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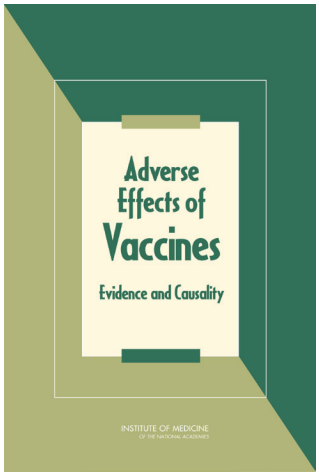
Adverse Effects of Vaccines

Evidence and Causality



Immunizations are a cornerstone of the nation's efforts to protect people from a host of infectious diseases. As required by the Food and Drug Administration, vaccines are tested for safety before they enter the market, and their performance is continually evaluated to identify any risks that might appear over time.

Vaccines are not free from side effects, or "adverse effects," but most are very rare or very mild. Importantly, some adverse health problems following a vaccine may be due to coincidence and are not caused by the vaccine. As part of the evaluation of vaccines over time, researchers assess evidence to determine if adverse events following vaccination are causally linked to a specific vaccine, and if so, they are referred to as adverse effects. Under the National Childhood Vaccine Injury Act of 1986, Congress established the National Vaccine Injury Compensation Program (VICP) to provide compensation to people injured by vaccines. Anyone who thinks they or a family member—often a child—has been injured can file a claim.

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The Health Resources and Services Administration (HRSA), the agency within the Department of Health and Human Services that administers VICP, can use evidence that demonstrates a causal link between an adverse event and a vaccine to streamline the claim process. As such, HRSA asked the Institute of Medicine (IOM) to review a list of adverse events associated with vaccines covered by VICP and to evaluate the scientific evidence about the event—vaccine relationship. The vaccines covered by VICP include all vaccines recommended by the Centers for Disease Control and Prevention (CDC) for routine administration in children. Adults who experience an adverse event following one of these childhood vaccines also are covered by the program. HRSA

asked the IOM to review 8 of the 12 covered vaccines. These eight are the varicella zoster vaccine (used against chickenpox); the influenza vaccines (except for the H1N1 influenza vaccine distributed in 2009); the hepatitis B vaccine; the human papillomavirus (HPV) vaccine; the measles, mumps, and rubella (MMR) vaccine; the hepatitis A vaccine; the meningococcal vaccines, and tetanus-containing vaccines that do not carry the whole-cell pertussis component.

Examining the Evidence

The adverse events selected by HRSA for IOM review are ones for which people have submitted claims—successful or not—to VICP. The committee appointed to this study was not asked to assess the benefits or effectiveness of vaccines but only the risk of specific adverse events. Its conclusions reflect the best evidence available at the time. Some of the adverse events the committee examined already are accepted in the medical community, but they are minor or manageable—for example, a sudden allergic reaction called anaphylaxis that can follow the administration of some vaccines.

In its report, the committee explains its process for evaluating the list of adverse events and provides a set of 158 causality conclusions. The committee examined two types of evidence: epidemiologic evidence, which derives from studies of populations, and mechanistic evidence, which draws from biological and clinical studies. The committee evaluated each scientific article for its strengths and weaknesses and then assigned a "weight of evidence" ranking to both the epidemiologic and mechanistic bodies of studies.

The committee considered the weights of evidence and then reached a conclusion about the causal relationship between each vaccine and adverse health problem pairing. The committee began from a position of neutrality, presuming neither causation nor lack of causation, and moved from that position only when the combination of evidence suggested a more definitive assessment regarding causation. The figure provides an explanation of how the evidence influenced the causality conclusions.

Based on the totality of the evidence, the committee assigned each relationship to one of four categories of causation in which the evidence:

- convincingly supports a causal relationship;
- favors acceptance of a causal relationship;
- favors rejection of a causal relationship; or
- is inadequate to accept or reject a causal relationship.

The committee did not use a category to designate evidence that convincingly supports no causal relationship, because it is virtually impossible to prove the absence of a very rare relationship with the same certainty that is possible to establish the presence of one.

Evidence Convincingly Supports a Causal Relationship

The committee concludes that the evidence convincingly supports a causal relationship between some vaccines and some adverse events.

As a live vaccine, the varicella zoster vaccine is linked to four specific adverse events, all due to infection from the vaccine virus strain:

- Disseminated varicella infection (widespread chickenpox rash shortly after vaccination)
- Disseminated varicella infection with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies
- Vaccine strain viral reactivation (appearance of chickenpox rash months to years after vaccination)
- Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis (inflammation of the brain)

The MMR vaccine is linked to a disease called measles inclusion body encephalitis, which in very rare cases can affect people whose immune

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systems are compromised and usually occurs within a year of acute measles infection or vaccination. The MMR vaccine also is linked to febrile seizures, which are a type of seizure that occurs in infants and young children in association with fever. Febrile seizures are generally benign and hold no long-term consequences.

