned to alleviate, but not completely eliminate, manufacturer liability and encourage research and development of more and safer vaccines. The compensation program is administered by the federal government and is financed by an excise tax on the sale of vaccines covered by the program (Iglehart, 1987; Mariner, 1992).

In addition to establishing the compensation program, the NCVIA set forth other vaccine-related efforts to be carried out by the U.S. Department of Health and Human Services, including mandatory reporting of specific adverse events following childhood immunizations against diphtheria, tetanus, pertussis, measles, mumps, rubella, and polio (see box entitled The Vaccine Injury Table in Chapter 10); voluntary reporting of any reaction to any immunization to the Vaccine Adverse Event Reporting System (see Chapter 10 for a discussion of this passive surveillance system and Figure B-1 for a copy of the reporting form); the creation of a National Vaccine Program Office to coordinate federal vaccine initiatives and to help meet immunization coverage goals; the establishment of advisory groups to the National Vaccine Program and the National Vaccine Injury Compensation Program; and better communication of the potential risks of vaccines through public information pamphlets that are distributed at the time of vaccination (under the direction of the Centers for Disease Control and Prevention) and changes in vaccine package inserts (under the direction of the U.S. Food and Drug Administration).

The NCVIA also mandated that the Secretary of the U.S. Department of Health and Human Services enlist the help of the Institute of Medicine (IOM) of the National Academy of Sciences to study the adverse effects of childhood vaccines. The NCVIA called for two specific studies. The first,

mandated under Section 312 of P.L. 99-660, was to address the serious adverse effects of pertussis and rubella vaccines. The Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines published its findings in 1991 (Howson et al., 1991). Appendix A contains the Executive Summary of that report.

The second study, mandated under Section 313 of P.L. 99-660, was to review adverse events associated with other vaccines commonly administered during childhood. The Vaccine Safety Committee, which was charged with performing the second study, was convened early in 1992. The results of that inquiry are provided in this report.

THE CHARGE TO THE COMMITTEE

The members of the interdisciplinary, 14-member Vaccine Safety Committee have expertise in such areas as immunology, pediatrics, internal medicine, infectious diseases, neurology, virology, microbiology, epidemiology, and public health. The committee was charged with (1) reviewing the relevant scientific and medical literature on specific risks to children associated with the vaccines or vaccine components directed against tetanus, diphtheria, measles, mumps, polio, *Haemophilus influenzae* type b, and hepatitis B currently licensed for use in the United States and (2) reviewing the available data on specific risk-modifying factors, that is, circumstances under which administration of these vaccines increases the risk of an adverse event, characteristics of groups known to be at increased risk of an adverse event, and timing of vaccination that increases the risk of an adverse event.

Risk-benefit comparisons or recommendations about immunization schedules were not within the charge to the Vaccine Safety Committee. Despite the name of the committee, many aspects of vaccine safety, such as purity standards or production techniques, also were beyond the committee's charge.

Both IOM studies mandated in P.L. 99-660 entailed the evaluation of the weight of scientific and medical evidence bearing on the question of whether a causal relation exists between certain vaccines and specific serious adverse events. Like the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines, the Vaccine Safety Committee approached its task from a position of neutrality, presuming neither the presence nor the absence of a causal relation between the vaccines and the adverse events under consideration.

THE STUDY PROCESS

Over the course of 18 months, the committee met six times, reviewed more than 7,000 abstracts of scientific and medical studies, read more than 1,700 published books and articles (including many sources in the non-

English literature), analyzed information from U.S. Public Health Service-administered reporting systems for adverse reactions to vaccines, and considered material submitted by interested parties. The committee solicited input from scientists who were invited to participate in two open scientific meetings and from other interested parties at two open public meetings. Details regarding how the committee gathered information are given in Appendix B. All salient information from those reviews is contained in this report.

