The Science of Evaluation of Adverse Events Associated with Vaccination

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All vaccines cause some adverse events; serious adverse events are rare. Causal associations between a vaccine and an adverse event rarely can be determined by specific tests such as identifying a vaccine agent in the affected tissue of patients. In the absence of such data, epidemiologic studies can be used to determine if the risk of the disorder is increased in vaccinated compared to unvaccinated individuals. Common mistakes include assuming a causal relationship based on a temporal association only or a series of affected patients. Careful studies have demonstrated that many hypothesized causal associations between vaccines and adverse events were not substantiated. False assumptions regarding causality are likely to occur for illnesses without a carefully defined etiology or pathogenesis.

Vaccines are the most effective tools available for prevention and control of infectious diseases. Widespread use of vaccines has prevented millions of premature deaths, paralysis, blindness, and neurologic damage. Nevertheless, since smallpox vaccine was developed more than 200 years ago, vaccines have been controversial because of concerns about safety.

In recent years, the tolerance for adverse events associated with vaccines has decreased as part of an overall increased public awareness of product safety. As with air and highway travel, food products, and toys, the general public has insisted that federal agencies work to assure safer products for children and advocacy groups have argued for increased attention to the safety of medications and vaccines. Vaccines, which are administered to healthy people, are held to a higher safety standard than are medications used to treat people who are already ill because vaccines often are given universally to infants and children. Even a very low risk of having serious side effects can result in a substantial population-attributable risk if the vaccine is given universally. The tolerance for adverse events associated with vaccines varies because of real and perceived differences in the risks and severity of the illness prevented. When infections such as measles, diphtheria, and polio were common occurrences in our society, accepting occasional rare serious side effects from vaccines as a necessary risk was easier. As immunization programs have become more successful and the risk of contracting those diseases has diminished, the acceptance of side effects from immunizations also has decreased.

Smallpox vaccine caused several serious adverse events, including eczema vaccinatum, encephalitis, and progressive debilitating infections in patients with immunodeficiency disorders.[1] When the risk of contracting smallpox diminished to near zero in the United States, the acceptance of these serious adverse events decreased, and routine immunization against smallpox ended in 1972, 5 years before the interruption of transmission of smallpox in Africa. Communication about the benefits and the risks from vaccination has become much more complicated in recent years because of the increased number of vaccines available, the declining incidence of some vaccine-preventable diseases, and development of new vaccines against diseases that normally do not cause serious complications.

How Vaccines are Evaluated for Causal Associations with Adverse Events

Causal associations usually can be determined by isolating a live vaccine agent in affected tissue or by demonstrating, through epidemiologic studies, an increased risk of the disorder in vaccine recipients as compared to appropriate controls. A more detailed discussion of this process can be found in a recent publication on measles-mumps-rubella (MMR) vaccine and autistic spectrum disorder.[2]

Identification of Vaccine Agents in Affected Tissues

Individual case reports usually provide insufficient evidence to establish causal associations. However, if a vaccine virus

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or bacterium is isolated from affected tissue, the organism is not found in controls, no evidence of contamination of specimen is found, and no other explanation for the illness exists, the evidence is strongly suggestive of a causal association. For example, Bacillus of Calmette-Guérin (BCG) vaccine occasionally causes osteomyelitis or joint infections as evidenced by the isolation of the organism from bone or joint tissue in affected patients.[3] Similarly, measles vaccine virus has been identified in lung tissue of children with leukemia and from 1 patient with human immunodeficiency virus (HIV) infection.[4,5] If the vaccine organism routinely infects the affected tissue and the identification is made during the window of time when the organism would normally be found, other possible explanations need to be excluded before accepting the evidence that the agent caused the disorder. However, most vaccine agents are detectable in the blood or body tissues for only a short window of time after vaccination. Identification of the vaccine agent in people who had been vaccinated much earlier provides suggestive evidence that persistence of the agent may contribute to a causal relationship. One must be cautious, however, when interpreting the findings because some infectious agents might persist in lymph nodes, brain, or other tissues.[2,6,7] Numerous false assumptions about agents possibly causing multiple sclerosis have been made based on laboratory tests that later were found to be false-positives or the agent was found in normal tissue as well as persons affected by the disease.[6] Contamination of specimens at the time of collection, during processing, or during laboratory analyses have resulted in false assumptions that the agent was present in affected tissue. The use of molecular techniques to identify infectious agents, including immunohistochemical staining or polymerase chain reaction, has resulted in a proliferation of investigations of infectious agents as possible causes of chronic disorders. Unfortunately, these techniques often are associated with false-positive results.[7] Therefore, most experts await confirmation by several investigators using specimens collected and processed separately before accepting evidence of the presence of the organism in affected tissue.

