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Vaccine safety

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Hailed as one of the crowning public health achievements of the past century [1,2], routine childhood vaccination remains at the forefront of public debate because of safety concerns. Experts believe that this debate reflects a broad insecurity that has led to undervaccination and disease outbreaks [3–9]. The often rancorous debate also has led or contributed to the withdrawal of vaccines and vaccine manufacturers from the marketplace [10,11]. The author addresses issues that concern most or all vaccines as a class and specific vaccines that routinely are used in children and adults.

Overview of the nature and magnitude of adverse events associated with vaccination

The best measure of adverse consequences resulting from vaccination is the Vaccine Adverse Events Reporting System (VAERS). Established by the United States in 1990, VAERS functions as a passive surveillance system for vaccine-related adverse events. From 1991 to 2001, VAERS received 128,717 reports of adverse events associated with vaccines [12]. It is estimated that more than 1.9 billion vaccine doses were distributed in the United States during this time period (this distribution rate, which the author refers to throughout the following sections, is a net distribution rate, representing the total doses distributed minus the doses returned) [12]. The adverse event rate approximates 11.4 reports per 100,000 vaccine doses distributed. This rate is not a true incidence rate; VAERS has the typical problems of a passive surveillance system, including under-reporting, causality, temporality, denominators, and comparisons. Nonetheless, it provides a sense of the type and the magnitude of the safety issues associated with vaccines. Of all of the adverse events reported to VAERS during the 1991 to 2001, fever most commonly was reported, appearing in 25.8% of the reports [12]. Injection-site hypersensitivity appeared in 15.8% of the reports, rash appeared in

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11.0%, injection-site edema appeared in 10.8%, and vasodilation (skin redness) appeared in 10.8%.

Serious adverse events (SAEs), including death, hospitalization, or incapacitation, appeared in 14.2% of the reports [12]. The following SAEs were reported: life-threatening illness (2.0% of the reports), hospitalization (10.4%), prolongation of hospitalization (1.1%), permanent disability (2.5%), and death (1.7%) [12]. These reports include events temporally associated with the vaccine but not necessarily causally linked. Most of the reported deaths that were associated with vaccines eventually were attributed to sudden infant death syndrome (SIDS) [12]. On review of the 206 deaths reported to VAERS in 1990 to 1991, the Institute of Medicine (IOM) concluded that only one case clearly resulted from vaccination. This death involved an adult patient who died of complications of Guillain-Barré syndrome after the receipt of a tetanus vaccine [13]. The IOM concluded that most of the deaths reported to VAERS are not linked causally [13].

VAERS provides one of several tools for public health officials in monitoring vaccine safety and demonstrates that the characteristics and the rates of adverse events vary substantially by individual vaccine. Its design results in a number of limitations that are discussed later in this article; a discussion of other tools that are available for evaluating vaccine safety is included. The following section explores specific vaccines and their safety profiles, using the VAERS data as a launching point for the exploration.

Specific vaccines and their safety profiles

Influenza

The most common vaccine distributed in the United States is the influenza vaccine [12]. The influenza vaccines consist of the viruses that most likely will circulate in the winter months in United States; these viruses have included an influenza B virus and two influenza A viruses [14]. The viruses initially are grown in embryonated hen's eggs and then are inactivated or killed. The vaccines consist of the whole, inactivated viruses, subvirions, or surface antigens. A number of manufacturers produce the vaccine in the United States, so manufacturing processes and constituents vary. Some vaccines contain thimerosal as a preservative. Thimerosal previously was used in a number of vaccines; the controversy regarding thimerosal is summarized later in this article.