P.L. 99-660 stated that the review was to include those vaccines covered by the National Vaccine Injury Compensation Program. *Haemophilus influenzae* type b (Hib) and hepatitis B vaccines were added for consideration because of the increasing use of these vaccines and the supposition that in the near future they could be mandatory vaccines covered by the National Vaccine Injury Compensation Program. The list of adverse events investigated for this report derived primarily from negotiations with representatives of the U.S. Public Health Service. However, preliminary investigations into additional adverse events were prompted by queries from interested parties or committee members. After considering the information from these preliminary investigations, the committee added several vaccine-adverse event relations to the original list. Table B-1 in Appendix B contains a complete listing of the specific vaccine-adverse event relations under study.

The report begins with background information. Chapter 2 contains an in-depth discussion of the approach used by the committee to weight the evidence and assess causality. Information on the neurologic disorders and immunologic reactions discussed in much of the report is contained in Chapters 3 and 4. Chapters 5 through 9 include the vaccine-specific evidence and conclusions. All information (evidence, causality argument, and conclusions) regarding death as an adverse event associated with vaccination is contained in Chapter 10.

Adverse Effects of Pertussis and Rubella Vaccines (Howson et al., 1991), the report of the predecessor IOM committee, provides an in-depth review of the literature concerning the adverse events associated with diphtheria and tetanus toxoids and pertussis vaccine (DPT), as well as pertussis vaccine, and should be referred to for conclusions regarding DPT. Appendix A contains the Executive Summary of that report. The charge to the Vaccine Safety Committee was to examine adverse events associated with tetanus toxoid as well as tetanus and diphtheria toxoid combination preparations. The committee reviewed data concerning DPT if the data also concerned diphtheria and tetanus toxoids for pediatric use (DT); however, it was beyond the committee's scope to make conclusions about pertussis vaccine or DPT.

The IOM Committee to Review the Adverse Consequences of Pertussis

and Rubella Vaccines made determinations of causality only for rubella vaccine and the rubella vaccine component of multivalent vaccines, but not for measles-mumps-rubella vaccine (MMR). Thus, the Vaccine Safety Committee reviewed data regarding immunization with MMR as well as data on monovalent measles and mumps preparations. The committee has made separate determinations of causality for the measles and mumps vaccine components for the adverse events for which data were available, particularly if measles or mumps vaccine-strain virus was isolated from the patient. In circumstances in which a causality assessment specific to monovalent measles or mumps vaccine was not possible, this is stated in the conclusion regarding that specific adverse event.

In circumstances in which the committee determined that a component of a multivalent preparation was causally related to a specific adverse event, but there is no direct experience of such an adverse event being caused by the multivalent preparation, the committee states this, but judges that the combined preparation also is causally related to that adverse event.

Many case reports described an adverse event(s) in a patient who received more than one vaccine. A common combination, as a result of the immunization schedules recommended in the United States, is DPT, oral polio vaccine, and Hib vaccine. Assessment of causality in those reports was more difficult than if the patient had received only one vaccine or vaccine component, but the committee considered that the reports could be theoretically supportive of causality for the combination but not in themselves sufficient to allow a firm judgment regarding causality.

CAUSALITY AND WEIGHT OF EVIDENCE

As discussed in detail in Chapter 2, the committee considered four types of evidence: biologic plausibility; case reports, case series, and uncontrolled observational studies; controlled observational studies; and controlled clinical trials. The committee used qualitative and quantitative approaches to weigh each type of evidence. Table 1-1 contains a summary of the different types of evidence for every vaccine-adverse event relation studied. The committee believes that although it is plausible that there is a causal relation between any of the vaccine-adverse event associations under review, plausibility has been demonstrated only for certain ones of these. Therefore, information on the plausibility of a causal relation was classified in Table 1-1 as either theoretical only or as demonstrated. The other types of evidence were classified in Table 1-1 as nonexistent, indeterminate, or as weighing, on the whole, for or against a determination of a causal relation. The consideration of all four types of evidence as a whole led to a conclusion of the final weight of evidence regarding causality. Table 1-2 contains these conclusions.

