Adverse Events Associated With Childhood Vaccines Other Than Pertussis and Rubella

Summary of a Report From the Institute of Medicine

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In September 1993, the Institute of Medicine released a report entitled *Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality.* The report examined putative serious adverse consequences associated with administration of diphtheria and tetanus toxoids; measles, mumps, and measles-mumps-rubella vaccines; oral polio vaccine and inactivated polio vaccine; hepatitis B vaccines; and *Haemophilus influenzae* type b (Hib) vaccines. The committee spent 18 months reviewing all available scientific and medical data, from individual case reports (published and unpublished) to controlled clinical trials. The committee found that the evidence favored the rejection of a causal relation between diphtheria and tetanus toxoids and encephalopathy, infantile spasms, and sudden infant death syndrome, and between conjugate Hib vaccines and susceptibility to Hib disease. The committee found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and Guillain-Barré syndrome and brachial neuritis, between measles vaccine and anaphylaxis, between oral polio vaccine and Guillain-Barré syndrome, and between unconjugated Hib vaccine and susceptibility to Hib disease. The committee found that the evidence established causality between diphtheria and tetanus toxoids and anaphylaxis, between measles vaccine and death from measles vaccine–strain viral infection, between measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis, between oral polio vaccine and poliomyelitis and death from polio vaccine–strain viral infection, and between hepatitis B vaccine and anaphylaxis. For five vaccine-related adverse events, there was no evidence identified. For the remaining 33 vaccine-related adverse events, the evidence was inadequate to accept or reject a causal relation.

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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 such as measles, paralytic polio, and congenital rubella. This revolution has occurred within the life span of middle-aged Americans, and it has led to major savings in medical costs, gains in work productivity, and reductions in death and suffering.

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 US Congress passed the National Childhood Vaccine Injury Act (Public Law 99-660) in 1986. This legislation had broad impact on childhood vaccination programs and policies and included the establishment of a federal compensation program for those who have been injured by a vaccine.[1] The legislation called for two reviews to be conducted by committees under the aegis of the Institute of Medicine (IOM) of the National Academy of Sciences, Washington, DC. The charge to these committees was to review the medical and scientific evidence regarding the causal relations between childhood vaccines currently administered in the United States and serious health consequences. Neither of these studies was charged with assessing risk-benefit or cost-benefit relations. The results of the first review, *Adverse Effects of Pertussis and Rubella Vaccines*, were released in 1991.[2] Those results have been summarized.[3,4] This article summarizes the second review, *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality.*[5]

The committee conducted its review and analysis over an 18-month period. The 14-member interdisciplinary committee reviewed scientific and medical data bearing on the causal relation between serious health outcomes and diphtheria and tetanus toxoids, measles and mumps vaccines, including measles-mumps-rubella (MMR) vaccine, oral polio vaccine (OPV), inactivated polio vaccine (IPV), conjugated and unconjugated *Haemophilus influenzae* type b (Hib) vaccines, and plasma-derived and recombinant hepatitis B vaccines (HBVs). Altogether, the committee studied 18 serious outcomes putatively associated with those vaccines. Not all of these

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A complete list of the Institute of Medicine committee that conducted the study and associated staff appears at the end of this article.

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outcomes were considered for each vaccine. The list of outcomes was assembled by the committee, IOM staff, and the US Public Health Service.

We review hereinafter the methods used to accumulate the evidence, the framework by which the committee considered causality, the conclusions, and some identified needs for research and surveillance. Readers wishing further explanation of the committee's methods and complete discussion of the evidence are referred to the committee's report, which is available through the National Academy Press, 2101 Constitution Ave NW, Box 285, Washington, DC 20055.

ACCUMULATING THE EVIDENCE

The principal purpose of the committee's work was to describe as precisely as possible, on the basis of all available evidence, the relation between the vaccines under review and the specific adverse events. 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 putative adverse events until the evidence indicated otherwise.