Epidemiologic Studies

Before vaccines are licensed by regulatory authorities, controlled trials are performed to compare individuals who receive vaccine with those who receive placebo or a control vaccine. Eligible people are randomly assigned to receive vaccine or placebo (or control vaccine) and then followed to collect outcome data. These controlled studies provide the most powerful evidence for establishing causal associations between vaccines and adverse events. For example, when the first live attenuated measles vaccines were developed, children who received measles vaccine had increased rates of fever from 5 to 10 days in those receiving vaccine compared with those who received only immune serum globulin (Fig 1).[8] The rates of fever after vaccination in this study were higher than the 5 to 15 percent rates of fever noted after administration of attenuated vaccines that are in use today. During the study, a small proportion of children who did not receive vaccine developed febrile illnesses caused by

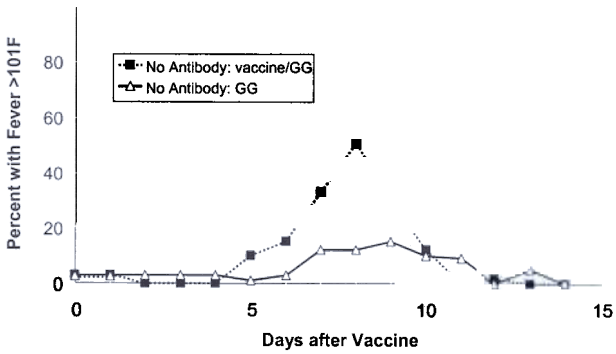

Figure 1. Percent of children who were susceptible to measles with fever after receiving Edmonston B measles vaccine and immunoglobulin (GG) or GG alone (1963). (Adapted from CM Martin 1963, ref #[8].)

intercurrent infections. Therefore, determining in any individual child if a fever (or other adverse event) occurring during the window of time when an increased risk occurs is due to a reaction to the vaccine or to some other illness can be difficult. However, these studies can establish whether the risk of a disorder during a specified period of time after vaccination is increased.

Controlled trials are useful for identifying common adverse events that occur within a relatively short time after vaccination. Prelicensure, prospective, randomized studies usually are not designed to detect adverse events with delayed onset. Also, these studies usually are limited to a few thousand vaccinees and an equal number of controls. These studies can detect a doubling of the rates of adverse events that occur in the control population at a rate of 1 in 100 or higher, but the studies have insufficient power to detect rare adverse events or adverse events that might occur months or years after vaccination.[9] To increase the ability of studies to detect these rare events, expanded trials involving 10,000 to 50,000 individuals are needed, and some experts have argued for these studies. For vaccines that are likely to be given to all children, such studies might be justified, but the cost of studies on such a large scale would be very high, and manufacturers are reluctant to delay licensure and general use of the vaccine, especially if the vaccine protects against serious diseases.[13]

After licensure, monitoring of adverse events after vaccination involves healthcare providers who observe and report such events, vaccine manufacturers, and regulatory authorities. In the United States, reports of adverse events are submitted to the Vaccine Adverse Events Reporting System (VAERS), which is maintained jointly by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).[10] The purpose of this system is to monitor reports of adverse events that might signal the need for further study. For example, prelicensure studies identified only 5 children who developed intussusception among the 10,000 who participated in clinical trials of rhesus rotavirus vaccine, with no consistent pattern of timing or dose of vaccine in the children who

developed the intussusception.[11] After several hundred thousand children had been vaccinated, 9 reports to VAERS of intussusception occurring within 15 days after vaccination triggered case-control and cohort studies conducted by the CDC that demonstrated a causal association.[12] The risk of developing intussusception now is estimated to be approximately 1 in every 5,000 to 10,000 children vaccinated, a rate too low to be detected in the prelicensure studies.