TABLE 1-1 Summary of the Evidence For or Against a Determination of a Causal Relation[a]

Vaccine and Adverse Event	Biologic Plausibility[b]	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Diphtheria and Tetanus Toxoids[c]			
Encephalopathy	Demonstrated	Indeterminate	Against (DT) No data (Td, T)
Infantile spasms[d] (DT only)	Theoretical only	No data	Against
Residual seizure disorders other than infantile spasms	Theoretical only	Indeterminate (DT, T) No data (Td)	No data
Demyelinating diseases of the central nervous system	Demonstrated	For	No data
Guillain-Barré syndrome	Demonstrated	For (T) Indeterminate (DT, Td)	No data
Mononeuropathy	Theoretical only	Indeterminate (T, Td) No data (DT)	No data
Brachial neuritis	Theoretical only	For (T) Indeterminate (Td) No data (DT)	No data

Arthritis	Theoretical only	Indeterminate	No data
Erythema multiforme	Theoretical only	Indeterminate (DT, Td) No data (T)	No data
Anaphylaxis	Demonstrated	For (T) Indeterminate (DT, Td)	No data
Death from SIDS (DT only)[e]	Theoretical only	Indeterminate	Against
Measles Vaccine[f]			
Encephalopathy	Demonstrated	Indeterminate	Indeterminate
Subacute sclerosing panencephalitis	Demonstrated	Indeterminate	Indeterminate
Residual seizure disorder	Demonstrated	Indeterminate	No data
Sensorineural deafness	Theoretical only	Indeterminate (MMR)	No data
Optic neuritis	Demonstrated	Indeterminate	No data
Transverse myelitis	Demonstrated	Indeterminate	No data
Guillain-Barré syndrome	Demonstrated	Indeterminate	No data
Thrombocytopenia	Demonstrated	Indeterminate (measles) For (MMR)	Indeterminate (measles) No data (MMR)
Insulin-dependent diabetes mellitus	Theoretical only	Indeterminate	Indeterminate

continued

TABLE 1-1 *(continued)*

Vaccine and Adverse Event	Biologic Plausibility[b]	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Anaphylaxis	Theoretical only	For	No data
Death from vaccine-strain viral infection[e]	Demonstrated	For	No data
Mumps Vaccine[f]			
Encephalopathy	Demonstrated	Indeterminate	No data
Aseptic meningitis	Demonstrated	Indeterminate	No data
Residual seizure disorder	Theoretical only	No data	No data
Neuropathy	Theoretical only	No data	No data
Sensorineural deafness	Demonstrated	Indeterminate (MMR)	No data
Insulin-dependent diabetes mellitus	Demonstrated	Indeterminate	Indeterminate
Sterility	Demonstrated	No data	No data
Thrombocytopenia	Demonstrated	Indeterminate	No data
Anaphylaxis	Theoretical only	Indeterminate (MMR)	No data

Polio Vaccine (OPV and IPV)[g]

Guillain-Barré syndrome	Demonstrated (OPV) Theoretical only (IPV)	For (OPV) No data (IPV)	For (OPV) No data (IPV)
Transverse myelitis	Demonstrated (OPV) Theoretical only (IPV)	Indeterminate (OPV) No data (IPV)	No data
Poliomyelitis (OPV only)	Demonstrated	For	No data
Thrombocytopenia (IPV)	Theoretical only	No data	No data
Anaphylaxis (IPV)	Theoretical only	No data	No data
Death from SIDS[e]	Theoretical only	Indeterminate	Indeterminate
Death from vaccine-strain viral infection, including from paralytic polio-myelitis (OPV only)[e]	Demonstrated	For	No data

Hepatitis B Vaccine

Guillain-Barré syndrome	Demonstrated	Indeterminate	No data
Demyelinating diseases of the central nervous system	Demonstrated	Indeterminate	No data
Arthritis	Demonstrated	Indeterminate	No data
Anaphylaxis	Theoretical only	For	No data
Death from SIDS[e]	Theoretical only	Indeterminate	No data

continued

TABLE 1-1 *(continued)*

Vaccine and Adverse Event	Biologic Plausibility[b]	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
Haemophilus influenzae type b Vaccine			
Guillain-Barré syndrome	Theoretical only	Indeterminate	No data
Transverse myelitis	Theoretical only	Indeterminate	No data
Thrombocytopenia	Theoretical only	Indeterminate	Indeterminate
Susceptibility to early Hib disease[h]	Demonstrated	Indeterminate	For (PRP) Against (conjugated)
Anaphylaxis	Theoretical only	Indeterminate	No data
Death from SIDS[e]	Theoretical only	Indeterminate	No data