Six types of vaccines—MMR, varicella zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines—are linked to anaphylaxis.

The committee also found convincing evidence of a causal relationship between injection of vaccine, independent of the antigen involved, and two types of adverse events, including syncope, or fainting, and deltoid bursitis, or frozen shoulder, characterized by shoulder pain and loss of motion.

Evidence Favors Acceptance of a Causal Relationship

The evidence favors acceptance of four vaccine–adverse event relationships. In these cases, the evidence is strong and generally suggestive, but not firm enough to be described as convincing. These relationships include:

- HPV vaccine and anaphylaxis;
- MMR vaccine and transient arthralgia (temporary joint pain) in female adults;
- MMR vaccine and transient arthralgia in children; and
- certain trivalent inactivated influenza vaccines used in Canada in some recent years and a mild and temporary oculorespiratory syndrome, which is characterized by conjunctivitis, facial swelling, and upper respiratory symptoms, including coughing and wheezing.

Evidence Favors Rejection of a Causal Relationship

The evidence favors rejection of five vaccine–adverse event relationships:

- MMR vaccine and autism
- MMR vaccine and type 1 diabetes
- DTaP (tetanus) vaccine and type 1 diabetes
- Inactivated influenza vaccine and Bell's palsy (weakness of the facial nerve)
- Inactivated influenza vaccine and exacerbation of asthma or reactive airway disease episodes in children and adults

Evidence Inadequate to Accept or Reject a Causal Relationship

For the vast majority, (135 vaccine-adverse event pairs), the evidence is inadequate to accept or reject a causal relationship. In many cases, the adverse event being examined is an extremely rare condition, making it hard to study. In these cases, there was not adequate evidence to determine if the vaccine was or was not causally associated.

Study Sponsor

The Health Resources and Services Administration
The Centers for Disease Control and Prevention
The National Vaccine Program Office

Susceptibility

As some of the conclusions suggest, individuals with certain characteristics are more likely to suffer certain adverse effects from particular immunizations. Individuals who have serious immunodeficiencies are clearly at increased risk for specific adverse reactions to live viral vaccines, such as MMR and varicella vaccines. Thus, the committee was able at times to reach more limited conclusions for subgroups of the population.

Conclusion

In applying consistent standards across all the evidence, the committee found that some conclusions were easy to reach: the evidence was clear and consistent or, in the extreme, completely absent. Others required substantial discussion and debate.

The committee was not charged with making recommendations, and it did not pinpoint any particular areas for continued research. Much research already occurs to determine the safety of vaccines for the populations for whom they are recommended. However, there is much to learn about the human immune system, autoimmunity, and the effects of genetic variation, all of which may influence how people respond to vaccines.

Vaccines offer the promise of protection against a variety of infectious diseases. Despite much media attention and strong opinions from many quarters, vaccines remain one of the greatest tools in the public health arsenal. Certainly, some vaccines result in adverse effects that must be acknowledged. But the latest evidence shows that few adverse effects are caused by the vaccines reviewed in this report.