Between 1991 and 2001, more than a half billion doses of influenza vaccine were distributed [12]. Despite this fact, among VAERS reports, influenza vaccine had the lowest vaccine-specific adverse-event–reporting rate per dose among the 27 frequently reported vaccine types, with a rate of 3.0 reports per 100,000 doses. Local reactions are the most frequently reported by recipients, and almost all reactions are mild. Ten percent to 64% of recipients report soreness at the vaccination site that lasts less than 2 days [14]. Fever, myalgia, and malaise commonly are reported in the first 2 days after vaccination and especially among

first-time recipients. In one double-blind, placebo-controlled, randomized, cross-over study of 1952 adults and children with asthma, however, body aches occurred more frequently among vaccine recipients than among placebo recipients (25.1% versus 20.8%, respectively) [15].

An increased risk for Guillain-Barré syndrome was associated with the swine influenza vaccination in 1976 in the United States [14]. Associations of Guillain-Barré syndrome with vaccine use in subsequent years have been more questionable. After examining the increased number of reports of Guillain-Barré syndrome to VAERS during 1993 to 1994, investigators concluded that the relative risk increased by approximately 1.7 (95% confidence interval, 1.0–2.8; $P = 0.04$) but that there was no increase during that particular season after adjusting for age and sex [16]. The relative risk of 1.7 amounts to slightly more than one additional case per million persons vaccinated against influenza. When understood in the context of the risk for influenza and its complications, this risk was deemed tolerable by experts [12,14].

Hepatitis B virus

The second most commonly given vaccine in the United States is the hepatitis B virus vaccine [12]. In the United States, recombinant DNA technology is used to manufacture this vaccine [17]. The vaccine contains the surface antigen of hepatitis B virus (HBsAg) that is synthesized by *Saccharomyces cerevisiae* or common bakers' yeast, into which the gene for HBsAg has been inserted. The vaccine contains aluminum hydroxide. Although the vaccine's distribution rate to infants, children, and adults is approximately half of that for the influenza vaccine, the overall adverse-event–reporting rate is nearly four times that for the influenza vaccine, with 11.8 reports per 100,000 doses distributed [12].

Adverse events include pain at the injection site (3%–29%) and temperature greater than 37.7°C (1%–6%) [17]. These adverse events occur no more frequently than those that occur with a placebo injection. Although the surveillance of adverse events detected a possible association of Guillain-Barré syndrome with the plasma-derived vaccine containing HBsAg, the data do not support such an association with the recombinant vaccine. Despite claims that there is a possible association between hepatitis B virus vaccine and multiple sclerosis and that a weak, theoretical basis can be made for an etiologic association between vaccines as a class of biologic agents and multiple sclerosis, the IOM rejected the former claim based on a careful review of epidemiologic evidence [18]. This plasma-derived vaccine is no longer used in the United States.

Diphtheria, tetanus, and acellular pertussis

The vaccines directed against diphtheria and tetanus contain diphtheria and tetanus toxoids that result from formaldehyde treatment of the respective toxins [19]. The diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine contains inactivated *Bordetella pertussis* cells. Tetanus toxoid is available in a fluid form;

the other toxins are available in aluminum-salt-adsorbed preparations as single agents or in combination with the tetanus toxoid.

Local injection-site reactions commonly occur with this family of vaccines. Local reactions include injection-site erythema (~33%); swelling (~40%); and pain and tenderness (50%) [19]. Occasionally, a nodule may form at the injection site that can last for weeks. Sterile abscesses occur rarely (6–10 million doses of diphtheria, tetanus, and acellular-pertussis [DTaP] vaccine). Local reactions seem to increase with increasing doses of diphtheria, tetanus, and pertussis (DTP) vaccine.

Mild systemic reactions also occur frequently and are transient and self-limited [19]. These reactions include fever (~50%), drowsiness (~33%), irritability (~50%), vomiting (~7%), and anorexia (~20%) [19]. The occurrence of fever seems to increase in frequency with the increase in the number of doses received, whereas other adverse events seem to decrease in frequency. More severe systemic reactions include fevers greater than or equal to 40.5°C (105°F; 0.03%); persistent, inconsolable crying lasting at least 3 hours (1%); hypotonic-hyporesponsive episodes (0.06%) [20]; and convulsions usually associated with fever (0.06%) [21]. These reactions are also transient and self-limited without sequelae [22].