[a]*Indeterminate* indicates that there is evidence in this category, but the committee did not consider that, on the whole, it weighed either for or against a causal relation. *No data* indicates that the committee did not find data of this type directly bearing on a causal relation between the vaccine and the adverse event.

[b]The committee considered all adverse events to be theoretically plausible and, therefore, classified plausibility in support of causality as either theoretical only or demonstrated. Demonstrated biologic plausibility refers to information on the known effects of the natural disease against which the vaccine is given and the results of animal experiments and in vitro studies.

[c]Unless noted otherwise, the classification for tetanus toxoid (T), diphtheria-tetanus toxoid for pediatric use (DT), and tetanus-diphtheria toxoid for adult use (Td) is the same. The committee was not charged with assessing monovalent diphtheria toxoid or the combined diphtheria and tetanus toxoids and pertussis vaccine (DPT). In Appendix A, see the Executive Summary of *Adverse Effects of Pertussis and Rubella Vaccines* for conclusions about DPT.

[d]Infantile spasms occur only in the age group that receives DT but not Td or T. A possible causal relation between infantile spasms and Td and T was not examined.

[e]In this table, the committee summarizes the data regarding the causal relation between the vaccine and only those deaths that are classified as sudden infant death syndrome (SIDS) or that are a consequence of vaccine-strain viral infection. SIDS occurs primarily in infants too young to receive tetanus and diphtheria toxoids for adult use, measles vaccine, mumps vaccine, or usually, tetanus toxoid. Therefore, a relation between these vaccines and SIDS was not assessed. If the evidence favors the acceptance of (or establishes) a causal relation between a vaccine and an adverse event, and if that adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is limited to tetanus-diphtheria toxoid for adult use and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and oral polio vaccine (OPV) and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *Haemophilus influenzae* type b unconjugated PRP vaccine and early-onset *Haemophilus influenzae* type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See Chapter 10 for details. The data are indeterminate regarding the causal relation between the vaccine and causes of death other than those discussed above. Data regarding death as an adverse consequence of the vaccines under review are discussed in Chapter 10 rather than in the vaccine-specific chapters.

[f]The committee was charged with assessing the causal relation between several adverse events and measles vaccine or mumps vaccine. The committee was not charged with assessing monovalent rubella vaccine. In Appendix A, see the Executive Summary of *Adverse Effects of Pertussis and Rubella Vaccines* for conclusions regarding rubella vaccine. (MMR) indicates that the data derive exclusively from the multivalent preparation.

[g]OPV is oral polio vaccine; IPV is inactivated polio vaccine.

[h]The committee assessed data regarding the increased susceptibility to *Haemophilus influenzae* type b disease within 7 days of immunization with *Haemophilus influenzae* type b vaccine. For this adverse event only, the committee was able to separate the data regarding the unconjugated (PRP) vaccine from the data regarding the conjugated vaccines.