Black et al[13] have demonstrated that generating controlled data from large numbers (10,000 to 40,000) of individuals postlicensure is possible and practical in large health maintenance organizations. Such studies have been conducted with the recently licensed pneumococcal conjugate vaccine. Chen et al[14] have noted the potential limitations of such studies, including the potential for less healthy children to not receive vaccines (i.e., "confounding by contraindication"). Efforts are made in the analyses of data generated from these studies to evaluate and adjust for other measures of health care seeking behavior.

CDC has implemented a program to collect controlled data from large numbers of individuals by linking immunization records with all health outcomes in the Vaccine Safety Datalink.[15] This program includes approximately 2.5 percent of the entire United States birth cohort and provides the opportunity to compare vaccinated and unvaccinated individuals in the same geographic area for adverse events and to adjust for factors that might contribute to these events.

Misunderstanding Causality Assessment

Unfortunately, the use of case reports and the VAERS system has been misunderstood by some individuals.[10,14] Limitations of this program include incomplete reporting, which precludes the verification of diagnoses; the absence of denominator information regarding the number of individuals vaccinated; and absence of rates of the disorder in people who did not receive the vaccine.

Too often, affected individuals and their physicians incorrectly assume that a vaccine administered before the onset of a disorder provides evidence that the vaccine caused the disorder. Reports of temporal associations do not constitute evidence for causal associations, but these reports can provide clues to indicate the need for additional studies to determine if a causal association with the vaccine exists. In the absence of a specific laboratory test, as previously mentioned, temporal associations can be used only to generate hypotheses. The number of reported events alone is not evidence of a causal association, but if the number of events exceeds the number expected because of chance, it can signal the need for more formal controlled studies. In large countries such as the United States, collecting many hundred people who have developed specific disorders after vaccination is possible, even if the disorders are relatively rare. For example, based on collections of reports of women who had breast implants and subsequently developed autoimmune disorders, false assumptions were made that silicone breast implants were responsible for causing autoimmune disorders.[16] Because of these reports, the use of silicon breast implants was stopped and the manufacturer filed for bankruptcy because of the large number of lawsuits. Several years later, the scientific evidence from controlled observations indicated no increased risk of developing autoimmune disorders associated with silicon breast implants.[16] Increased efforts need to be made to introduce better science into the legal process and to avoid making similar mistakes with regard to adverse events after vaccination.

Table 1. Mechanisms Involved in Adverse Events Caused by Vaccines

1.	Injection process
2.	Incomplete inactivation of vaccine agent
3.	Replication of a live vaccine agent
4.	Inadvertent contamination of vaccine with other live agent
5.	Direct effect of vaccine component (e.g., pyrogens, adjuvants, preservatives)
6.	Host immune response to vaccine component (normal or aberrant)

Table 2. Injection-related Serious Adverse Events

1.	Pain
2.	Fainting and associated injuries
3.	Tissue injury
4.	Provocation polio
5.	Errors in reconstitution
6.	Contamination of multidose vials

Types of Adverse Events Caused by Vaccines

Vaccines are known to cause adverse events by several different mechanisms (Table 1).

Injection Process

Pain. Most vaccines are given by injections, which cause pain at the site. Pain, the most common adverse event associated with immunizations, usually is mild to moderate in severity and short-lived. Pain can be reduced by stimulation of other areas such as pressure or rubbing, distraction techniques, or feeding sugar to the patient just prior to giving the injection.[17]

Fainting. Rarely, serious adverse events, including skull fractures, cerebral bleeding, or cerebral contusions, have occurred as a result of the patient fainting after receiving vaccines.[18] In 1 study, 63 percent of fainting episodes occurred within 15 minutes after vaccination, and a disproportionate number of episodes occurred in adolescents.[18] Expert committees often advise that individuals be observed for 15 minutes after immunization to minimize the occurrence of potential adverse events associated with fainting while walking down stairways or other places more prone to cause injury than sitting in a chair.[19]

Other serious events associated with the injection process are listed in Table 2.

Tissue Injury. The most common injury associated with needle sticks has been damage to nerves from the needlestick. Sciatic nerve damage now occurs less frequently since the World Health Organization (WHO), the CDC, and the American Academy of Pediatrics (AAP) have discouraged use of the buttocks as a site for vaccine administration.[19-21] Because alternative sites almost always are available for administering vaccines, little justification exists to administer vaccine in the buttock region. Moreover, the large fat pad in this region can result in subcutaneous injections and decreased immunogenicity, as occurred with hepatitis B vaccines.