The family of DTP vaccines has served as a lightning rod for vaccine-safety issues. The DTwP vaccine raised concerns because of the commonly resulting fever and irritability [23,24] and rare but well-known associations with prolonged crying spells, hypotonic-hyporesponsive events, and febrile convulsions [25]. This adverse event profile suggested that possible neurologic insult or injury was involved [23]. By the nature of its frequency, the primary series, in which dosing occurred at 2, 4, and 6 months of life, would precede the emergence of signs and symptoms of metabolic, neurologic, or developmental abnormalities that predated the vaccination series [23]. Because pertussis is associated with neurologic injury [19], it is logical that parents and practitioners would suspect causal links to rare, chronic neurologic concerns [23].

The DTwP vaccine was used widely until 2000 and has been replaced by the DTaP vaccine because of the substantial reduction in the frequency of the common local and systemic adverse reactions, including local reactions, fever, and other common systemic symptoms [26]. From 1991 until 1994, approximately 19 to 20 million DTwP vaccine doses were distributed each year [12]. In 2001, only 68,000 DTwP vaccine doses were distributed [12]. The number of adverse events reports from VAERS has declined with the use of the DTaP vaccine. For 1991–2001, the adverse event rate for the DTwP vaccine was 26.2 reports per 100,000 doses, and the rate for the DTaP vaccine was 12.5 [12].

Scientific review of the data regarding SAEs associated with DTwP vaccination failed to substantiate claims of permanent neurologic injury. In 1991, the IOM published its thorough review and found inadequate evidence to accept or reject a causal relationship with chronic neurologic insult or injury [27]. It also rejected a relation between the vaccine and SIDS [27]. It did find, however, evidence of a causal association with a shock-collapse syndrome, persistent crying, febrile convulsions, peripheral neuritis, and a rare acute encephalopathy [27]. Any vaccine

that can produce fever can result in febrile convulsions. These febrile convulsions resolve quickly and do not indicate epilepsy or result in chronic neurologic disability [28]. A better tolerated vaccine was sought, because the DTwP vaccine was associated with rare acute encephalopathy, and such chronic central nervous system dysfunctions cannot be dissociated as a rare possibility from children who develop a serious acute neurologic illness after receiving the DTwP vaccine [27,28]. DTaP vaccines were developed to address concerns with the tolerability of the DTwP vaccine. In precensure studies, the DTaP vaccine demonstrated a lower rate of fever and irritability. Postlicensure study has indicated reduced rates of seizures and hypotonic-hyporesponsive episodes [29].

The DTaP vaccine seems to be associated with higher rates of local inflammatory reactions, including skin redness and swelling at the injection site with the fourth and fifth injections of DTaP vaccine after a primary series of the vaccine. During 1991, there were approximately 100 cases of injection-site edema or swelling after the fourth and fifth dose of DTwP vaccine. In the years when DTaP vaccine primarily was used, the cases climbed from approximately 300 in 1999, to 450 in 2000, and to nearly 600 in 2001 [12]. The Food and Drug Administration (FDA) has licensed a new combination vaccine containing DTaP, hepatitis B virus, and inactivated poliovirus (IPV) [30]. The rate of fever after administration of this new vaccine was higher than the rates observed after separate administration of the licensed vaccines. The rates of most other adverse reactions were comparable.

Poliovirus

The IPV vaccine consists of a suspension of three poliovirus serotypes grown in a cell line of monkey kidney cells and inactivated by formaldehyde. The suspension contains formaldehyde, 2-phenoxyethanol, and trace amounts of streptomycin, neomycin, and polymyxin-B used in production [31]. In the United States, this form of the vaccine has replaced the use of an oral poliovirus (OPV) vaccine that still is used throughout the world. OPV vaccine once was the primary form of the vaccine used in the United States. It consists of three attenuated poliovirus serotypes grown in a cell line of monkey kidney cells and contains streptomycin and neomycin [31].