Extensive searches by the IOM librarian of 31 relevant electronic databases identified much of the published literature reviewed by the committee. Each database was searched in its entirety, using deliberately broad search strategies. More than 8000 citations were identified. Approximately one fourth of those were judged to be relevant and were retrieved. A bibliography of cited references organized both by vaccine and by adverse event is available through the National Technical Information Service (5285 Port Royal Rd, Springfield, VA 22161; [703] 487-4650). Articles in the non-English language literature were translated by committee members or by professional translation services. Additional sources for pertinent literature included the personal collections of committee members and reference lists of textbooks and review articles. The committee also reviewed more than 550 unpublished case reports. Some came from interested members of the public; most had been submitted to the Vaccine Adverse Events Reporting System, a passive surveillance system under the supervision of the US Centers for Disease Control and Prevention and the Food and Drug Administration and established by Public Law 99-660. These case reports, coded for the vaccines and adverse events under study, were submitted to the Vaccine Adverse Events Reporting System between its inception in November 1990 and July 1992. Additionally, the committee held four meetings open to the public. At two, the committee encouraged members of the public to speak of their concerns; at the other two meetings, invited scientists spoke on technical issues. Transcripts of these meetings are also available from the National Technical Information Service.

CONSIDERING CAUSALITY

In its approach to determining causality, the committee asked three questions. Can the vaccine cause the adverse event (at least in some people in some circumstances)? Did the vaccine cause the adverse event? Will (or how often will) the vaccine cause the adverse event? The committee's charge was related most closely to the first question. The first and third questions are best answered by epidemiologic studies. A quantitative answer to the third question was rarely possible. Although the committee was not asked to assess causality in individual cases, an affirmative answer to the question of whether the vaccine did cause the adverse event, based on one or more individual cases, means that the first question is answered in the affirmative as well. That is, if the vaccine did cause the adverse event in at least one person, then the vaccine can cause the adverse event. For example, if a patient receives a live viral vaccine, experiences a pathological condition known to be associated with the natural virus, and molecular biological techniques identify virus isolated from the patient as vaccine strain rather than the natural virus, causality between the vaccine and the pathological condition is established for this patient. The logical extension is that if the vaccine did cause the adverse event in this patient, then it can cause the adverse event. Population-based studies that support an affirmative answer to the question of whether the vaccine can cause the adverse event do not, of course, tell whether a vaccine did cause the adverse event in any one specific individual.

As another example, anaphylaxis usually presents within a very short time after exposure to foreign protein, has pathognomonic symptoms, and occurs rarely without obvious exposure.[6] Given an anaphylactic reaction in a short period of time after vaccination and in the absence of other possibly causal antecedents such as drugs or foods, it is easy to assess a positive causal relation between the vaccine and the adverse outcome. Controlled epidemiologic studies are not necessary to show, in these cases, that the vaccine can cause the adverse event. However, controlled studies would be useful to determine how frequently the vaccine causes the events.

The committee evaluated evidence of four main types: biological plausibility; case reports, case series, and uncontrolled observational studies; controlled observational studies (primarily case-control studies and cohort studies); and controlled clinical trials. The committee considered that all of the putative adverse events were biologically plausible, at least theoretically. However, only demonstrated biological plausibility weighed in favor of a causal relation. Demonstrated biological plausibility consisted of evidence concerning the known effects of the natural disease against which the vaccine is directed or results of animal experiments or in vitro studies. Most of the data available were case reports, case series, and uncontrolled observational studies. The committee used qualitative and quantitative means to evaluate the data and weigh the evidence. Meta-analysis was used to pool results from studies where possible. Controlled studies weighed more heavily than uncontrolled studies in the final analysis, but, because controlled studies were rarely available, several conclusions favoring causality were based primarily on case reports.

When categorizing the conclusions regarding the nature of the causal relation between a vaccine and an adverse event, for consistency, the committee maintained the same number and order used by the committee involved in the 1991 IOM report on pertussis and rubella vaccines. However, the conclusions were reworded for clarity. The committee believes it has maintained the intent of the categories used by the 1991 committee. The conclusions are as follows: (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, and (5) the evidence establishes a causal relation.

