Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

82 Vaccine Safety

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During the past 100 years, pharmaceutical companies have made vaccines against diphtheria, tetanus, pertussis, polio, measles, mumps, rubella, varicella, hepatitis A, hepatitis B, *Haemophilus influenzae* type B (Hib), pneumococcus, meningococcus, rotavirus, and human papillomavirus, among others (Table 82.1). As a consequence, the number of children in the United States killed by pertussis decreased from 8000 each year in the early 20th century to fewer than 20; the number paralyzed by polio decreased from 15,000 to 0; the number killed by measles decreased from 3000 to 0; the number with severe birth defects caused by rubella decreased from 20,000 to 0; and the number with meningitis and bloodstream infections caused by Hib decreased from 25,000 to fewer than 100.

Vaccines have been among the most powerful forces in determining how long we live.[1] However, the landscape of vaccines is also littered with tragedy. In the late 1800s, starting with Louis Pasteur, scientists made rabies vaccines using cells from nervous tissue, including animal brains and spinal cords. Although the vaccine prevented a uniformly fatal infection, it also caused seizures, paralysis, and coma in as many as 1 of every 230 people who used it.[2–5]

In 1942, the military injected hundreds of thousands of American servicemen with a yellow fever vaccine. To stabilize the vaccine virus, scientists added human serum. Unfortunately, some of the serum came from people unknowingly infected with hepatitis B virus. As a consequence, 330,000 soldiers were infected with hepatitis B, severe disease developed in 50,000, and 62 died.[6–9]

In 1955, five companies made Jonas Salk's new formaldehyde-inactivated polio vaccine. However, one company, Cutter Laboratories of Berkeley, California, failed to completely inactivate poliovirus with formaldehyde. Because of this failure, 120,000 children were injected with live poliovirus; 40,000, developed mild polio, 200 were permanently paralyzed, and 10 died. It was one of the worst biological disasters in American history.[10]

Vaccines have also caused uncommon but severe adverse events not associated with production problems. For example, acute encephalopathy after whole-cell pertussis vaccine,[11,12] Guillain-Barré syndrome (GBS) after swine flu vaccine,[13] paralytic polio following live attenuated oral polio vaccine,[14] anaphylaxis following several different vaccines,[15] severe or fatal viscerotropic disease following yellow fever vaccine,[16] and intussusception following rotavirus vaccine,[17–19] are problems associated with the use of vaccines, albeit rarely. As vaccine use increases and the incidence of vaccine-preventable diseases decreases, vaccine-related adverse events become more prominent (Fig. 82.1). Even unfounded safety concerns can lead to decreased vaccine acceptance and resurgence of vaccine-preventable diseases, as occurred in the 1970s and 1980s as a public reaction to allegations that the whole-cell pertussis vaccine caused encephalopathy (Fig. 82.1). Recent outbreaks of measles, mumps, and pertussis in the United States are important reminders of how immunization delays and refusals can result in resurgences of vaccine-preventable diseases.[20–22]

METHODS OF MONITORING IMMUNIZATION SAFETY

Because vaccines are given to healthy children and adults, a higher standard of safety is expected of immunizations compared with other medical interventions. Tolerance of adverse reactions to pharmaceutical products (e.g., vaccines, contraceptives) given to healthy people—especially infants and toddlers—is substantially lower than to therapeutic agents (e.g., antibiotics, insulin) used to treat illness.[23] This translates into a need to investigate the possible causes of much rarer adverse events after vaccinations than would be acceptable for other pharmaceutical products. For example, severe side effects are essentially universal for cancer chemotherapy, and 10% to 30% of people receiving high-dose aspirin therapy experience gastrointestinal symptoms.[24]

Safety monitoring is performed both before and after vaccine licensure, with slightly different goals based on the methodological strengths and weaknesses of each step.[25–28] Although the general principles are similar irrespective of country, the specific approaches may differ because of the organization of immunization services and the level of available resources.[29]

Prelicensure Evaluations of Vaccine Safety

Vaccines, similar to other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in phased human clinical trials before licensure.[30,31] Phase I trials usually involved smaller numbers of subjects and are able to detect only extremely common adverse events. Phase II trials generally enroll several hundred people in each vaccine arm, as in the comparative infant diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine trials,[32] and provide data on the impact of antigen content, number of vaccine components, vaccine formulation, effect of successive doses, and profile of common reactions. These data can inform the choice of the candidate vaccines for Phase III trials.[33,34] Sample sizes for Phase III vaccine trials are often based on efficacy considerations, and resultant safety data are dependent on the sample size (approximately 10^2 to 10^5) and the duration of observation (often <30 days).[33] Typically, only observations of rates of common local and systemic reactions (e.g., injection site swelling, fever, fussiness) are feasible. The experimental design of most clinical trials includes a control group (a placebo or an alternative vaccine) and the detection of adverse events by researchers who are "blinded" to which vaccine the patient received. This allows relatively straightforward inferences on the causal relationship between most adverse events and vaccination.[35]

Several ways of enhancing prelicensure safety assessment of vaccines have been developed. One of these ways includes the Brighton Collaboration (www.brightoncollaboration.org), which was established to develop and implement globally accepted standard case definitions for assessing adverse events following immunizations.[36] Without such defined standards, it was often difficult, if not impossible, to compare and

contrast safety data across trials. The Brighton case definitions for each adverse event are further arrayed by the level of evidence provided (insufficient, low, intermediate, and highest); therefore, they also can be used in settings with fewer resources (e.g., studies in less-developed settings or postlicensure surveillance). For example, in the large multisite Phase III infant DTaP trials, definitions of high fever across trials varied by temperature (39.5°C vs 40.5°C), measurement (oral vs rectal), and time (measured at 48 vs 72 hours).[37] This was unfortunate because standardized case definitions had been developed in these trials for efficacy but not for safety, even though the safety concerns provided the original impetus for the development of DTaP.[38,39]

There has been a greater recognition of the need for much larger safety databases before licensure. Because of pragmatic limits on the sample sizes of prelicensure studies, there are inherent limitations to the extent to which they can detect very rare, yet real, adverse events related to vaccination. Even if no adverse event has been observed in a trial of 10,000 vaccinees, one can only be reasonably certain that the real incidence of the adverse event is no higher than one in 3333 vaccinees.[40]

TABLE 82.1 Maximum and Number of Cases Reported in 2004: Morbidity From Vaccine-Preventable Diseases Events, United States

Disease	Maximum Cases (Year)	Cases Reported in 2014	% Change
Smallpox	206,939 (1921)	0	–100
Diphtheria	894,134 (1941)	1	>–99
Measles	152,209 (1968)	667	>–99
Mumps	265,269 (1934)	1223	–99
Polio (paralytic)	57,686 (1952)	0	–100
Congenital rubella syndrome	20,000[a] (1964–65)	1	>–99
Haemophilus influenzae type b	25,000[a]	306	–98

[a]Estimated because no national reporting existed in prevaccine era.

Thus, to be able to detect an attributable risk of one per 10,000 vaccinees (e.g., such as the approximate risk found for intussusception in the postlicensure evaluation of the simian–human reassortant rotavirus vaccine, RotaShield vaccine), a prelicensure trial of at least 30,000 vaccinees and 30,000 control subjects is needed. Both second-generation rotavirus vaccines (the bovine human reassortant vaccine, RotaTeq, and the attenuated human rotavirus vaccine, Rotarix) were subjected to Phase III trials that included at least 60,000 infants.[41,42] While these trials were adequately powered to detect intussusception at the rate seen with RotaShield, they were not adequately powered to detect the rates ultimately seen with either RotaTeq or Rotarix. In addition, the cost of such large safety trials could limit the number of vaccine candidates that could be studied.[43]

Postlicensure Evaluations of Vaccine Safety

Because reactions that are rare, delayed, or which occur in only certain subpopulations may not be detected before vaccines are licensed, postlicensure evaluation of vaccine safety is critical. Historically, this evaluation has relied on passive surveillance and ad hoc epidemiologic studies, but, more recently, Phase IV trials and preestablished large, linked databases have enhanced the capabilities to study rare adverse events after specific immunizations.[35] Such systems may detect variation in rates of adverse events by manufacturer[44,45] or specific lot.[46] More recently, clinical centers for the study of immunization safety have emerged as another useful infrastructure to advance our knowledge about safety.[47]

In contrast with the methodological strengths of prelicensure randomized trials, however, postlicensure observational studies of vaccine safety pose a formidable set of methodological difficulties.[48] Confounding by contraindication is especially problematic for nonexperimental designs. Specifically, persons who do not receive vaccine (e.g., because of a medical contraindication) might have a different risk for an adverse event than vaccinated persons. Therefore, direct comparisons of vaccinated and unvaccinated children are often inherently confounded, and teasing out these confounding issues requires understanding of the complex interactions of multiple, poorly quantified factors.