Provocation Polio. When children incubating wild-type poliovirus infections receive injections, the likelihood of residual paralytic diseases developing in the injected extremity is increased.[22] The damage to small nerve endings probably provides entrance to the nervous system for polioviruses circulating in the bloodstream, which subsequently travel to the spinal cord and damage the motor neuron. A study in Romania revealed that multiple injections were associated with development of residual paralysis from oral poliovirus vaccines (discussed subsequently).[23]

Errors in Reconstitution. Vaccines that have been lyophilized require reconstitution in a diluent (usually water) provided by the manufacturer. Occasionally, healthcare workers have mistakenly used vials of medications with similar appearances to reconstitute vaccines, resulting in overdoses and unintended effects.[24] Recognized mistakes have included administration of agents such as succinyl choline or pavulon (pancuronium bromide), resulting in temporary paralysis or respiratory arrest. These problems can be avoided by storing vaccines separately from other medications, packaging vaccines with the diluents, and training healthcare workers to carefully read the vials on all diluents before administration.

Contamination of Multidose Vials. Vaccines in multidose vials should be used within a few hours of opening if they do not contain a preservative. In at least 3 countries, multidose vials of measles vaccines that were inappropriately stored overnight became contaminated with *Staphylococcus aureus* that multiplied and caused septic shock or toxic shock syndrome.[24] Multidose vials of diphtheria-tetanus-pertussis (DTP) vaccine contain preservatives to minimize the potential for bacterial contamination. However, thimerosal in whole-cell DTP was insufficient to prevent growth of *Streptococcus pyogenes*, and several clusters of cellulitis, sepsis, and abscesses have been reported.[24,25] These problems could be prevented by using more effective preservatives or single-dose vials without preservatives.

Incomplete Inactivation of the Vaccine Agent

Historically, serious adverse events have been caused by the inadvertent administration of wild-type infectious agents instead of inactivated agents. In 1955, several companies produced inactivated poliovirus vaccines following procedures modified from methods used for vaccines produced for experimental field trials.[26] One manufacturer's product was associated with paralytic disease because of incomplete inactivation of the wild-type polioviruses. When the manufacturer scaled up production from 50 mL to 500 mL vials, sediment formed at the bottom of the vials, allowing for protection of the wild-type virus from to formaldehyde.[26] This event resulted in the establishment of the Division of Biological Standards, currently the Center for Biologics Evaluation and Research of the Food and Drug Administration (FDA), which monitors the safety of all vaccines and related biological products.[27] Current good manufacturing practices should prevent recurrences of this type of problem because all lots of inactivated vaccines must be demonstrated to have complete inactivation of vaccine agents. Rigorous safety testing and annual review also are performed for all steps in the manufacture of vaccines.[28]

Replication of Live Vaccine Agent

For live attenuated vaccines, replication of the vaccine agent in the body produces a mild infection that results in fever, malaise, myalgias, and other adverse events. An example is the increased rates of fever that occurred in the 5 to 10 days after vaccination in children who received the original attenuated measles vaccine as compared to children who received immune globulin only (Fig 1).[8]

Increased rates of rash occurred during a similar time window. Similarly, approximately 15 percent of children who receive varicella vaccine develop mild fever, and 3 to 4 percent develop a mild varicella-like rash 10 to 42 days after vaccination.[29] Some live attenuated vaccine agents can cause diseases similar to those caused by the wild-type agent. For example, BCG can cause bone or joint infections.[3] In normal hosts, these infections usually are self-limited and mild.

Vaccine-associated paralytic poliomyelitis (VAPP) is a rare complication of live oral poliovirus vaccine (OPV), occurring in approximately 1 in 760,000 first vaccinations.[30] Approximately one-fourth of affected individuals are found to have a definable immunodeficiency disorder, but most cases of VAPP occur in otherwise normal hosts. Future technologic developments, such as use of genetic arrays, may provide further insight into why some people develop these complications in the absence of other definable immunodeficiency states.