Dose distributions of the poliovirus vaccines rival those of the DTP vaccines. During 1991 to 2001, approximately 18 to 19 million doses of the poliovirus vaccines are distributed each year [12]. During this period, recommendations were made to switch from OPV to IPV vaccine to reduce and eliminate the risk for vaccine-associated paralytic poliovirus. The live attenuated trivalent OPV vaccine was associated with rare occurrences (1 case per 2.4 million doses) of vaccine-associated paralytic poliovirus in the recipient and in contacts, with higher risks among immunocompromised people. The rate of vaccine-associated paralytic poliovirus for first-dose recipients was 1 case per 750,000 doses. The rate of adverse events associated with poliovirus vaccine declined slightly from 15.1 cases per 100,000 doses with OPV vaccine to 13.1 with IPV vaccine. No case of vaccine-associated paralytic poliovirus has been reported to VAERS since 1997.

Some of the poliovirus vaccines that were manufactured from 1955 to 1963 were produced using monkey kidney cells contaminated with simian virus 40 (SV 40). SV 40 has properties similar to cancer-causing viruses, although it has not been shown to cause cancer in humans. Once the contamination with SV 40 was discovered, efforts were made successfully to eliminate the contamination. Most of the contamination affected IPV vaccines. The IOM has reviewed the data and has found that studies of humans who received the vaccine during this time had no increase in cancer rates [32].

Haemophilus influenzae

The first vaccines directed against *Haemophilus influenzae* (Hib) consisted of polyribosylribitol phosphate, which is a polysaccharide [33]. To overcome infants' poor immune response to polysaccharides, manufacturers covalently bonded the polysaccharide to one of several proteins, including a mutant *Corynebacterium diphtheriae* protein (CRM197), a *Neisseria meningitidis* outer membrane protein complex, and the diphtheria toxoid.

Reactions to this vaccine are mild [33]. Local and systemic reactions occurring in the first 24 to 48 hours after vaccination are infrequent but increase with an increasing number of doses. Injection-site adverse events that occur after the second and third doses include redness (0.7%–2.2%), swelling (0.9%–1.1%), and warmth (<1%); 2.2% to 4.3% had fever greater than 38.3°C (101°F) [33]. SAEs are rare, and safety studies have found that SAE rates are not greater than those that occur with placebo vaccines.

The VAERS rate of reported adverse events of the Hib vaccine is 18.1 events per 100,000 doses [12], but this rate belies the temporal association that the Hib vaccine has with the DTP vaccines. In 1991, the rate was 28.2 events per 100,000 doses, as the DTwP vaccine routinely was given at that time [12]. This rate resembled that associated with the OPV vaccine, which also was given with the DTP and Hib vaccines at 2, 4, 6, and 15 months of life. In 2001, the rate of reported adverse events for the Hib vaccine, now routinely given with the DTap vaccine, was 12.8.

Rotavirus

In 1998, the United States licensed the first vaccine directed against rotavirus disease. The vaccine was a live, oral, rhesus reassortant rotavirus vaccine that consisted of four serotypes. Despite a relatively small distribution in the United States (estimated to be less than 0.5 million doses in 1999), the vaccine resulted in 708 adverse event reports, giving the highest rate among vaccines of 156.3 reports per 100,000 doses [12].

From licensure in August 1998 through July 7, 1999, VAERS received 15 reports of intussusception associated with the use of this vaccine in infants, the first case occurring in December 1999 [12]. In July 1999, the Advisory Committee on Immunization Practices (ACIP) called for a temporary halt in vaccination while

further study was conducted; the vaccine manufacturer voluntarily ceased distribution at the same time. Reports of 107 cases of intussusception were reported from July 1999 through December 1999, and most cases were reported between July and August 1999 after the publication of the concern for an association with intussusception. Before August 1998, VAERS only received three reports of intussusception. In October 1999, after a review of data from a variety of sources, the ACIP concluded that the vaccine resulted in a substantial increase in the frequency of intussusception in the first 2 weeks after vaccination and particularly with the first dose. At that time, the ACIP withdrew its recommendation for routine use in children [34].