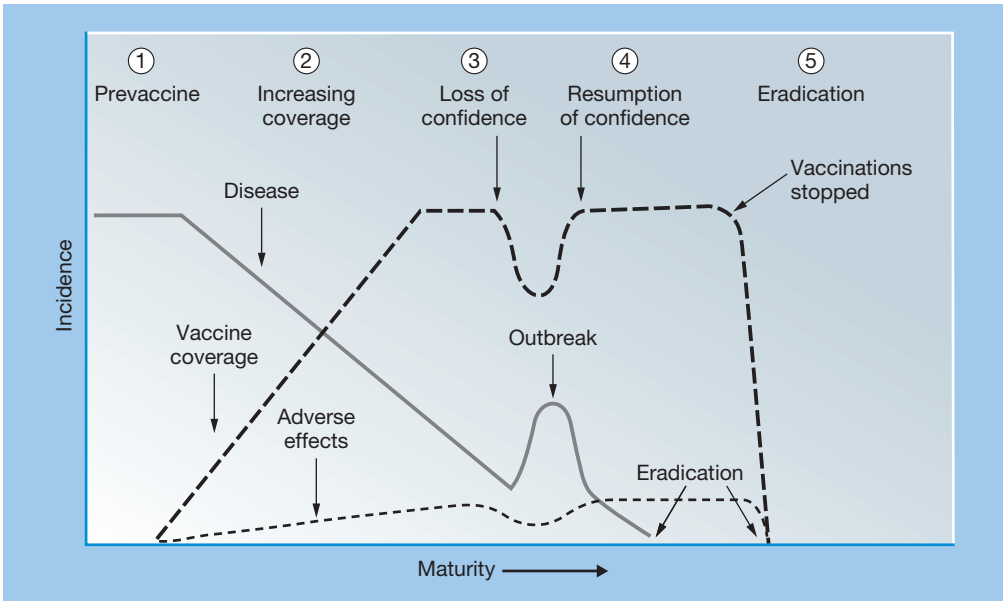

Figure 82.1. Evolution of immunization program and prominence of vaccine safety.

Passive Reporting Systems, Including the Vaccine Adverse Event Reporting System

Informal or formal passive surveillance or spontaneous reporting systems (SRSs) have been the cornerstone of most postlicensure safety monitoring systems because of their relative low cost of operations.[49–51] The national reporting of adverse events following immunizations can be done through the same reporting channels as those used for other adverse drug reactions,[51] as is the practice in France,[52] Japan,[53] New Zealand,[54] Sweden,[55] and the United Kingdom,[56] or with reporting forms or surveillance systems different from the drug safety monitoring systems, as is the practice in Australia,[57] Canada,[58,59] Cuba,[60] Denmark,[61] India,[62] Italy,[63] Germany,[64] Mexico,[65] The Netherlands,[66] Brazil,[67] and the United States.[68] Vaccine manufacturers also maintain SRSs for their products and they forward reports to appropriate national regulatory authorities.[30,65]

In the United States, the National Childhood Vaccine Injury Act of 1986 mandated that healthcare providers report certain adverse events after immunizations.[69] The Vaccine Adverse Events Reporting System (VAERS) was implemented jointly by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) in 1990 to provide a unified national focus for collection of all reports of clinically significant adverse events, including, but not limited to, those mandated for reporting.[68]

The VAERS form permits narrative descriptions of adverse events. Patients and their parents—not just healthcare professionals—are permitted to report to VAERS, and there is no restriction on the interval between vaccination and symptoms that can be reported. Report forms, assistance in completing the form, answers to other questions about VAERS, and additional information about the reported reactions, including whether or not the patient recovered, are available on the VAERS website (vaers.hhs.gov). Web-based reporting and simple data analyses are also available.

A contractor, under CDC and FDA supervision, distributes, collects, codes (currently using the Medical Dictionary for Regulatory Activities), and enters VAERS reports into a database. Reporters of selected serious events are contacted by trained clinical staff on report receipt and are sent letters at 1 year after report receipt to provide additional information about the VAERS report, including the patient's recovery. Approximately 30,000 VAERS reports are now received annually, and these data (without personal identifiers) are also available to the public (at vaers.hhs.gov and at wonder.cdc.gov/vaers.html).

Several other countries also have substantial experience with passive surveillance for immunization safety. In 1987, Canada developed the Vaccine Associated Adverse Event reporting system,[59,70] which is supplemented by an active, pediatric hospital–based surveillance system that searches all admissions for possible relationships to immunizations (Immunization Monitoring Program-Active [IMPACT]).[71] Serious Vaccine Associated Adverse Event reports are reviewed by the Advisory Committee on Causality Assessment consisting of a panel of experts.[72] The Netherlands also convenes an annual panel to categorize reports, which are then published.[66] The United Kingdom and most members of the former Commonwealth use the yellow card system, whereby a reporting form is attached to officially issued prescription pads.[50,55] Data on adverse drug events (including vaccine) from several countries are compiled by the World Health Organization (WHO) Collaborating Center for International Drug Monitoring in Uppsala, Sweden.[73]

With so many different passive surveillance systems that collect information on various medical events following vaccination, standardized definitions of vaccine-related adverse events are optimal. Implementation of similar standards across national boundaries has been advanced by the International Conference on Harmonization[74] and the Brighton Collaboration.[36]

Because VAERS is the only surveillance system covering the entire U.S. population with data available on a relatively timely basis, it is the major means available to currently detect possible new, unusual, or extremely rare adverse events. For example, in 1999, passive reports to VAERS of intussusception among children vaccinated with RotaShield was the first postlicensure signal of a problem,[75] leading to epidemiologic studies that verified the association.[17,76] Similarly, initial reports to VAERS of a previously unrecognized serious yellow fever vaccine–associated neurotropic disease[77] and viscerotropic disease[78,79] have since been confirmed elsewhere.[80] Because of the success in detecting these signals, there have been various attempts to automate screening for signals using SRSs reports. New tools developed for pattern recognition in extremely large databases are beginning to be applied.[81] These include empirical Bayesian data mining to identify vaccine-event adverse event combinations that are reported more frequently following a specific vaccine than following all other vaccines combined.[82]

Despite the aforementioned uses, SRSs for drug and vaccine safety have a number of major methodological weaknesses. Underreporting, biased reporting, and incomplete reporting are inherent to all such passive systems, and potential safety concerns might be missed.[83–85] Some increases in adverse events detected by VAERS might not be true increases, but instead might be the result of increases in reporting efficiency or vaccine coverage. For example, an increase in GBS reports was noted in VAERS shortly after the introduction of a new meningococcal conjugate vaccine (MCV4) in 2005, but a larger study conducted in five U.S. health plans with more than 1.4 million MCV4 vaccinations found no increased risk of GBS.[86] As another example, pending litigation resulted in the filing of a large number of VAERS reports claiming that vaccines caused autism.[87,88]

Perhaps the most important methodological weakness of VAERS, however, is that it does not contain the information necessary for formal epidemiologic analyses. Such analyses require calculation of the rate of the adverse event after vaccination and a comparison rate among unvaccinated persons. The VAERS database provides data only for the number of persons who may have experienced an adverse event following immunization and, even then, only in a biased and underreported manner. VAERS lacks data on the denominator of total number of people vaccinated and the corresponding data on number of cases and denominator population of unvaccinated people. Sometimes reporting rates can be calculated by using VAERS case reports for the numerator and, if available, doses of vaccines administered (or, if unavailable, data on vaccine doses distributed or vaccine coverage survey data) for the denominator. These rates can then be compared with the background rate of the same adverse event in the absence of vaccination, if available. Because of underreporting, however, VAERS reporting rates will usually be lower than the actual rates of adverse events following immunization.

A higher proportion of serious events, such as seizures, that follow vaccinations are likely to be reported to VAERS than milder events, such as rash, or delayed events requiring laboratory assessment, such as thrombocytopenic purpura after measles-mumps-rubella (MMR) vaccination.[83] The reporting efficiency or sensitivity of SRSs can sometimes be estimated if an independent source of cases of specific adverse events following immunization is available to conduct capture-recapture analyses.[89]

Formal evaluation has been limited by the quality of diagnostic information on VAERS reports, especially whether a serious event reported to VAERS has been diagnosed accurately. Of 26 cases reported to VAERS in which GBS developed after influenza vaccination during the 1990–91 season, and for which hospital charts were reviewed by an independent panel of neurologists blinded to immunization status, the diagnosis of GBS was confirmed in only 22 (85%).[90] Intussusception was verified in 88% of VAERS reports filed after Rotashield vaccination.[75] Clinical reviews of VAERS reports submitted following 2009 H1N1 influenza vaccine were able to verify 56% of possible GBS reports and 42% of reports of possible anaphylaxis.[91] Clinical review verification rates were similar for VAERS reports following human papillomavirus (HPV) vaccination: 57% for GBS and 38% for anaphylaxis.[92]

These studies highlight the often crude nature of signals generated by VAERS and the difficulty in ascertaining which potential vaccine safety concerns warrant further investigation. The problems with reporting efficiency and potentially biased reporting and the inherent lack of an adequate control group limit the certainty with which conclusions can be drawn. Recognition of these limitations in large part has helped stimulate the creation of more population-based methods of assessing vaccine safety.