Inadvertent Contamination of Vaccines with Other Live Agents

In 1962, Simian Virus 40 (SV_{40}) was discovered to be a contaminant of monkey kidney cells used to produce oral and inactivated polio vaccines.[31] This infectious agent had not been identified previously because the virus does not cause cytopathic effects in the cell lines used for safety testing. SV_{40} infection was found to be associated with selected tumors in animals, and several investigators have identified SV_{40} in mesotheliomas and other tumors.[31] However, SV_{40} has been identified in people who never received vaccines that might have contained the virus, and other investigators have not found evidence of these viruses in tumors. A causal relationship with SV_{40} and any human disease has not been demonstrated.

In 1942, an outbreak of hepatitis occurred involving 25,585 United States military recruits who had received

yellow fever vaccine. The source of the infection immediately was suspected to be the human sera used as a stabilizer in the vaccine, which was replaced with bovine serum in 1942. In 1987, epidemiologic studies of individuals who had received the contaminated vaccines and controls demonstrated that the human sera had been contaminated with hepatitis B virus.[32] Also, avian leukosis virus was found in 1966 to be a contaminant in 17D yellow fever vaccines[32]; all vaccines produced since the early 1970s are free of this virus.

Current manufacturing practices include intensive testing of all vaccine additives to assure the absence of detectable infectious agents. Although questions have been raised with regard to the use of bovine serum because of theoretical concerns about the possibility of transmission of bovine spongioform encephalopathy, experts agree that this risk is extremely unlikely.[33] Nevertheless, regulatory authorities now require that any bovine products used in vaccine production must come from countries that are free of bovine spongioform encephalopathy.[33] (For more information, go to: http://www.who.int/vaccines-diseases/safety/hottop/bse.shtml or http://www.fda.gov/cber/bse/risk.htm.)

Some vaccines being considered for human testing will require new cell lines for production, including continuous cell lines that have been transformed by molecular techniques. These considerations have raised theoretical concerns about potential infectious agents, including oncogenic viruses in cell lines that might be used for vaccine production. A recent conference on this topic summarized the concerns and the steps that can be taken to test for these effects.[34] Regulatory authorities must depend upon applying the best scientific methods available at any point to assure the safest possible production of vaccine. As new information and tools become available, testing methods need to be updated and manufacturing methods may need to be modified.

Direct Effect of Vaccine Component

Vaccines, especially whole bacterial vaccines, often contain pyrogens that cause fever by release of chemicals from macrophages. For example, whole-cell pertussis vaccines induce fever in 30 to 50 percent of vaccine recipients.[35] Adjuvants enhance the antibody response to vaccines, but aluminum hydroxide and aluminum phosphate often induce local reactions, such as induration and swelling by stimulating or enhancing an inflammatory response. Other vaccine components may have undesirable effects. The preservative thimerosal has been used for many years in a variety of vaccine products. Thimerosal can induce hypersensitivity reactions, which usually are localized.[36] One of the breakdown products of thimerosal is ethylmercury, which can cause neurologic damage when administered in large doses.[37] An FDA analysis revealed that the use of multiple thimerosal-containing vaccines in infants could result in cumulative exposures that exceeded some federal guidelines for methylmercury.[36] In 1999, the U.S. Public Health Service, the AAP, and the European Agency for the Evaluation of Medicinal Products issued statements encouraging the reduction or elimination as soon as possible of the use of thimerosal in vaccines administered to infants.[38] Preliminary data from one study suggest the possibility of a dose-related increased risk of developing some mild neurologic disorders from thimerosal, but the data are inconclusive.[39] A review by the Institute of Medicine concluded that current evidence was insufficient to determine whether harmful effects were caused by thimerosal exposures in vaccines.[40] Ongoing follow-up studies of children who had high and low exposures should provide further information about any evidence of neurodevelopmental effects from these exposures in the United States.[41] The amount of exposure to thimerosal was much less in most other countries of the world because many European authorities had been phasing out this preservative and other countries had not added as many new vaccines that contain thimerosal as a preservative to the routine infant schedule.