TABLE 1-2 Conclusions Based on the Evidence Bearing on Causality

DT/Td/T	Measles[a]	Mumps[a]	OPV/IPV[b]	Hepatitis B	*H. influenzae* type b
Category 1: No Evidence Bearing on a Causal Relation					
		Neuropathy	Transverse myelitis (IPV)		
		Residual seizure disorder	Thrombocytopenia (IPV)		
			Anaphylaxis (IPV)		
Category 2: The Evidence Is Inadequate to Accept or Reject a Causal Relation					
Residual seizure disorder other than infantile spasms	Encephalopathy	Encephalopathy	Transverse myelitis (OPV)	Guillain-Barré syndrome	Guillain-Barré syndrome
Demyelinating diseases of the central nervous system	Subacute sclerosing panencephalitis	Aseptic meningitis	Guillain-Barré syndrome (IPV)	Demyelinating diseases of the central nervous system	Transverse myelitis
Mononeuropathy	Residual seizure disorder	Sensorineural deafness (MMR)	Death from SIDS[c]	Arthritis	Thrombocytopenia
Arthritis	Sensorineural deafness (MMR)	Insulin-dependent diabetes mellitus		Death from SIDS[c]	Anaphylaxis
	Optic neuritis	Sterility			Death from SIDS[c]

Erythema multiforme	Transverse myelitis	Thrombocytopenia		
		Anaphylaxis[d]		
	Guillain-Barré syndrome			
	Thrombocytopenia			
	Insulin-dependent diabetes mellitus			
Category 3: The Evidence Favors Rejection of a Causal Relation				
Encephalopathy[e]				Early onset *H. influenzae* b disease (conjugate vaccines)
Infantile spasms (DT only)[f]				
Death from SIDS (DT only)[f,g]				
Category 4: The Evidence Favors Acceptance of a Causal Relation				
Guillain-Barré syndrome[h]	Anaphylaxis[d]		Guillain-Barré syndrome (OPV)	Early-onset *H. influenzae* b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine
Brachial neuritis[h]				

continued

TABLE 1-2 *(continued)*

DT/Td/T	Measles[a]	Mumps[a]	OPV/IPV[b]	Hepatitis B	*H. influenzae* type b
Category 5: The Evidence Establishes a Causal Relation					
Anaphylaxis[h]	Thrombocytopenia (MMR)		Poliomyelitis in recipient or contact (OPV)	Anaphylaxis	
	Anaphylaxis (MMR)[d]				
	Death from measles vaccine-strain viral infection[c,i]		Death from polio vaccine-strain viral infection[c,i]		

[a]If the data derive from a monovalent preparation, then in the committee's judgment the causal relation extends to multivalent preparations. If the data derive exclusively from MMR, that is so indicated by (MMR). In the absence of any data on the monovalent preparation, in the committee's judgment the causal relation determined for the multivalent preparations does not extend to the monovalent components.

[b]For some adverse events, the committee was charged with assessing the causal relation between the adverse event and only oral polio vaccine (OPV) (paralytic and nonparalytic poliomyelitis) or only inactivated polio vaccine (IPV) (anaphylaxis and thrombocytopenia). If the conclusions are different for OPV than for IPV for the other adverse events, that is so noted.

[c]This table lists weight-of-evidence determinations only for deaths that are classified as SIDS and deaths that are a consequence of vaccine-strain viral infection. However, if the evidence favors the acceptance of (or establishes) a causal relation between a vaccine and an adverse event, and that adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a vaccine-associated adverse event is limited to tetanus-diphtheria toxoid for adult use (Td) and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and OPV and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *H. influenzae* type b unconjugated PRP vaccine and early-onset *H. influenzae* type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See Chapter 10 for details.

[d]The evidence that establishes a causal relation for anaphylaxis derives from MMR. The evidence regarding monovalent measles vaccine favors acceptance of a causal relation, but are less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

[e]The evidence derives from studies of diphtheria-tetanus toxoid for pediatric use (DT). If the evidence favors rejection of a causal relation between DT and encephalopathy, then in the committee's judgment the evidence favors rejection of a causal relation between Td and tetanus toxoid and encephalopathy.

[f]Infantile spasms and SIDS occur only in an age group that receives DT but not Td or tetanus toxoid.

[g]The evidence derives mostly from DPT. Because there are supportive data favoring rejection of a causal relation between DT and SIDS as well, if the evidence favors rejection of a causal relation between DPT and SIDS, then in the committee's judgment the evidence favors rejection of a causal relation between DT and SIDS.