Postlicensure Clinical Trials and Phase IV Surveillance Studies

To improve the ability to detect adverse events that are not detected during prelicensure trials, some recently licensed vaccines in developed countries have undergone formal Phase IV surveillance studies on populations with sample sizes that have included as many as 100,000 people. These studies usually have included cohorts in managed care organizations (MCOs) supplemented by diary or phone interviews. These methods were first used extensively after the licensure of polysaccharide and conjugated Hib vaccines.[93–95] Large postlicensure studies on safety and efficacy have also been conducted for several other vaccines, including those for DTaP,[38] varicella, and herpes zoster,[96,97] as well as for less-frequently used vaccines, such as Japanese encephalitis vaccine.[98]

Large Linked Databases, Including the Vaccine Safety Datalink. Historically, ad hoc epidemiologic studies have been used to assess signals of potential adverse events detected by SRSs, the medical literature, or other mechanisms. Some examples of such studies include the investigations of poliomyelitis after inactivated[10,99] and oral[100] polio vaccines, sudden infant death syndrome (SIDS) after diphtheria-tetanus-pertussis (DTP) vaccination,[101–104] encephalopathy after DTP vaccination,[105,106] meningoencephalitis after mumps vaccination,[107] injection-site abscesses after vaccination,[108] and GBS after influenza vaccination.[13,90,109] The Institute of Medicine (IOM) has compiled and reviewed many of these studies.[11,110,111]

Unfortunately, such ad hoc studies are often costly, time-consuming, and limited to assessment of a single event or a few events or outcomes. Given these drawbacks and the methodological limitations of passive surveillance systems (such as described for VAERS), pharmacoepidemiologists turned to large databases linking computerized pharmacy prescriptions (and later immunization records) and medical outcome records.[85] These databases include defined populations such as members of MCOs, single-provider healthcare systems, and Medicaid programs. Such databases cover enrollee populations numbering from thousands to millions, and, because the data are generated from the routine administration of the full range of medical care, underreporting and recall bias are reduced. With denominator data on doses administered and the ready availability of appropriate comparison (i.e., unvaccinated) groups, these large databases provide an economical and rapid means of conducting postlicensure studies of safety of drugs and vaccines.[112–116]

The CDC initiated the Vaccine Safety Datalink (VSD) project in 1990[113] to conduct postmarketing evaluations of vaccine safety and to establish an infrastructure allowing for high-quality research and surveillance. Several MCOs or integrated healthcare systems in the United States, comprising a population of more than 9 million members, participate in the VSD. Each site prepares computerized data files using a standardized data dictionary containing demographic and medical information on their members, such as age and sex, health plan enrollment, vaccinations, hospitalizations, outpatient clinic visits, emergency department visits, urgent care visits, and mortality data, as well as additional birth information (e.g., birth weight) when available. Other information sources, such as medical chart review; member surveys; and pharmacy, laboratory, and radiology data are often used in VSD studies to validate outcomes and vaccination data. There is rigorous attention to the maintenance of patient confidentiality, and each study undergoes institutional review board review.

The VSD project's main priorities include evaluating new vaccine safety concerns that may arise from the medical literature,[11,110] from VAERS,[76,117] from changes in immunization schedules,[118] or from introduction of new vaccines.[94,95] The creation of frequently updated data files has enabled the development of near real-time postmarketing surveillance for newly licensed vaccines and changes in vaccine recommendations. Many studies have been performed within the VSD project,[116] including general screening studies of the safety of inactivated influenza vaccines among children and of thimerosal-containing vaccines; and disease-specific investigations, including studies investigating autism, multiple sclerosis, thyroid disease, acute ataxia, alopecia, rheumatoid arthritis, asthma, diabetes, and idiopathic thrombocytopenic purpura following vaccination.

Among these advantages, a few caveats are appropriate. Although diverse, the population in the MCOs currently in the VSD project is not wholly representative of the United States in terms of geography or socioeconomic status. More important, because of the high coverage attained in the MCOs for most vaccines, few nonvaccinated control subjects are available. Therefore, VSD studies often rely on risk-interval analyses (e.g., to study the question of whether outcome "x" is more common in period "y" following vaccination compared with other periods) (Table 82.2).[119] This approach, although powerful for evaluating acute adverse events, has limited ability to assess associations between vaccination and adverse events with delayed or insidious onset (e.g., autism). The VSD project also cannot easily assess mild adverse events (such as fever) that do not always come to medical attention.[113] Finally, because vaccines are not delivered in the context of randomized, controlled trials, the VSD project may not be able to successfully control for confounding and bias in each analysis,[120] and inferences on causality may be limited.[121]

Despite these potential shortcomings, the VSD project provides an essential, powerful, and cost-effective complement to ongoing evaluations of vaccine safety in the United States.[115,116] In view of the methodological and logistic advantages offered by large-linked databases, the United Kingdom and Canada also have developed systems linking immunization records with medical files.[71,112] Certain countries, such as Sweden and Denmark, have the capability to conduct important

TABLE 82.2 Example of Method for Risk-Interval Analysis of Association Between a Universally Recommended Three-Dose Vaccine and an Adverse Event

1. Define biologically plausible risk interval for adverse event after vaccination (e.g., 30 days after each dose).

2. Partition observation time for each child in the study into periods within and outside of risk intervals, and sum respectively (e.g., for a child observed for 365 days during which 3 doses of vaccine were received, total risk interval time = 3 × 30 person-days = 90 person-days; total non-risk interval time = 365 – 90 = 275 person-days).

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Birth Dose 1 Dose 2 Dose 3 365 days

3. Add up (a) total risk interval and nonrisk interval observation times for each child in the study (Person-Time Observed; for mathematical convenience, example below uses 100 and 1000 person-months of observation), and (b) adverse events occurring in each time period to complete 2 × 2 table (for illustration, example below uses 3 and 10 cases):

Vaccinated in Risk Interval	Adverse Event: Yes	Person-Time Observed (mo)	Incidence Rate
Yes	3	100	0.03
No	10	1000	0.01
TOTAL	13	1100	

Incidence rate adverse event vaccinated = 3/100 = 0.03
Incidence rate adverse event unvaccinated = 10/1,000 = 0.01
Relative rate vaccinated: unvaccinated = 0.03/0.01 = 3.0
Probability finding is the result of chance: <5/100
Conclusion: There is a threefold increase in risk for developing the adverse event within the 30-day interval after vaccination compared to other time periods.

vaccine safety assessments by linking data across national registries.[122–124]

Clinical Centers, Including the Clinical Immunization Safety Assessment Centers. More recently, the immunization safety infrastructure has been augmented by tertiary clinical centers, such as were first developed in certain regions in Italy[47] and Australia.[125,126]

In the United States, the CDC's Clinical Immunization Safety Assessment (CISA) Project was established in 2001 to address unmet vaccine safety clinical research needs. CISA is a national network of vaccine safety experts from the CDC, seven medical research centers, and subject-matter experts. The CISA mission is to improve understanding of adverse events following immunization at the individual patient level. CISA serves as a vaccine safety resource providing expert consultation on clinical vaccine safety issues and with its partners conducts studies to identify risk factors and preventive strategies for vaccine adverse events, particularly in special populations.[28] The CISA investigators bring in-depth clinical, pathophysiological, and vaccinology expertise to assessing causal relationships between vaccines and adverse events,[127] and to understanding the pathogenesis of adverse events following vaccinations. The CISA investigators have published a standardized algorithm for evaluating and managing persons who have suspected or definite immediate hypersensitivity reactions such as urticaria, angioedema, and anaphylaxis following vaccines.[128] Some of the studies undertaken by CISA include an assessment of extensive limb swelling after DTaP,[129] a study of the usefulness of irritant skin test reactions for managing hypersensitivity to vaccines,[130] the clinical evaluation of patients with serious adverse events following yellow fever vaccine administration,[131] and evaluation of vaccine safety among children with inborn errors of metabolism.[132,133] New understanding of the human genome, pharmacogenomics, and immunology hold promise for future CISA studies and may make it possible to elucidate some of the biological mechanisms of vaccine adverse reactions, which, in turn, could lead to the development of safer vaccines and safer vaccination practices, including revaccination when indicated.[134]

SAFETY OF MASS IMMUNIZATION CAMPAIGNS

In mass-immunization campaigns during which many people are vaccinated in a short time, it is critical to have a vaccine safety monitoring system in place that can detect potential safety problems early so that corrective actions can be taken as soon as possible.[135] Mass-immunization campaigns are often conducted in developing countries, which poses a particular challenge of ensuring injection safety.[136] In any setting in which large numbers of immunizations are being administered, more adverse events will coincidentally occur following immunization. Thus, it is important to have background rates available of expected adverse events to allow rapid evaluation of whether reported adverse events are occurring at a rate following immunization that is higher than would be expected by chance alone. The resources devoted to mass vaccination campaigns also provide opportunities to enhance existing immunization safety monitoring systems or to establish a system if none exists and these may lead to long-term improvements in immunization safety monitoring beyond the specific mass immunization campaign.