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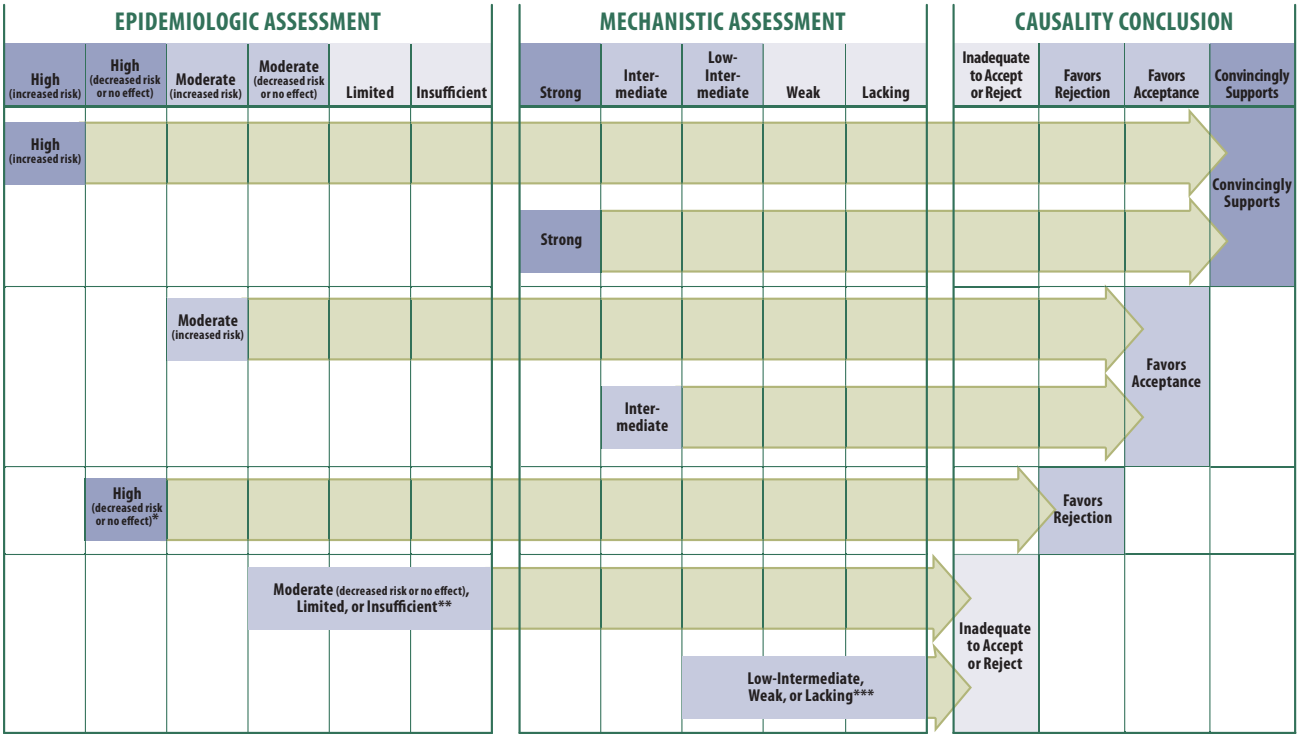
FIGURE

Strength of Evidence that Determined the Causality Conclusions



* Causality conclusion is favors rejection only if mechanistic assessment is ***not*** strong or intermediate.
** Causality conclusion is inadequate to accept or reject only if mechanistic assessment is ***not*** strong or intermediate.
*** Causality conclusion is inadequate to accept or reject only if epidemiologic assessment is ***not*** high (increased risk), high (decreased risk or no effect), or moderate (increased risk).

TABLE: Summary of Causality Conclusions

Vaccine	Adverse Event	Causality Conclusion
Varicella	Disseminated varicella infection (widespread chickenpox rash shortly after vaccination)	Convincingly Supports
Varicella	Disseminated varicella infection with subsequent infection resulting in pneumonia, meningitis, or hepatitis	Convincingly Supports [a]
Varicella	Vaccine strain viral reactivation (appearance of chickenpox rash months to years after vaccination)	Convincingly Supports
Varicella	Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis (inflammation of the brain)	Convincingly Supports
MMR	Measles inclusion body encephalitis	Convincingly Supports [a, b]
MMR	Febrile seizures (a type of seizure that occurs in association with fever and is generally regarded as benign)	Convincingly Supports
MMR	Anaphylaxis (a very rare but sudden allergic reaction)	Convincingly Supports
Varicella	Anaphylaxis	Convincingly Supports
Influenza	Anaphylaxis	Convincingly Supports
Hepatitis B	Anaphylaxis	Convincingly Supports [c]
Tetanus Toxoid	Anaphylaxis	Convincingly Supports
Meningococcal	Anaphylaxis	Convincingly Supports
Injection-Related Event	Deltoid bursitis (frozen shoulder, characterized by shoulder pain and loss of motion)	Convincingly Supports
Injection-Related Event	Syncope (fainting)	Convincingly Supports
HPV	Anaphylaxis	Favors Acceptance
MMR	Transient arthralgia (temporary joint pain) in women	Favors Acceptance [d]
MMR	Transient arthralgia in children	Favors Acceptance
Influenza	Oculorespiratory syndrome (a mild and temporary syndrome characterized by conjunctivitis, facial swelling, and upper respiratory symptoms)	Favors Acceptance [e]
MMR	Autism	Favors Rejection
Influenza	Inactivated influenza vaccine and Bell's palsy (weakness or paralysis of the facial nerve)	Favors Rejection
Influenza	Inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults	Favors Rejection
MMR	Type 1 diabetes	Favors Rejection
DT, TT, or aP containing	Type 1 diabetes	Favors Rejection

[a] The committee attributes causation to individuals with demonstrated immunodeficiencies.
[b] The committee attributes causation to the measles component of the vaccine.
[c] The committee attributes causation to yeast-sensitive individuals.
[d] The committee attributes causation to the rubella component of the vaccine.
[e] The committee attributes causation to two particular vaccines used in three particular years in Canada.

All other causality conclusions are the evidence is inadequate to accept or reject a causal relationship.