Rotavirus is the most common cause of severe diarrhea worldwide, and despite the withdrawal of the vaccine, the need for a vaccine persists [35]. Studies of bovine rotavirus vaccine have been promising [36–38], and reanalysis of the rhesus rotavirus vaccine indicates that the vaccine may not have caused an actual increase in the frequency of intussusception, which has fueled speculation that the benefits of the rhesus rotavalent vaccine still may outweigh the risks of the vaccine [39].

Varicella

The varicella vaccine was licensed in 1995 and routinely is given to infants at 12 to 15 months of age [40]. The vaccine consists of a live, attenuated varicella virus and the Oka strain, which has been isolated from an infected, healthy child, and attenuated through sequential passages through three cell lines, including human embryonic lung cells, embryonic guinea-pig cells, and human diploid cells.

From 1999 to 2001, about 6 million doses were distributed annually [12]. Approximately 50 adverse events are reported per 100,000 doses; however, only 5% of events are reported as SAEs. Typical reactions primarily consist of local injection-site redness and pain [40]. In the month after vaccination, approximately 3% to 4% of vaccine recipients develop a varicella-like rash (averaging two lesions at the injection site), and another 3% to 4% of recipients develop a generalized varicella-like rash, averaging five lesions. Both rashes occur no sooner than 5 days after vaccination.

Herpes zoster has been reported to occur after varicella vaccination. These cases have been limited to mild and completing remitting forms. It is suspected that the rate of herpes zoster is higher among unvaccinated individuals compared with vaccinated individuals [40].

Measles, mumps, and rubella

The primary form of vaccination against measles, mumps, and rubella (MMR) is the trivalent vaccine. The MMR vaccine is composed of three live, attenuated viruses, including a further attenuated preparation of the Enders-Edmonston virus strain grown in chick embryo cell culture, the Jeryl-Lynn mumps strain also

grown in chick-embryo cell culture, and the RA 27/3 rubella strain grown in human diploid cell culture [41].

Approximately 12 to 14 million doses are distributed each year, resulting in approximately 16.3 adverse events per 100,000 doses [12]. Typical reactions include injection-site pain, edema, and induration [41]. Syncope and anaphylaxis occur occasionally, and adverse events occur primarily among first time, nonimmune recipients. The IOM reviewed the association of the MMR vaccine and found evidence supporting an etiologic association with thrombocytopenia, febrile convulsions, anaphylaxis, and acute arthritis [42,43]. The IOM could not confirm or reject reported associations with vasculitis, otitis media, conjunctivitis, optic neuritis, ocular palsies, Guillain-Barré syndrome, and ataxia.

In 1993, Wakefield et al [44] reported immunohistopathologic evidence of measles virus in tissue samples in patients with Crohn's disease. Later, in collaboration with Thompson et al [45], they reported case-control evidence of an increased association of Crohn's disease and ulcerative colitis with measles vaccination. In 1998, Wakefield et al [46] studied a series of patients with an inflammatory bowel condition associated with a pervasive developmental disorder with features of autism. In 8 of 12 patients, the parents reported the onset of symptoms at the time of the MMR vaccination. These claims led to a concern that the apparent contemporary increase in rates of autism was the result of concurrent increases in rates of measles vaccination. Other investigators argued that the autism resulted not from increased rates of measles vaccination alone but from the relatively recent practice of combining the measles vaccine with the rubella and mumps vaccines [47]. These concerns resulted in decreased use of the measles and MMR vaccines and perhaps led to some outbreaks of disease [3–9,48]. A number of epidemiologic studies have been performed that indicate no association between measles vaccine and autism [49–52]. On review of such studies and other scientific evidence, the IOM rejected these claims [53]. Similarly, the weight of evidence fails to link the measles vaccine or MMR vaccine to Crohn's disease. No association was found in a large, prospective, population-based, British birth cohort, [54] and other investigators were also unable to discern an association [55,56].