The response to the 2009 H1N1 influenza pandemic involved probably the largest and most intense immunization safety monitoring effort ever undertaken in the United States and internationally. The emergence of a novel influenza A (H1N1) virus prompted the development of 2009 influenza A (H1N1) monovalent vaccines. The FDA licensed the first 2009-H1N1vaccines in September 2009. With potentially hundreds of millions of people expected to be vaccinated, adverse events were anticipated to occur in some recently vaccinated people. To address the question of whether the vaccine could be causing the adverse events, background rates for several adverse events were developed.[137] To rapidly detect any unforeseen safety problems, the federal government implemented enhanced postlicensure 2009-H1N1 vaccine safety monitoring,[138] including in VAERS and VSD. A new collaboration was initiated that also performed rapid ongoing analyses similar to VSD and included the databases of several large health insurance plans, the Department of Defense, Medicare, and the Veterans Administration. In addition, active case

finding for GBS was conducted in 10 areas of the United States with a combined population of approximately 50 million people. Initial safety data were provided by VAERS, which found that the adverse event profile after 2009-H1N1 vaccine in VAERS (>10,000 reports) was consistent with that of seasonal influenza vaccines.[91,138] Combined results from the U.S. monitoring systems found 1.6 excess cases of GBS per 1 million vaccinations, which is similar to the increased risk found with some seasonal influenza vaccines.[139]

Similar efforts to intensely monitor the safety of influenza A (H1N1) 2009 vaccines occurred in other countries, primarily in North America, Europe, and Australia, but also included the development of new immunization safety monitoring systems in countries such as Taiwan[140] and a multicountry study of GBS.[141] These extensive international safety monitoring activities and collaborations represented an unprecedented commitment to ensuring the safety of influenza A (H1N1) 2009 vaccines, as well as a model for how we might improve tracking of safety for all vaccines going forward.

WEIGHING THE EVIDENCE AND ASSESSING CAUSALITY

A central function of vaccine safety monitoring and assessment activities is to determine if particular adverse events following immunization are caused by a vaccine. This determination is important in guiding immunization policy and individual care and possibly compensation decisions. Causality assessment may be performed at the individual or population level. Epidemiologic studies provide measures of risk on a population level, but they do not provide evidence that a particular vaccine caused an adverse event in a particular individual. It is often not possible to infer causality in individual cases of adverse events following immunization, except in certain special situations. Circumstances in which a causal association in individual cases can reasonably be inferred include: (a) local reactions at a vaccine injection site; (b) immediate hypersensitivity reactions (in absence of other exposures); (c) recurrence–same adverse event recurs in same individual following repeat exposure to same vaccine; (d) isolation of vaccine virus (from typically sterile site), as, for example, Urabe mumps vaccine and aseptic meningitis; and (e) a unique clinical syndrome, such as vaccine-associated paralytic polio.

More general causality assessments rely on weighing different pieces of evidence using criteria such as strength of association, consistency of findings, temporal relationships, potential biases, and possible biological mechanisms. In the United States, the most authoritative assessments of causality have been conducted by the IOM, whose findings have been particularly influential in compiling the vaccine injury table of the National Vaccine Injury Compensation Program. The IOM has conducted three comprehensive reviews of adverse effects of vaccines,[111,142,143] as well as several focused reviews of specific vaccine safety topics. As highlighted in Table 82.3, the adverse reactions for which there is strong evidence of a causal association with recommended childhood vaccines in the United States are few and tend to occur rarely. Newer vaccines and certain other vaccines, however, were not covered in the latest IOM review in 2012. This gap was addressed by a systematic review of the literature commissioned by the Agency for Healthcare Research and Quality.[144] That review identified a few additional adverse events where the evidence favors a causal association, including rotavirus vaccines and intussusception, pneumococcal conjugate vaccine and febrile seizure, hepatitis A vaccine and purpura, and varicella vaccine and thrombocytopenic purpura.

In addition to identifying causal associations, IOM reviews have also been influential in clarifying particularly controversial issues where the evidence does not favor a causal association. These include pertussis vaccines and SIDS,[145] vaccines and autism,[146] hepatitis B vaccine and multiple sclerosis,[147] and vaccines and type 1 diabetes.[148]

TABLE 82.3 Vaccines and Adverse Events for Which Evidence Favors a Causal Association

Vaccine(s)	Adverse Event	Source	Rate Per Million Doses
Tetanus toxoid, pertussis, measles, mumps, rubella, inactivated polio vaccine, hepatitis B, varicella, influenza, meningitis, human papillomavirus	Anaphylaxis	VIT, IOM 2012	1–2[a]
Pertussis (whole cell)	Encephalopathy/encephalitis	VIT	<1[b]
Measles-mumps-rubella (MMR)	Encephalopathy/measles inclusion body encephalitis	VIT, IOM 2012	Case reports only
MMR	Febrile seizures	IOM 2012	333[b]
MMR	Transient arthralgia, women & children	IOM 2012	~5% (postpartum women); <1% (children)
Measles	Thrombocytopenic purpura	VIT	33[b]
Rubella	Chronic arthritis	VIT	Unknown[c]
Varicella	Vaccine strain dissemination	IOM 2012	Case reports
Any vaccine	Injection-related syncope, deltoid bursitis	IOM 2012	Case reports

[a]Data from McNeil MM, Weintraub E, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868–178.
[b]Data from World Health Organization (WHO), Department of Vaccines and Biologicals. Supplementary information on vaccine safety, Part 2: Background rates of adverse events following immunization. December 2000. WHO/V&B/00.36. Available at: http://apps.who.int/iris/bitstream/10665/66675/1/WHO_V-B_00.36_eng.pdf
[c]IOM 2012 review determined evidence to be inadequate.
IOM, Institute of Medicine; U.S.; VIT, Vaccine Injury Table, U.S..

VACCINE SAFETY CONTROVERSIES AND MISCONCEPTIONS

Unfortunately, vaccine safety issues have increasingly taken on a life of their own outside of the scientific arena—arguably to society's overall detriment. In particular, various chronic diseases (and their advocates) in search of a simple cause, for which immunizations—as a relatively universal exposure—have made all too convenient a hypothesized link. Case studies of some of these controversies are discussed in the following sections.

Whole-Cell Pertussis Vaccine Causes Permanent Brain Damage

In 1974, Kulenkampff and coworkers[149] reported a series of 22 cases of children with mental retardation and epilepsy following receipt of the whole-cell pertussis vaccine. During the next several years, fear of the pertussis vaccine generated by media coverage of this report caused a decrease in pertussis immunization rates in British children from 81% to 31% and resulted in more than 100,000 cases and 36 deaths from pertussis.[150] Media coverage of the Kulenkampff report also caused decreased immunization rates and increased pertussis deaths in Japan, Sweden, and Wales.[150]

However, many subsequent, excellent, well-controlled studies found that the incidence of mental retardation and epilepsy following whole-cell pertussis vaccine was similar in vaccinated children to that in children who did not receive the vaccine.[151–156]

Deaths Following Vaccination: Temporal Association Versus Causality

When a death occurs shortly following vaccination, there might be a natural tendency to question if the death was caused by the vaccine. Suspected associations of deaths with vaccination can have a negative impact on vaccination programs even when investigations do not find any evidence of a direct causal relationship. For example, when a combination pentavalent vaccine replacing the diphtheria-tetanus-whole-cell pertussis (DTwP) vaccine or DTwP-hepatitis B vaccine was introduced into Sri Lanka, India, and Vietnam in 2008–10, deaths were reported among a small number of vaccine recipients prompting authorities to suspend the use of these vaccines.[157] In 2010, an HPV demonstration project in India was suspended in response to demands from advocacy groups when four deaths occurred following receipt of HPV vaccine.[158] In December 2013, the deaths of 17 infants following hepatitis B virus vaccine made by a manufacturer in China generated widespread media and public interest, leading to a temporary suspension of the vaccine.[159] Investigations in all these examples found that the deaths were not caused by the vaccines.