Host Immune Response to Vaccine Component

Hypersensitivity reactions, including hives, anaphylaxis, and Stevens Johnson syndrome, have been observed after administration of many different vaccines (see Table 1).[42,43] Although these reactions usually are very rare, they can be life-threatening. Hypersensitivity can be generated to vaccine agents, preservatives, stabilizers, adjuvants, or residual antimicrobial agents. For many years, immediate hypersensitivity reactions to measles vaccines produced in chick embryo tissue culture and given to children with egg allergies was a concern. Careful studies using sensitive techniques have not detected residual egg protein in measles and other vaccines produced in chick embryo tissue culture. Children who have had hypersensitivity reactions after receiving measles-containing vaccines have been demonstrated to react to the gelatin stabilizer and not to egg protein.[44] In addition, children with true hypersensitivity reactions to egg protein can be administered MMR vaccine safely.[19,45] Administration of vaccines produced in eggs, such as influenza and yellow fever vaccines, is contraindicated in people with immediate hypersensitivity reactions to eggs because some residual egg protein is present in these vaccines.

Most hypersensitivity reactions to neomycin, which commonly is used during vaccine production, are mild local reactions, and adverse reactions to the small amounts in vaccines have not been documented.[21] Other antibiotics that are used commonly for treating infections, such as penicillin and cephalosporins, are not used in production of vaccines.

Increased risk of developing Gullain-Barré syndrome, an autoimmune disorder, was observed in people who received the swine influenza vaccine developed in 1976.[46] The attributable risk was approximately 1 in every 110,000 people vaccinated. Subsequent studies demonstrated no increased risk associated with influenza vaccines administered in the late 1970s and 1980s, but a small increased risk of approximately 1 per million vaccinees was noted after influenza vaccine was administered in the United States from 1992 through 1994.[47] No other autoimmune disorders have been

Table 3. Vaccines Contraindicated in Patients with Underlying Immune Deficiency Disorders—United States Guidelines

Immune Deficiency	*Contraindicated Vaccine*
B cell	OPV and live bacterial (BCG and *S. typhi* 21a and BCG); "consider" giving measles and varicella vaccines
T cell	All live vaccines
Phagocyte	Live bacterial (BCG and *S. typhi* 21a)
HIV	OPV and BCG (measles and varicella)
Suppressive therapy	All live, depending on immune status

Abbreviations: OPV, oral poliovirus vaccine; BCG, Bacillus of Calmette-Guérin; HIV, human immunodeficiency virus.

found to be caused by any vaccine (as subsequently discussed).

Immune Deficiency Disorders. Although people with underlying immune deficiency disorders may not benefit, they are not at increased risk of developing complications from inactivated and subunit vaccines. Because these vaccines may provide partial or complete protection, most expert groups recommend administration of these vaccines to all immunodeficient patients if the vaccines are indicated otherwise.[19,48]

Many disorders of the immune system are mild and do not alter the risk of developing adverse events from vaccines. People with disorders of macrophage function, such as chronic granulomatous disease, are not at increased risk of developing complications from viral infections. Therefore, no reason exists to expect increased complications from live viral vaccines.[19] Many affected individuals were vaccinated with live oral poliovirus and MMR vaccines without serious adverse events, before they were diagnosed with immune deficiency disorders. However, people with macrophage disorders are at potential increased risk from BCG vaccine (Table 3).[19]

In patients with T-cell immunodeficiency disorders, unchecked replication of live vaccine agents can result in severe infections and death. Progressive fatal pneumonitis developed when measles vaccine was administered to children with leukemia.[4] Children with leukemia in prolonged remission and patients who are 2 or more years after successful bone marrow transplants can receive live viral vaccines if they are not on severe immunosuppressive therapy.[48] In general, patients with underlying T-cell immunodeficiency disorders should not receive live viral vaccines, with the exceptions of selected patients with HIV infection discussed below. In cases of doubts about specific disorders, consultation with an immunologist or infectious disease specialist is indicated.[19]

HIV Infection. Infection with HIV induces a progressive immune deficiency state and increased risk of developing complications from numerous infectious agents. Severe complications from BCG vaccine have occurred in HIV-infected children and adults.[49] An HIV-infected adult with severe immune deficiency developed a progressive fatal pneumonitis after receiving measles vaccine, and, in another case, pneumonia caused by varicella vaccine was reported.[50,51] However, HIV-infected people with no or minimal evidence of immune suppression can be immunized safely with these vaccines.[49] In the United States, where resources are available for routine testing, advisory groups have recommended administration of these vaccines to some HIV-infected people depending on their CD4 lymphocyte counts. Although 2 people have developed VAPP after receiving OPV, many hundreds of thousands of HIV-infected people have been immunized, with no convincing evidence that the risk of developing VAPP is increased in HIV-infected children.[49] In developing countries where routine HIV testing is not performed, the advantages of routine administration of OPV and measles vaccines far outweigh the theoretical risks of complications from these vaccines. Also, vaccination early in life often results in an adequate immune response before HIV-induced immunosuppression develops. Therefore, WHO and individual countries recommend routine universal immunization with these vaccines.[49]