Although pregnancy remains a contraindication to the receipt of live viral vaccines in general, review of the data of congenital rubella syndrome revealed no cases of disease among infants who were born to women vaccinated inadvertently against rubella within 3 months of pregnancy or early in pregnancy [57]. On the basis of this finding, the ACIP shortened its recommended period to avoid pregnancy after receipt of a rubella-containing vaccine from 3 months to 28 days.

Lyme disease

Licensed in December 1998, approximately 1.5 million doses were distributed of LYMERix (recombinant OspA; GlaxoSmithKline) from 1999 to 2001. The vaccine consisted of a lipidated recombinant outer-surface protein A of the

Borrelia burgdorferi spirochete; the recombinant protein is produced by recombinant *Escherichia coli* and is absorbed on aluminum hydroxide [58]. Vaccination involves two doses given 1 month apart and a third dose given 1 year after the first dose.

During 1999 to 2001, VAERS received 1534 reports of adverse events (rate, 103.1 events per 100,000 doses) [12]. These events included injection-site reactions, transient arthralgia and myalgia, fever, flu-like symptoms, and hypersensitivity reactions. Fourteen cases of arthritis were confirmed by further study; in seven of these cases, a history of a concomitant exposure to Lyme disease or a history of Lyme disease or another medical condition provided an etiologic alternative.

GlaxoSmithKline (GSK) discontinued the sale and manufacture of LYMERix in February 2002 (John F. Jabara, Vice President, GSK Vaccines Business Unit, corporate communication, 2002). In its letter to its customers, GlaxoSmithKline cited insufficient sales for this vaccine. The letter also requested that vaccine providers stop any further use of the vaccine and return unused supplies to the company for a full refund. The vaccine was developed specifically for the spirochete *B burgdorferi*. In North America, all cases of Lyme disease are caused by the *B burgdorferi sensu stricto* strain. LYMERix was the only vaccine against Lyme disease available in North America [59].

Vaccine-safety issues

The claims against LYMERix vaccine had origins in concerns generic to vaccines concerning the possibility that the vaccine might result negatively in an alteration in the body's immune function and perhaps result in an autoimmune phenomenon. Related concerns include atopy and a weakening of the immune system. Another concern across the class of vaccines is the commonly used vaccine preservative thimerosal. These issues are discussed and are followed by a discussion of the procedures in place in the United States to discern safety issues with individual vaccines.

Atopic tendencies, autoimmunity, and a weakening of the immune system

A substantial number of parents believe that multiple vaccines, as the routine childhood vaccine schedule requires, lead to immunologic overload [60,61]. Some authorities have posited that routine vaccination removes natural exposure to childhood illness and results in an allergic and atopic tendencies [62]. The hygiene hypothesis holds that the lack of infection results in a persistence of IgE-promoting, helper T-cell type 2 responses. Review of published studies indicates that there is no evidence that vaccines result in the elimination of the overwhelming number of self-limited childhood infections or a tendency toward allergic or autoimmune disorders [62]. A similar review indicates that there is no

evidence that multiple vaccines, whether given simultaneously or not, weaken a child's immune system [63].

Thimerosal

Vaccine manufacturers have used thimerosal, a mercury-containing compound, as a preservative since the 1930s. Although no one has reported evidence of actual harm resulting from the relatively low levels of thimerosal found in vaccines, the US Public Health Service and the American Academy of Pediatrics issued a joint statement in 1999 recommending that manufacturers reduce the thimerosal content in vaccines to decrease the total mercury exposure related to vaccination, especially among infants and pregnant woman [64]. Since 2001, routinely administered childhood vaccines used in the United States contain trace or no amounts of thimerosal, with the exception of influenza vaccines [14,65].