Historically, SIDS has garnered the greatest concern with respect to a possible association with vaccination. In the mid-1980s, the antivaccine group Dissatisfied Parents Together raised the notion that the whole-cell pertussis vaccine could cause SIDS. In the early 1990s, when the hepatitis B vaccine was recommended for routine use in newborns, a popular television news program raised the question of whether vaccines could cause SIDS. SIDS peaks between 2 and 3 months of age, a time when infants are receiving a relatively large number of recommended vaccinations; thus, it would not be unexpected to observe a coincidental close temporal relationship between vaccination and SIDS. SIDS deaths in the United States have been declining since the early 1990s for a variety of reasons, including recommended changes in sleeping position.[160] This downward trend in SIDS has also been observed in SIDS reports submitted to VAERS.[161] Considerable evidence supports the notion that vaccination is not causally associated with SIDS,[162–165] including an IOM review in 2003 that rejected a causal association between the whole cell pertussis–containing vaccine and SIDS and between exposure to multiple simultaneous vaccines and SIDS.[145]

More recently, the misconception of mistakenly attributing temporally related events as causal was highlighted in the U.S. multistate measles outbreak of 2014–15. Early on, unsubstantiated claims of deaths caused by the MMR vaccine appeared on the Internet.[166–168] These claims were largely based on publicly available VAERS data. VAERS, however, is a voluntary reporting system that accepts any submitted report of an adverse event without judging whether it was caused by a vaccination. Any claims of cause and effect with respect to deaths following vaccination based on VAERS reports should be interpreted with caution. When the complete VAERS reports and accompanying medical records, autopsy reports, and death certificates were reviewed by FDA and CDC physicians, no concerning patterns were detected to suggest a causal relationship with MMR vaccination.[169,170]

With rare exceptions (e.g., anaphylaxis), the evidence does not suggest a causal relationship between vaccination and death. In addition to the 2003 review of SIDS, a previous IOM review of death reports in VAERS concluded that the vast majority of reported deaths were coincidental and not causally related to vaccination.[171] A newer VSD study of more than 13 million vaccinated persons compared rates and causes of death in the vaccinated study population to the general U.S. population. The death rate 1 or 2 months following vaccination was lower than that in the general U.S. population and the causes of death were similar,[172] providing persuasive evidence that vaccinations are not associated with an increased risk of death.

Vaccines Cause Cancer

Simian virus 40 (SV40) was present in monkey kidney cells used to make the inactivated polio vaccine, live attenuated polio vaccine, and inactivated adenovirus vaccines in the late 1950s and early 1960s. Later, investigators found SV40 DNA in biopsy specimens obtained from patients with certain unusual cancers—mesothelioma, osteosarcoma, and non-Hodgkin lymphoma—leading some to hypothesize a link between vaccination and the subsequent development of cancer.[173] However, genetic remnants of SV40 were present in cancers of people who had or had not received contaminated polio vaccines; people with cancers who never received SV40-contaminated vaccines were found to have evidence for SV40 in their cancerous cells; and epidemiologic studies did not show an increased risk of cancers in people who received polio vaccine between 1955 and 1963 compared with people who did not receive these vaccines.[173] Taken together, these findings do not support the hypothesis that the SV40 contained in polio vaccines administered before 1963 caused cancers.

Several studies have evaluated the possible relationship between vaccination and leukemia. The findings from these studies indicate that MMR, DTaP, diphtheria and tetanus toxoids–adult (Td), Hib, hepatitis B, and polio vaccines are not associated with childhood leukemia.[174–177]

Safety of the Immunization Schedule and Simultaneous Vaccinations

One hundred years ago, children received one vaccine—smallpox. Today, children receive 14 vaccines routinely.

Although some vaccines are given in combination, infants and young children could receive more than 20 shots and three oral doses of vaccines by 2 years of age, including as many as five shots at one time.[178–181] A prevalent concern is that little is known about the safety of the recommended immunization schedule as a whole. Parents have expressed the opinion, for example, that too many vaccines are given to children at too young an age and that early childhood immunization overwhelms the immune system. These sentiments reflect concern about the number, frequency, and timing of recommended vaccines rather than about the specific properties of particular vaccines.[178,182–184]

In response to this public concern, the IOM, in 2012, convened a committee to examine stakeholder concerns and scientific evidence regarding the safety of the recommended childhood immunization schedule, and to identify study settings, designs, and methods that would be appropriate to rigorously address this issue.[185] The IOM committee concluded that, although few published investigations had specifically examined the safety of the recommended childhood schedule as a whole, the accumulation of available evidence indicated that the current U.S. immunization schedule is safe. That evidence was based in part on concomitant use studies required by the FDA prior to licensure of a vaccine. Concomitant use studies determine whether new vaccines alter either the safety or immunogenicity profile of existing vaccines that will be given at the same time as the new vaccine and whether existing vaccines alter the safety or immunogenicity profiles of the new vaccine.

Although we have witnessed a dramatic increase in the number of vaccines routinely recommended for infants and young children, the number of immunogenic proteins and polysaccharides contained in vaccines has declined (Table 82.4). The decrease in the number of immunogenic proteins and polysaccharides contained in vaccines is attributable to discontinuation of the smallpox vaccine and advances in the field of protein purification that allowed for a switch from whole-cell to acellular pertussis vaccine, and recombinant DNA technology that allowed for the relatively easy manufacture of single protein vaccines.

A practical way to determine the capacity of the immune system to respond to vaccines is to consider the number of B and T cells required to generate adequate levels of binding antibodies per milliliter of blood.[186] Calculations are based on the following assumptions:

1. Approximately 10 ng/mL is likely to be an effective concentration of antibody directed against a specific epitope.
2. Approximately 10^3 B cells/mL are required to generate 10 ng of antibody/mL.
3. Given a doubling time of approximately 0.75 days for B cells, it would take approximately 7 days to generate 10^3 B cells/mL from a single B-cell clone.
4. Because vaccine-specific humoral immune responses are first detected approximately 7 days after immunization, those responses could initially be generated from a single B-cell clone per milliliter.
5. One vaccine contains approximately 10 immunogenic proteins or polysaccharides (see Table 82.4).
6. Each immunogenic protein or polysaccharide contains approximately 10 epitopes (i.e., 10^2 epitopes per vaccine).
7. Approximately 10^7 B cells are present per milliliter of blood.

Given these assumptions, the number of vaccines to which a person could respond would be determined by dividing the number of circulating B cells ($\approx 10^7$) by the average number of epitopes per vaccine (10^2). Therefore, a person could theoretically respond to approximately 10^5 vaccines at one time. This is probably a conservative estimate for several factors, including consideration of only vaccine-specific B-cell responses and ignoring the dynamic nature of the immune system. For example, a study of T-cell population dynamics in HIV-infected persons found that adults have the capacity to generate approximately 2×10^9 new T lymphocytes each day.[187] Although the quantity of new B and T cells generated each day in healthy people is unknown, studies of HIV-infected persons demonstrate the enormous capacity of the immune system to generate lymphocytes when needed.

TABLE 82.4 Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines

Vaccine	Year of Introduction	Number of Proteins or Polysaccharides or Both
Smallpox[a]	1796	198
Rabies	1885	5
Diphtheria[b]	1923	1
Pertussis (whole cell)[a]	1926	~3000
Tetanus[b]	1927	1
Yellow fever	1936	11
Influenza[b]	1945	10
Polio (inactivated)[b]	1955	15
Polio (live, attenuated)[a]	1961	15
Measles[b]	1963	10
Mumps[b]	1967	9
Rubella[b]	1969	5
Hepatitis B[b]	1981	1
Haemophilus influenzae type b (conjugate)[b]	1990	2
Pertussis (acellular)[b]	1991	2–5
Hepatitis A[b]	1995	4
Varicella[b]	1995	69
Pneumococcus (conjugate)[b]	2000	8
Meningococcus (conjugate)[b]	2005	5
Rotavirus[b]	2006	16
Human papillomavirus[b]	2006	4

[a]Formerly in the U.S. routine child and adolescent immunization schedule.
[b]Currently in the U.S. routine child and adolescent immunization schedule.

Vaccines Weaken the Immune System

Infection with wild-type viruses can cause a suppression of specific immunologic functions. For example, infection with wild-type measles virus causes a reduction in the number of circulating B and T cells during the viremic phase of infection and a delay in the development of cell-mediated immunity.[188,189] Similarly, wild-type measles virus infection can cause long-term loss of memory B and T cells, resulting in an increased mortality from other infections.[190] Downregulation of cell-mediated immunity by wild-type measles virus probably results from downregulation of the production of

interleukin-12 by measles-infected macrophages and dendritic cells.[188] Taken together, the immunosuppressive effects of wild-type measles virus account, in part, for the increase in morbidity and mortality from measles infection. Similarly, the immunosuppressive effects of infections with wild-type varicella virus[191] or wild-type influenza virus[192] cause an increase in the incidence of severe invasive bacterial infections.