Recent Misunderstandings and False Accusations Regarding the Safety of Commonly Used Vaccines

During the past few years, several concerns have been raised about vaccines causing serious diseases. In most of these cases, the etiology or pathogenesis of the disease is unknown or incompletely understood, allowing for speculation about the role of vaccines. In several instances, individual investigators have made observations and speculated beyond their data to imply causal relationships between vaccines and the disorders.

Hepatitis B, Multiple Sclerosis, and Other Demyelinating Diseases

Multiple sclerosis is an autoimmune disorder. Epidemiologic evidence from many countries indicates that environmental factors and genetic predisposition contribute to the risk of developing multiple sclerosis. Infectious agents have been suggested as possible priming or triggering factors.[6] Individuals who developed their first episode of multiple sclerosis after receiving a vaccine (and some of their physicians) hypothesized that the immune response to the hepatitis B vaccine (or other vaccines) contributed to the development of the disease. In 1994, the Institute of Medicine Vaccine Safety Committee reviewed the available evidence regarding multiple sclerosis and hepatitis B vaccine and concluded that the available data provided insufficient evidence to establish a causal relationship.[42] The Committee also determined that there was biologic plausibility for a possible association between hepatitis B vaccine and multiple sclerosis on the basis of 1 study in rabbits in which investigators had found a short amino acid sequence in the myelin basic protein of rabbits that was identical to a sequence in the hepatitis B virus.[52] When these investiga-

tors immunized rabbits with an experimental protein based upon the sequence with complete Freund adjuvant, some of the rabbits developed an autoimmune encephalomyelitis. However, the protein is not present in hepatitis B surface antigen vaccines, and the genetic sequence in question is not present in human myelin basic protein. Nonetheless, some individuals misinterpreted the Institute of Medicine's conclusion that "the evidence was inadequate to accept or reject a possible causal relationship" to mean that evidence supported the relationship.

In France, large-scale programs were implemented in 1997 and 1998 to immunize adolescents and young adults, including individuals in the age group 20 to 40 years of age when multiple sclerosis usually presents, against hepatitis B. Some individuals developed the onset of multiple sclerosis symptoms within 2 months after receiving hepatitis B vaccine. Although a quickly conducted case-control study disclosed no significant increased odds ratio for multiple sclerosis patients having received hepatitis B vaccine in comparison to people without multiple sclerosis, the Minister of Health of France decided on October 1, 1998, to terminate the hepatitis B vaccine program for adolescents and adults pending further investigations.[53] Some individuals in the popular press interpreted this action to indicate that the government of France had evidence that hepatitis B vaccine caused multiple sclerosis. Subsequently, carefully conducted cohort and case-control studies documented no increased risk of developing multiple sclerosis or other demyelinating diseases after receiving hepatitis B immunization, and no evidence of any vaccines triggering relapses of multiple sclerosis was found.[54,55]

Type One Diabetes Mellitus and Vaccines

Type one diabetes mellitus is an autoimmune disease. Based on individual case reports of temporal associations and population-based increases in incidence of type one diabetes, Classen[56] believed that introduction of *Haemophilus influenzae* type b (Hib) vaccines caused diabetes in children. He also thought, based on animal studies, that diabetes could be prevented by early immunization with BCG or other vaccines.[57] However, Classen misunderstood the limitations of how ecological data, which are population-based changes in incidence, can be used for assessing causal relationships. The incidence of diabetes is increasing in various age groups in countries throughout the world.[58] Noting an increased incidence of any disease (or any other change in the population) after the introduction of a vaccine does not provide evidence to support a causal relationship. Careful studies in Finland demonstrated a continuous increasing incidence of type one diabetes before and after the introduction of Hib vaccines and no evidence of any significant difference in risk of developing diabetes for children who received multiple doses of this vaccine in infancy as compared to children who received only a single dose at 18 months of age.[59] Two separate expert panels reviewed those data and data from numerous other studies and concluded that there is no evidence to suggest a causal relationship between vaccines and increased risk of developing diabetes.[60,61]