[h]The evidence derives from tetanus toxoid. If the evidence favors acceptance of (or establishes) a causal relation between tetanus toxoid and an adverse event, then in the committee's judgment the evidence favors acceptance of (or establishes) a causal relation between DT and Td and the adverse event as well.

[i]The data come primarily from individuals proven to be immunocompromised.

The committee organized these conclusions into five categories. Because some confusion has arisen over the meaning of the category descriptions used by the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines, despite extensive explanations in both the footnotes and the text, the Vaccine Safety Committee adopted some minor modifications in wording intended to help in the interpretation of the present report. To facilitate reading by those familiar with the report of the previous committee, the present committee maintained both the number of categories (five) and the order of those categories but modified the wording in an attempt to clarify its meaning. However, the Vaccine Safety Committee (which has some overlap in committee membership and staff with the earlier committee) believes that the categories represent the same concepts intended by the predecessor committee. The categories are:

1. No evidence bearing on a causal relation.
2. The evidence is inadequate to accept or reject a causal relation.
3. The evidence favors rejection of a causal relation.
4. The evidence favors acceptance of a causal relation.
5. The evidence establishes a causal relation.

Chapter 2 contains a discussion of the criteria used by the committee for each determination of the final weight of evidence.

The evidence favors rejection of, favors acceptance of, or establishes a causal relation between a vaccine and an adverse event in approximately one-third of the relations studied. For the other relations the evidence was inadequate to accept or reject a causal relation or there was no evidence bearing on the relation. It is important to note that the use of the term *inadequate* does not necessarily imply that the data were scarce. In some cases the committee identified an abundance of data. However, as a whole, it did not favor either acceptance or rejection of a causal relation. In the lists below, the superscript letters refer to the appropriate notes in Table 1-2. The notes in Tables 1-1 and 1-2 are integral to interpretation of the findings. The committee reached the following conclusions regarding causality.

The evidence favors rejection of a causal relation between:

- diphtheria and tetanus toxoids and encephalopathy,[e] infantile spasms,[f] and death from sudden infant death syndrome (SIDS),[f,g] and
- conjugate Hib vaccines and early-onset Hib disease.

The evidence favors acceptance of a causal relation between:

- diphtheria and tetanus toxoids and Guillain-Barré syndrome[h] and brachial neuritis,[h]
- measles vaccine and anaphylaxis,[d]

- oral polio vaccine and Guillain-Barré syndrome, and
- unconjugated (PRP) Hib vaccine and early-onset Hib disease in children age 18 months or older who receive their first Hib immunization with unconjugated (PRP) vaccine.

The evidence establishes a causal relation between:

- diphtheria and tetanus toxoids and anaphylaxis,[h]
- measles vaccine and death from measles vaccine-strain viral infection,[c,i]
- measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis,
- oral polio vaccine and poliomyelitis and death from polio-vaccine-strain viral infection,[c,i] and
- hepatitis B vaccine and anaphylaxis.

For the vast majority of vaccine-adverse event relations studied, the data came predominantly from uncontrolled studies and case reports. Most of the pathologic conditions studied are rare in the general population. The risk of developing these conditions because of vaccination would *seem* to be low. Without age-specific incidence rates and relative risk estimates, however, it is not possible to calculate the proportion of individuals whose condition is causally related to a vaccine. When the data permitted, such calculations (relative risk, risk difference, and population attributable risk) were made and can be found in the conclusions in Chapters 5 through 9. Because age-specific incidence rates were not available for many of the pathologic conditions studied and because controlled epidemiologic studies of these relations are lacking, few such estimates could be made.

NEED FOR RESEARCH AND SURVEILLANCE

During its attempt to find evidence regarding causality, the committee identified needs for research and surveillance of adverse events. Work in these areas will help to ensure that all vaccines used are as free from the risk of causing adverse events as possible. Some of the needs identified are for increased surveillance of reports of demyelinating disease and arthritis following hepatitis B vaccination, better follow-up of reports of death and other serious adverse events following vaccination, increased use of large databases (currently used only on a small scale) to supplement passive surveillance reporting systems, and disease registries for the rare pathologic conditions studied by the committee.

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