Live viral vaccines replicate (albeit far less efficiently than wild-type viruses) in the host and, therefore, can mimic events that occur after natural infection. For example, measles, mumps, or rubella vaccines can significantly depress reactivity to the tuberculin skin test,[193–199] measles-containing vaccines can cause a decrease in protective immune responses to varicella vaccine,[200] and high-titered measles vaccine (Edmonston-Zagreb strain) can cause an excess of cases of invasive bacterial infections in developing countries.[201] All these phenomena are explained by the likely immunosuppressive effects of measles vaccine viruses. However, current vaccines (including the highly attenuated Moraten strain of measles vaccine) do not seem to cause clinically relevant immunosuppression in healthy children. Studies have found that the incidence of invasive bacterial infections following immunization with diphtheria, pertussis, tetanus, bacille Calmette-Guérin (BCG), measles, mumps, rubella, or live attenuated poliovirus vaccines was not greater than that found in unimmunized children.[202–206]

Vaccines Cause Autoimmunity

Mechanisms are present at birth to prevent the development of immune responses directed against self-antigens (autoimmunity). T- and B-cell receptors of the fetus and newborn develop with a random repertoire of specificities. In the thymus, T cells that bind strongly to self-peptide–major histocompatibility complexes die, while those that bind with a lesser affinity survive to populate the body. This central selection process eliminates strongly self-reactive T cells, while selecting for T cells that recognize antigens in the context of self–major histocompatibility complex. In the fetal liver, and later in the bone marrow, B-cell receptors (i.e., immunoglobulins) that bind self-antigens strongly are also eliminated. Therefore, the thymus and bone marrow, by expressing antigens from many tissues of the body, enable the removal of the majority of potentially dangerous autoreactive T and B cells before they mature—a process termed *central tolerance*.[207]

It is not simply the presence of autoreactive T and B cells, however, that result in autoimmune disease. Autoreactive T and B cells are present in all people because it is not possible for every antigen from every tissue of the body to participate in the elimination of all potentially autoreactive cells. A process termed *peripheral tolerance* further limits the activation of autoreactive cells.[208,209] Mechanisms of peripheral tolerance include: (a) antigen sequestration (antigens of the central nervous system, eyes, and testes are not regularly exposed to the immune system unless injury or infection occurs); (b) anergy (lymphocytes partially triggered by antigen but without costimulatory signals are unable to respond to subsequent antigen exposure); (c) activation-induced cell death (a self-limiting mechanism involved in terminating immune responses after antigen is cleared); and (d) inhibition of immune responses by specific regulatory cells.[210–213]

Thus, the immune system anticipates that self-reactive T cells will be present and has mechanisms to control them. Any theory of vaccine causation of autoimmune diseases must take into account how these controls are circumvented. As discussed subsequently, epidemiologic studies have not supported the hypothesis that vaccines cause autoimmune diseases. This is consistent with the fact that no mechanisms have been advanced to explain how vaccines could account for all the prerequisites that would be required for the development of autoimmune disease.

At least four key conditions must be met for development of autoimmune disease. First, self-antigen–specific T cells or self-antigen–specific B cells must be present. Second, self-antigens must be presented in sufficient amounts to trigger autoreactive cells. Third, costimulatory signals, cytokines, and other activation signals produced by antigen-presenting cells (such as dendritic cells) must be present during activation of self-reactive T cells. Fourth, peripheral tolerance mechanisms must fail to control destructive autoimmune responses. If all these conditions are not met, the activation of self-reactive lymphocytes and progression to autoimmune disease are not likely.

Evidence That Vaccines Do Not Cause Autoimmunity

Rigorous epidemiologic studies of infant vaccines and type 1 diabetes found that measles vaccine was not associated with an increased risk for diabetes; other investigations found no association between BCG, smallpox, tetanus, pertussis, rubella, or mumps vaccine and diabetes.[214] Specifically, a Canadian study found no increase in risk for diabetes as a result of receipt of BCG vaccine.[215] In a large 10-year follow-up study among Finnish children enrolled in an Hib vaccination trial, no differences in risk for diabetes were found among children vaccinated at 3 months of age (followed later with a booster vaccine) and children vaccinated at 2 years only or with children born before the vaccine trial. The weight of currently available epidemiologic evidence does not support a causal association between currently recommended vaccines and type 1 diabetes in humans.[216–218]

The hypothesis that vaccines might cause multiple sclerosis was fueled by anecdotal reports of multiple sclerosis following hepatitis B immunization and two case-control studies showing a small increase in the incidence of multiple sclerosis in vaccinated persons that was not statistically significant.[219–221] However, the capacity of vaccines to cause or exacerbate multiple sclerosis has been evaluated in several excellent epidemiologic studies.[222–226] Two large case-control studies showed no association between hepatitis B vaccine and multiple sclerosis,[223] and found no evidence that hepatitis B, tetanus, or influenza vaccines exacerbated symptoms of multiple sclerosis.[224] Other well-controlled studies also found that influenza vaccine did not exacerbate symptoms of multiple sclerosis.[225–227] Indeed, in a retrospective study of 180 patients with relapsing multiple sclerosis, infection with influenza virus was more likely than immunization with influenza vaccine to cause an exacerbation of symtpoms.[227]

A 2009 review also showed that, with the possible exception of the swine flu vaccine in 1976, influenza vaccines are not a definite cause of GBS and that any possible increased risk following vaccination is outweighed by a higher risk following natural influenza infection.[228]

Vaccines Cause Allergies and Asthma

Allergic symptoms are caused by soluble factors (e.g., immunoglobulin E) that mediate immediate-type hypersensitivity; production of immunoglobulin E by B cells is dependent on release of cytokines such as interleukin-4 by T-helper type 2 (Th2) cells. Two theories have been advanced to explain how vaccines could enhance immunoglobulin E–mediated, Th2-dependent allergic responses. First, vaccines could shift immune responses to potential allergens from T-helper type 1 (Th1)-like to Th2-like.[229] Second, by preventing common prevalent infections (the "hygiene hypothesis"), vaccines

could prolong the length or increase the frequency of Th2-type responses.[230,231]

Although all factors that cause changes in the balance of Th1 and Th2 responses are not fully known,[232] it is clear that dendritic cells have a critical role. For example, adjuvants (e.g., aluminum hydroxide or aluminum phosphate ["alum"] contained in some vaccines) promote dendritic cells to stimulate Th2-type responses.[233,234] Adjuvants could cause allergies or asthma by stimulating bystander, allergen-specific Th2 cells. However, vaccine surveillance data show no evidence for environmental allergen priming by vaccination.[235] Furthermore, local inoculation of adjuvant does not cause a global shift of immune responses to Th1 or Th2 type.[236,237]

The other hypothesis advanced to explain how vaccines could promote allergies is that by preventing several childhood infections (the hygiene hypothesis), stimuli that evolution has relied on to cause a shift from the neonatal Th2-type immune response to the balanced Th1–Th2 response patterns of adults have been eliminated.[230,231] However, the diseases that are prevented by vaccines constitute only a small fraction of the total number of illnesses to which a child is exposed, and it is unlikely that the immune system would rely on only a few infections for the development of a normal balance between Th1 and Th2 responses. For example, a study of 25,000 illnesses performed in Cleveland, Ohio, in the 1960s found that children experienced six to eight infections per year in the first 6 years of life; most of these infections were caused by viruses such as coronaviruses, rhinoviruses, paramyxoviruses, and myxoviruses—diseases for which children are not routinely immunized.[238] Also at variance with the hygiene hypothesis is the fact that children in developing countries have lower rates of allergies and asthma than children in developed countries even though they are commonly infected with helminths and worms—organisms that induce strong Th2-type responses.[239]

Evidence That Vaccines Do Not Cause Asthma

Although some relatively small early observational studies supported the association between whole-cell pertussis vaccine and development of asthma,[240] newer studies suggest otherwise. A large clinical trial performed in Sweden found no increased risk,[241] and a very large longitudinal study in the United Kingdom found no association between pertussis vaccination and early- or late-onset wheezing or recurrent or intermittent wheezing.[242] Two studies from the VSD project have also lent data to this controversy. In one study of 1366 infants with wheezing during infancy, vaccination with DTP and other vaccines was not related to the risk of wheezing in full-term infants.[243] In another study of more than 165,000 children, childhood vaccinations were not associated with an increased risk for developing asthma.[244] Finally, a study from Finland also suggested that children with a history of natural measles were at increased risk for atopic illness. Such findings run contrary to the hypothesis that the increase in atopic illnesses seen in several countries is a consequence of the reduction in wild measles resulting from immunizations.[245]