There is an inherent asymmetry in assessing causality. Very strong evidence in favor of a causal relation can be said to establish a causal relation. Strong evidence would include one or more well-conducted epidemiologic studies that show a significant association between vaccination and the pathological condition under study. As described, case reports can also provide strong evidence to establish a causal relation under certain circumstances.

It is never possible, however, to be as sure about rejecting a causal relation as about establishing one, because even the largest population-based epidemiologic studies have insufficient statistical power to detect extremely rare causes of an outcome (eg, an excess risk of one

Conclusions Based on the Evidence Bearing on Causality*

DT/Td/T	Measles†	Mumps†	OPV/IPV‡	Hepatitis B	Hib
Category 1: No Evidence Bearing on a Causal Relation					
		Neuropathy Residual seizure disorder	Transverse myelitis (IPV) Thrombocytopenia (IPV) Anaphylaxis (IPV)		
Category 2: The Evidence Is Inadequate to Accept or Reject a Causal Relation					
Residual seizure disorder other than infantile spasms Demyelinating diseases of the central nervous system Mononeuropathy Arthritis Erythema multiforme	Encephalopathy Subacute sclerosing panencephalitis Residual seizure disorder Sensorineural deafness (MMR) Optic neuritis Transverse myelitis GBS Thrombocytopenia Insulin-dependent diabetes mellitus	Encephalopathy Aseptic meningitis Sensorineural deafness (MMR) Insulin-dependent diabetes mellitus Sterility Thrombocytopenia Anaphylaxis‖	Transverse myelitis (OPV) GBS (IPV) SIDS§	GBS Demyelinating diseases of the central nervous system Arthritis SIDS§	GBS Transverse myelitis Thrombocytopenia Anaphylaxis SIDS§
Category 3: The Evidence Favors Rejection of a Causal Relation					
Encephalopathy¶ Infantile spasms (DT only)# SIDS (DT only)#**					Early-onset Hib disease (conjugate vaccine)
Category 4: The Evidence Favors Acceptance of a Causal Relation					
GBS‡‡ Brachial neuritis††	Anaphylaxis‖		GBS (OPV)		Early-onset Hib disease in children aged 18 mo or older who receive their first Hib immunization with unconjugated Hib vaccine
Category 5: The Evidence Establishes a Causal Relation					
Anaphylaxis††	Thrombocytopenia (MMR) Anaphylaxis (MMR)‖ Death from measles vaccine–strain viral infection§‡‡		Poliomyelitis in recipient or contact (OPV) Death from polio vaccine–strain viral infection§‡‡	Anaphylaxis	

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†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 measles-mumps-rubella (MMR) vaccine, 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.

‡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.

§This table lists weight-of-evidence determinations only for deaths that are classified as sudden infant death syndrome (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 (GBS), tetanus toxoid (T) 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 GBS, hepatitis B vaccine and anaphylaxis, and *Haemophilus influenzae* type b (Hib) unconjugated vaccine and early-onset Hib disease in children aged 18 months or older who receive their first Hib immunization with unconjugated HibP vaccine.

‖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 is less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

¶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 T and encephalopathy.

#Infantile spasms and SIDS occur only in an age group that receives DT, but not Td or T.

**The evidence derives mostly from diphtheria and tetanus toxoids and pertussis (DTP) vaccines. 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 DTP vaccine and SIDS, then in the committee's judgment the evidence favors rejection of a causal relation between DT and SIDS.

††The evidence derives from T. If the evidence favors acceptance of (or establishes) a causal relation between T 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.

‡‡The data come primarily from individuals proven to be immunocompromised.

per million population). Although one or more well-documented case reports can serve to favor acceptance of, or even establish, a causal relation, only controlled epidemiologic studies could be used as a basis for possible rejection of a causal relation. The absence of data favoring acceptance of a causal relation did not lead to rejection of a causal relation because of the possibility that adverse reactions might have occurred that have not been reported or recognized.