MMR and Autism

In 1998, a gastroenterologist published a brief article implying that MMR vaccine contributed to the development of autism.[61] He had been studying the possible role of measles in inflammatory bowel disease. Twelve children (average age of 6 years) with autism were referred to him for evaluation of gastrointestinal disorders; when he asked the children's parents if the onset of disease had started within 2 weeks of receiving MMR, 8 of the 12 parents said "yes." The investigator believed that he had evidence that MMR was the cause of these children's disease and that the incidence of autism increased in the United States and the United Kingdom after the introduction of MMR. In his view, the simultaneous administration of measles, mumps, and rubella vaccines constituted an "atypical" exposure to measles that predisposed the patient to persistent measles vaccine virus infection of the intestine and an associated inflammatory disorder resulting in the absorption of toxins from the gastrointestinal tract inducing neurologic damage.[3] Because the cause of autism was largely unknown, many parents of affected children were seeking explanations for their children's disease and were willing to accept the hypothesis. Expert panels for the AAP and the Institute of Medicine reviewed these hypotheses in-depth, and both groups concluded that the available data did not support a causal association between MMR and autism. [2,62]

Simultaneous administration of measles, mumps and rubella vaccines results in immunologic responses to each of the vaccines that are similar to the vaccines administered separately and poses no increased risk of developing adverse events, especially gastrointestinal disorders, with the combined vaccines.[2] The evidence for possible persistence of measles viruses and other paramyxoviruses in the intestinal tract and other body tissues is inconclusive, but several investigators in respected institutions around the world have been unable to find evidence of measles virus in tissue

Table 4. Relative Incidence of Severe Complications from Diseases and the Vaccines used to Protec Against these Diseases

Disease/Vaccine	*Complication*	*Disease*	*Vaccine*	*Ratio*
		·5/1000	1/1,000,000	> 1000
		1/1000	1/1,000,000	1000
		4/1000	1/1,000,000	> 4000
		1/10	1/1,000,000	> 100,000

Table 5. Web Sites for Vaccine Information

Organization	*Web Site*
	www.aap.org
	www.cdc.gov/
	www.immunize.org
	www.vaccinesafety.edu
	www.immunizationinfo.org
	www.fda.gov/cber/vaers/

biopsies from children or adults with inflammatory bowel disease.[63] No evidence supports the contention that inflammation of the gastrointestinal tract contributes to the abnormal absorption of toxins and neurologic damage. Several epidemiologic studies have demonstrated no association between the timing of introduction of MMR vaccine and apparent increases in the prevalence of autism in several countries.[64-66] The investigator had misinterpreted ecological data, which have limited value for the assessment of causal relationships, and he assumed that temporal associations implied causal associations. Expert groups in many countries strongly endorse the simultaneous administration of measles, mumps, and rubella vaccines in MMR as the most effective way to prevent these diseases.[19]

Other false assumptions and concerns about vaccines and diseases, including the development of asthma and neurologic damage after administration of whole-cell DTP, have been reviewed by McPhillips and Marcuse.[67] Allegations that administration of multiple vaccines can impair the immune system of infants and young children also have been reviewed recently and found not to be supported by the scientific evidence.[68,69]

Conclusion

All vaccines and related products have some risk of adverse events. Fortunately, most adverse events caused by vaccines are mild, and serious adverse events caused by vaccines rarely occur. When compared to the risk of serious complications from the diseases prevented by vaccines, the risks of serious consequences usually are far greater, 1,000-fold or more, from the natural disease than from the vaccine (Table 4).

Future vaccine safety issues undoubtedly will develop. Up-to-date information can be found at reputable Web sites (Table 5). To prevent future misunderstandings, efforts need to be made to increase understanding by the general public and healthcare practitioners about how vaccine safety issues are investigated and about what constitutes evidence for causal relationships. Efforts to monitor closely vaccines for safety before and after licensure must continue and expand as needed to ensure that the vaccines used to protect against disease are as safe as possible.

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