A separate concern is whether inactivated influenza vaccination may exacerbate asthma in children with preexisting asthma. Results of studies examining the potential associations between administration of inactivated influenza vaccine and various surrogate measures of asthma exacerbation, including decreased peak expiratory flow rate, increased use of bronchodilating drugs, and increase in asthma symptoms, have yielded mixed results. Most studies, however, have not supported such an association.[246] In fact, after controlling for asthma severity, acute asthma exacerbations were less common after inactivated influenza vaccination than before,[247] and inactivated influenza vaccination seems to be associated with a decreased risk for asthma exacerbations throughout influenza seasons.[248] Several more recent studies have also shown a lack of correlation between receipt of vaccines and the development of asthma.[249–252]

Vaccines Cause Autism and Other Developmental Disabilities

Probably one of the most contentious issues in recent years has been speculation that vaccines cause autism. Autism is a chronic developmental disorder characterized by problems in social interaction, communication, and responsiveness and by repetitive interests and activities. Although the causes of autism are largely unknown, family and twin studies suggest that genetics has a fundamental role.[253] In addition, overexpression of neuropeptides and neurotrophins has been found in the immediate perinatal period among children later diagnosed with autism, suggesting that prenatal or perinatal influences or both have a more important role than postnatal insults.[254] However, because autistic symptoms generally first become apparent in the second year of life, some scientists and parents have focused on the role of MMR vaccine because it is first administered around this time. Concern about the role of MMR vaccine was heightened in 1998 when the *Lancet* published a study based on 12 children that proposed an association between the vaccine and the development of ileonodular lymphoid hyperplasia, nonspecific colitis, and regressive developmental disorders (later termed by some as "autistic enterocolitis").[255] Among the proposed mechanisms was that MMR vaccine present in the intestinal tissues caused bowel problems, leading to the malabsorption of essential vitamins and other nutrients and eventually to autism or other developmental disorders. Concern about this issue led to a decline in measles vaccine coverage in the United Kingdom and elsewhere.[256] Significant concerns about the validity of the study included the lack of an adequate control or comparison group, inconsistent timing to support causality (several of the children had autistic symptoms preceding bowel symptoms), and the lack of an accepted definition of the syndrome.[257] Subsequently, population-based studies of autistic children in the United Kingdom found no association between receipt of MMR vaccine and autism onset or developmental regression.[258,259] Soon after publication of the *Lancet* article that ignited the controversy,[255] two ecologic analyses found no evidence that MMR vaccination was the cause of apparent increased trends in autism over time[260,261]; in addition, two other studies found no evidence of a new variant form of autism associated with bowel disorders secondary to vaccination.[262,263] Several newer studies also refuted the notion that MMR vaccine caused autism.[264–269] Perhaps the most powerful study involved younger siblings where the older child had autism; in this study, receipt of MMR vaccine did not increase the risk of autism in the younger child.[270]

Because of the level of concern surrounding this issue, the CDC and the National Institutes of Health requested an independent review by the IOM.[271] The Immunization Safety Review Committee appointed by the IOM to review this issue was unable to find evidence supporting a causal relationship at the population level between autistic spectrum disorders and MMR vaccination, nor did the committee find any evidence of biological mechanisms that would support or explain such a link. In February 2010, the *Lancet* retracted the 1998 article.[272]

The mercury-containing preservative, thimerosal, has also been suggested to possibly increase the risk of autism. Mercury is a naturally occurring element found in the earth's crust, air, soil, and water. Certain types of bacteria in the environment

can change inorganic mercury to organic mercury (methylmercury). Methylmercury makes its way through the food chain in fish, animals, and humans. At high levels, it can be neurotoxic. Thimerosal, however, contains ethylmercury, not methylmercury. Studies comparing ethylmercury and methylmercury suggest that they are processed differently; ethylmercury is broken down and excreted much more rapidly than methylmercury. Therefore, ethylmercury is much less likely than methylmercury to accumulate in the body and cause harm.

The FDA Modernization Act of 1997 called for the FDA to review and assess the risk of all mercury-containing food and drugs. This led to an examination of mercury content in vaccines. Public health officials found that infants up to 6 months old could receive as much as 187.5 μg of ethylmercury (thimerosal) from vaccines, a level that exceeded recommended safety guidelines for methylmercury from the Environmental Protection Agency, but not levels recommended by the FDA or the Agency for Toxic Substance Disease Registry.[273] Consequently, the United States began transitioning to a childhood vaccine schedule free of thimerosal as a precautionary measure.[274] Currently, only the multidose influenza vaccine contains preservative quantities (i.e., 25 μg per dose) of thimerosal.

Several pieces of biological[275] and epidemiologic evidence indicate that thimerosal does not cause autism. Importantly, several large epidemiologic studies have compared the risk of autism in children who received vaccines containing thimerosal with children who received vaccines without thimerosal or vaccines with lesser quantities of thimerosal; none of the studies found an increased risk of autism associated with thimerosal-containing vaccines.[276–281] The IOM has reviewed these studies and concluded that evidence favored rejection of a causal association between thimerosal in vaccines and autism.[111,282] Denmark, a country that abandoned thimerosal as a preservative in 1991, actually saw an increase in the disorder beginning several years later. In the United States, all childhood vaccines with thimerosal as a preservative (except multidose influenza vaccine) passed their expiration date by 2003 and were no longer available in the United States; nonetheless, autism prevalence increased in the subsequent years.[283]

The hypothesis for why vaccines might cause autism has continued to shift. In 1998, the concern was that the MMR vaccine caused autism. The following year, the concern shifted to include the fear that thimerosal in vaccines caused autism. As data continued to be generated showing that both of these concerns were ill founded, the hypothesis shifted again—this time to include the fear that too many vaccines given too soon caused autism. To address this concern, a CDC study published in 2013 compared the number of antigens from vaccines during the first 2 years of life in a group of children with autism and matched controls without autism. The results showed that the total amount of antigen from vaccines received was the same between children with autism and those who did not have autism.[284]

Related to concerns about autism, the possibility that vaccines could cause other developmental disabilities, such as speech problems or learning difficulties, has also been evaluated. Several studies have evaluated a possible association between exposure to thimerosal in vaccines and neurodevelopmental problems and have found no consistent increased risk.[285–287] The total number of vaccines and vaccine antigens has also not been found to have a relationship with neurodevelopmental problems. Smith and Woods compared children who had received vaccines according to the CDC/American Academy of Pediatrics schedule with children who were not vaccinated, only partially vaccinated, or received vaccines on a delayed schedule, noting no difference between the two groups in neurodevelopmental outcomes.[288] A separate analysis found no association between the number of antigens in vaccines and neurodevelopmental outcomes.[289]

Aluminum in Vaccines Is Harmful

Aluminum salts have safely been used to adjuvant vaccines since the 1930s. However, by the mid-2000s, parents became concerned that aluminum in vaccines might be harmful. Indeed, high levels of aluminum can cause osteomalacia, anemia, or encephalopathy, typically in preterm infants or infants with absent or severely compromised renal function who are also receiving high doses of aluminum from other sources (e.g., antacids).[290] Studies show that children who receive aluminum-containing vaccines have serum levels of aluminum that are well below the toxic range.[291–293]

A specific concern that has been raised about aluminum adjuvants is their possible relationship to macrophagic myofasciitis, a condition consisting of a variety of complaints along with findings in muscle biopsies of minute lesions that contain aluminum salts.[294,295] The WHO Global Advisory Committee on Vaccine Safety has reviewed the evidence regarding macrophagic myofasciitis on several occasions and concluded that aluminum salts can be found in cells at an injection site of an aluminum-containing vaccine, but associated systemic symptoms related to that finding have never been scientifically proven.[296]

Formaldehyde in Vaccines Is Harmful

Formaldehyde has been used in vaccines to detoxify bacterial toxins (i.e., diphtheria toxin, tetanus toxin, pertussis toxins) and to inactivate viruses (i.e., poliovirus). Because formaldehyde at high concentrations can cause mutational changes in cellular DNA in vitro,[297] some parents have become concerned that formaldehyde in vaccines might be dangerous. However, because formaldehyde is a product of single-carbon metabolism, everyone has formaldehyde that is detectable in serum.[298] Indeed, the level of formaldehyde in the circulation is approximately 10-fold more than would be contained in any vaccine.[299] Also, people exposed to high levels of formaldehyde in the workplace (e.g., morticians) are not at greater risk of cancer than people who are not exposed to formaldehyde.[300] Finally, the quantity of formaldehyde present in vaccines is at least 600-fold lower than that necessary to induce toxicity in experimental animals.[301]

Vaccines Contain DNA From Aborted Human Fetuses

Two cell lines, MRC-5 and WI-38, both derived from elective abortions performed in Europe in the early 1960s, have been used as cell substrates in vaccine manufacture. Four vaccines continue to require the use of these cell lines: varicella, rubella, hepatitis A, and one of the rabies vaccines. Human fetal cells were valuable in vaccine research because they support the growth of many human viruses and are sterile; they were first used at around the time that researchers found that primary monkey kidney cells were contaminated with SV40 virus.