SUMMARY AND CONCLUSIONS

The Table summarizes the conclusions about the causal relations between the vaccines under study and the adverse events evaluated in the report. The footnotes to the Table are integral to interpretation of the conclusions.

In Category 1 (No Evidence Bearing on a Causal Relation) of the Table, the committee identified no report of a person experiencing any of the five adverse reactions listed.

Thirty-three vaccine-event pairs were placed in Category 2 (The Evidence Is Inadequate to Accept or Reject a Causal Relation). It is important to note that "Inadequate" describes relations for which the data were scarce and relations for which the data were abundant, but did not, on the whole, weigh for or against acceptance of a causal relation. The committee did not distinguish between the two. An abundance of inconclusive data did not place a relation into Category 3 (The Evidence Favors Rejection of a Causal Relation). Only controlled epidemiologic studies of rigorous design and with adequate statistical power that did not detect a significant association between a vaccine and an adverse event were used to support a Category 3 evaluation.

Four vaccine-event pairs were placed in Category 3 (The Evidence Favors Rejection of a Causal Relation), and five were assigned to Category 4 (The Evidence Favors Acceptance of a Causal Relation). The early-onset Hib disease

referred to in Category 4 occurred within 7 days of receipt of unconjugated polysaccharide Hib vaccines in children 18 months of age or older in whom this was the first Hib vaccination.

Seven vaccine-event pairs were placed in Category 5 (The Evidence Establishes a Causal Relation). The individuals who died from measles vaccine–strain viral infection after measles vaccination were all immunocompromised. Death from polio vaccine–strain viral infection occurred primarily in individuals proved to be immunocompromised.

Of the conclusions favoring, more or less strongly, a causal relation between a vaccine and an adverse event, two (Guillain-Barré syndrome after OPV and Hib disease after unconjugated Hib vaccine) were based on controlled studies. Case reports and uncontrolled studies provided the evidence for most of the other positive causal relations. The apparent dependence on case reports is, perhaps, misleading and warrants explanation. It might appear that case reports carried more weight than controlled studies. Rather, the committee identified far fewer controlled studies than uncontrolled studies or case reports. A few case reports provided extraordinarily convincing evidence in support of causality. For example, anaphylaxis after MMR vaccine[7] or HBV (the most compelling case reports in support of this causal relation were unpublished case reports submitted to the Vaccine Adverse Events Reporting System), Guillain-Barré syndrome after tetanus toxoid,[8] and death from vaccine-strain viral infection after measles vaccine.[9,10] However, it is important to note that many case reports, published and unpublished, provided little help in assessing causality. Problems included incomplete documentation in support of the clinical diagnosis, latency to adverse event that is incompatible with a biologically plausible mechanism, simultaneous administration of more than one vaccine, and alternative etiologic explanations.

INCIDENCE OF VACCINE-RELATED ADVERSE EVENTS

Estimates of the incidence or risk of experiencing one of the vaccine-related adverse events requires data from controlled epidemiologic studies. For the vast majority of vaccine-related adverse events studied, the data came predominantly from uncontrolled studies and case reports. Most of the pathological conditions studied are rare in the general population. The risk of developing these conditions because of vaccination seems 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 (ie, the risk difference or excess risk). However, where possible, the committee tried to estimate the level of risk of the reactions from the vaccine.