Programs designed to ensure vaccine safety

Efforts to eliminate thimerosal resulted from theoretical concerns rather than empirical study, but the primary efforts in the United States and elsewhere to ensure vaccine safety have depended on a multiphasic empiric approach that begins with extensive preclinical and clinical studies that eventually lead to licensure for only a fraction of candidate vaccines. Although prelicensure vaccine trials study animals and humans for efficacy, safety, and tolerability, the numbers of humans studied before licensure does not provide a basis for detecting rare associations [66,67]. Postlicensure surveillance is necessary to ensure vaccine safety. In the United States, the FDA usually stipulates on licensure that the manufacturer conduct postlicensure studies to address general and specific concerns. The Centers for Disease Control and Prevention (CDC) direct three programs to provide vaccine-safety surveillance and adverse event detection and evaluation. These programs include VAERS, the Vaccine Safety Datalink project, and the Clinical Immunization Safety Assessment Centers.

As previously mentioned, VAERS serves as a passive surveillance mechanism to monitor postlicensure safety concerns with all active immunization agents that are directed against infectious diseases [12,68]. This system began on November 1, 1990, and is administered jointly by the CDC and FDA. Federal regulations require that vaccine manufacturers and health professionals report specific adverse events that occur in association with vaccines. VAERS accepts also reports from the public. Case report forms are used to collect detailed information on the patient, vaccine, adverse event, and reporter. All SAE reports are pursued for additional information, including medical reports. These data are collected and analyzed to permit the detection of new, unusual, or rare adverse events; increases in known adverse events; risk factors for types of adverse events; and associations with specific lots and newly licensed vaccines. Because VAERS is a passive collecting system, it lacks the ability to deliver comprehensive reporting of events and the

ability to generate direct rates through the measure of a population vaccinated with the agent under consideration.

The CDC led the establishment of a Vaccine Safety Datalink Project in 1991 to address these weaknesses. The project includes cohorts of more than 7 million individuals in eight health maintenance organizations across the United States and links adverse events with documentation of immunization [12,69]. It reduces or eliminates the underreporting of medical outcomes and provides a denominator to calculate rates of adverse events.

The CDC established a national network of Clinical Immunization Safety Assessment Centers [12]. These centers provide protocols to evaluate reported adverse events and consultative and referral resources to healthcare providers who are evaluating patients with an adverse event associated with vaccination.

Summary

Rates of reported adverse events are remarkably low. VAERS identifies an adverse event rate approximating 11.4 reports per 100,000 vaccine doses. Approximately 15% of these reports represent SAEs, but less than 2% involve death; in most cases, reviews have shown no causal relation between the events and the vaccine. Across the spectrum of vaccines in use (including those directed against influenza and hepatitis B virus), many claims of adverse events regarding vaccines represent typical reactions to vaccinations. These reactions can be thought of as foreign-body reactions and predominate among the inactivated vaccines. In controlled studies, the adverse event rates that occur with vaccination resemble those that occur with placebo injections. Typical reactions associated with live viral and bacterial vaccines, such as MMR and varicella vaccines, may resemble attenuated forms of the disease for which the vaccine is directed. Other claims against vaccines represent chance—coincidence or misunderstood data; further studies of claims have vindicated the overall safety of the vaccines in most cases. Two documented safety concerns with vaccines, however, have demonstrated that vaccines (like other biologics and pharmacologic) can result in harm (eg, rotavirus and OPV vaccines). The denouement with these vaccines indicates the broad postmarketing data collection and evaluation that extends efforts made with prelicensure study to balance the benefits from vaccination with the risk for harm. Overall, measures including prelicensure study and postlicensure surveillance, such as VAERS, the Vaccine Safety Datalink Project, and the Clinical Immunization Safety Assessment Centers, have resulted in an exceptional safety profile for the vaccines in use.

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