The relative risk of brachial neuritis after tetanus toxoid–containing vaccine is on the order of five to 10 and the 1-month attributable incidence (excess risk) is on the order of 0.5 to 1.0 per 100 000 tetanus toxoid recipients.[2] The incidence of thrombocytopenic purpura occurring within 2 months after MMR vaccine is on the order of one per 30 000 to 40 000 vaccinated children. This is approximately sixfold higher than the incidence of thrombocytopenia for a 2-month period in children younger than 15 years.[11]

The incidence of paralytic poliomyelitis from OPV is approximately one case per 500 000 first doses of OPV administered and approximately one case per 12 million subsequent doses administered.[12] The relative risk for developing Guillain-Barré syndrome after OPV in adults appears to be approximately 3.5 and the risk difference is approximately 2.5.[2] The relative risk for children is unclear. The attributable incidence for Hib disease within 7 days of Hib vaccination with the polysaccharide unconjugated Hib vaccine in children 18 months of age or older in whom this is the first Hib vaccination was calculated to be 1.62 cases per 100 000 vaccinees.[2] This figure may not be valid now, however, because the background incidence data were obtained from the prevaccine era; the figure is presumably less now owing to decreased colonization and transmission of disease.

The committee could not estimate the risk of the other adverse reactions because of a lack of controlled data. However, the risks seem to be extraordinarily low. For example, MMR vaccine has been used for 20 years, and the committee could find only two well-documented cases of anaphylaxis (neither of which was fatal) in the published literature.[8]

NEED FOR RESEARCH AND SURVEILLANCE

Committee distress over the large number of vaccine-related adverse events for which the data were inadequate to determine causality prompted a discussion of the need for research and surveillance. The committee did not recommend specific experiments or experimental designs, but it did suggest broad areas that might warrant attention. The suggestions include the following: (1) basic research into the biochemical basis of vaccine-induced Guillain-Barré syndrome and of the tendency of the Urabe strain mumps vaccine, but not the Jeryl Lynn strain used in the United States, to cause aseptic meningitis; (2) exploration of the possibility that HBV is causally related to demyelinating disorders or to the exacerbation of rheumatoid arthritis; (3) development of mutant diphtheria and tetanus toxins for use as vaccines; (4) development of an OPV with less tendency to revert to neurovirulence; (5) disease registries for some of the rare pathological conditions that might sometimes occur as vaccine-related adverse events; (6) research into the performance of passive surveillance systems for adverse reactions to vaccines; (7) creation of active surveillance measures; and (8) increased use of controlled studies in defined populations in which records of immunizations and medical care are linked.

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References

1. Mariner WK. The national vaccine injury compensation program: update. *Health Aff (Millwood).* 1992;11:255-265.
2. Howson CP, Howe CJ, Fineberg HV, eds. *Adverse Effects of Pertussis and Rubella Vaccines.* Washington, DC: National Academy Press; 1991.
3. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines: summary of a report of the Institute of Medicine. *JAMA.* 1992; 267:392-396.
4. Howson CP, Fineberg HV. The ricochet of magic bullets: summary of the Institute of Medicine report, *Adverse Effects of Pertussis and Rubella Vaccines. Pediatrics.* 1992;89:318-324.
5. Stratton KR, Howe CJ, Johnston RB Jr, eds. *Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality.* Washington, DC: National Academy Press; 1994.
6. Wiggins CA, Dykewicz MS, Patterson R. Idiopathic anaphylaxis: a review. *Ann Allergy.* 1989; 62:1-4.
7. Thurston A. Anaphylactic shock reaction to measles vaccine. *J R Coll Gen Pract Occas Pap.* 1987;37:41.
8. Pollard JD, Selby G. Relapsing neuropathy due to tetanus toxoid: report of a case. *Ital J Neurol Sci.* 1978;37:113-125.
9. Bellini WJ, Rota JS, Greer FW, et al. Measles vaccination death in a child with severe combined immunodeficiency: report of a case. *Lab Invest.* 1992;66:19A.
10. Coffin CM, Roberts RL, Monafo WJ, et al. Disseminated measles infection following vaccination in severe combined immune deficiency syndrome. *Pediatr Pathol.* 1993;13:102.
11. Cohn J. Thrombocytopenia in childhood: an evaluation of 433 patients. *Scand J Hematol.* 1976; 16:226-240.
12. Nkowane BM, Wassilak SG, Orenstein WA, et al. Vaccine-associated paralytic poliomyelitis, United States: 1973 through 1984. *JAMA.* 1987;257:1335-1340.