Some religious groups have become concerned about the use of cells originally obtained from elective abortions. However, the Catholic Church and other religions have deemed vaccines made using these cells worthy of continued use, despite their origins.[302,303]

SAFETY OF HUMAN PAPILLOMAVIRUS VACCINE

Concerns about safety have been a primary reason for not initiating HPV vaccination.[304] The WHO has noted that a

number of national immunization programs have experienced loss of confidence in their HPV vaccination programs as a result of negative publicity from perceived safety issues.[305] The postulated safety problems have included cerebral vasculitis, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome, and autoimmune diseases.[305–307] The suggestion that HPV vaccine could cause fatal cerebral vasculitis was raised in case reports that hypothesized that inflammation could be related to HPV L1 gene DNA fragments in the vaccine.[308,309] The FDA, however, determined that small amounts of HPV DNA fragments are to be expected as a result of the vaccine manufacturing process and do not represent a safety concern.[310] Moreover, the autopsy findings in the reported cases did not reveal evidence of inflammation and thus do not support a diagnosis of cerebral vasculitis. Concerns about CRPS have been limited to a few case reports in Japan that received considerable media attention.[311] Similar cases have not been reported from other countries. An expert review committee in Japan determined that information was not adequate to make a definitive diagnosis of CRPS in many of the reported cases and a causal relationship to vaccination could not be established.[312] A review by the European Medicines Agency concluded that the evidence does not support a causal association between HPV vaccines and CRPS or postural orthostatic tachycardia syndrome.[313]

Safety monitoring in the United States and internationally support the safety of HPV vaccine. In the United States, a review of VAERS found that reports of syncope and venous thromboembolism (VTE) were higher following HPV4 when compared to other vaccines. Continued monitoring in VAERS has not identified any new or unexpected safety concerns.[314] A population-based study of HPV4 safety from the VSD found no statistically significant increased risks of GBS, stroke, VTE, appendicitis, seizures, syncope, allergic reactions, or anaphylaxis.[315] A manufacturer-sponsored postlicensure safety assessment of HPV4 did not identify any major safety concerns except for an elevated relative risk of Hashimoto thyroiditis; however, further investigation of the temporal relationship and biological plausibility by the safety review committee revealed no consistent evidence for a safety signal for autoimmune thyroid conditions.[316] A national registry linkage study from Denmark found that HPV4 did not increase the risk of VTE.[317] A large population-based cohort study conducted in Denmark and Sweden analyzed more than 696,000 doses of HPV4 among females[318] and found no consistent evidence supporting causal associations with several autoimmune and neurologic conditions or VTE. A case-control study in France found no increased risk of several autoimmune outcomes (idiopathic thrombocytopenic purpura, central demyelination, GBS, connective tissue disorders, type 1 diabetes mellitus, and autoimmune thyroiditis) following HPV vaccination.[319] An analysis of national data from Sweden and Denmark covering 4 million women, including nearly 800,000 who had received HPV4, found no increased risk of multiple sclerosis or other demyelinating diseases following HPV4 vaccination.[124] Arguably, the HPV vaccine has been subjected to greater scrutiny postlicensure than most other vaccines.

NARCOLEPSY ASSOCIATED WITH AS03-ADJUVANTED PANDEMIC H1N1 INFLUENZA VACCINE

During the 2009 H1N1 influenza pandemic, GlaxoSmithKline's AS03-adjuvanted 2009 monovalent H1N1 influenza vaccine Pandemrix was used extensively in Europe and in other countries worldwide, although not in the United States. In August 2010, public health agencies in Sweden and Finland announced that they had received reports of narcolepsy after vaccination with Pandemrix.[320,321] Narcolepsy is a chronic central nervous system disorder characterized by excessive daytime sleepiness.[322] Its incidence is highest during the teen years,[323] but many individuals with narcolepsy are not diagnosed until several years after the onset of symptoms.[324] An increased risk of narcolepsy in Pandemrix-vaccinated compared with unvaccinated children and adolescents was found in Finland,[325] Sweden,[326] Ireland,[327] and Norway,[328] as well as in England [329] and France.[330] A case-control study that pooled data from eight European countries found an overall increased risk, although not in all countries.[331] Some European countries also reported an increased risk after vaccination in adults up to age 40 years, although the risk was smaller than the risk among vaccinees younger than 20 years of age.[326,330] A case-control study from Quebec of the Canadian AS03-adjuvanted vaccine, Arepanrix, found a small increased risk of narcolepsy, mainly in individuals younger than 20 years old, but a possible confounding effect of influenza infection could not be ruled out.[332] No increased risk of narcolepsy was found in a VSD study of the nonadjuvanted 2009 H1N1 pandemic influenza vaccines that were used in the United States.[333] Although no signals have been identified in SRSs,[334] risk of narcolepsy associated with MF59 adjuvanted vaccines has not been evaluated in formal epidemiologic studies. Questions remain about possible biological mechanisms and whether the association between Pandemrix and narcolepsy is confounded by other potential exposures or systematic biases, including publicity around the identified association.[331,335] Newer studies suggest that the issue may be more related to the influenza vaccine and not the adjuvant.[336] This is more fully discussed in Chapter 68.

Vaccine Risk Communication

Disease prevention with vaccination, especially if it requires continuous near-universal compliance, is a formidable task. In the preimmunization era, vaccine-preventable diseases such as measles and pertussis were so prevalent that the risks and benefits of disease versus vaccination were readily evident. As immunization programs successfully reduced the incidence of vaccine-preventable diseases, however, an increasing proportion of healthcare providers and parents have little or no personal experience with vaccine-preventable diseases. In contrast, some degree of personal discomfort, pain, and worry is generally associated with each immunization. In addition, parents searching for information about vaccines on the Internet are likely to encounter sites that encourage vaccine refusal or emphasize the dangers of vaccines alongside information from reputable sources.[337,338] Similarly, the media may sensationalize vaccine safety issues or, in an effort to present "both sides" of an argument, fail to provide perspective.[339,340] For reasons discussed earlier, there may be uncertainty if vaccines are associated with rare or delayed adverse reactions if only because the scientific method does not allow for acceptance of the null hypothesis; consequently, one cannot prove that a vaccine never causes a particular adverse event, only that an adverse event is unlikely to occur by a certain statistical probability.

The combination of these factors may affect parental beliefs about immunizations. Although the majority of parents support immunizations, surveys have found that many parents have concerns or misconceptions[180–182] that could erode their confidence in vaccines.[178] Within this context, the art of addressing vaccine safety concerns through effective risk communication has emerged as an increasingly important skill for managers of mature immunization programs and healthcare providers who administer vaccines.

Risk Perception

The science of risk perceptions and risk communications, which was developed initially for technology and environmental arenas,[341] can also be applied to immunizations.[342] For scientists and other experts, risk tends to be synonymous with the objective probability of morbidity and mortality resulting from exposure to a particular hazard.[343] In contrast, research shows that laypersons may have subjective, multidimensional, and value-laden conceptualizations of risk.[344] Individual people can vary in their perception of the magnitude of risks; studies show that various factors such as sex, race, political worldviews, emotional affect, and trust are associated with risk perception.[345] Risk perception factors such as involuntariness, uncertainty, lack of control, and high level of dread can lead to a heightened perception of risks.[346] All these can be seen as associated with childhood immunizations. Moreover, these factors are referred to as "outrage" factors in the risk communication literature. Outrage can lead to a person responding emotionally and can increase further the level of perceived risk.[346]

People care not only about the magnitude of risks, but also how risks are managed and whether they participate in the risk-management process.[347] In medical decision making, this has resulted in a transition from more paternalistic models to increasing degrees of shared decision making.[348] Some have argued that a similar transition also should occur with immunizations.[349] One study,[350] however, found that physicians who introduced vaccines using a participatory approach were more likely to encounter resistance compared to those who introduced vaccines as a presumptive or default choice. Furthermore, immunization is unlike most other medical procedures in that the consequences of the decision affect not only the individual person, but also others in society. Because of this important distinction, many countries have enacted immunization laws that, in part, are meant to limit an individual person's right to infect others. Without such mandates, persons may attempt to avoid the risks of vaccination while being protected by the herd immunity resulting from others being vaccinated.[351] Unfortunately, the protection provided by herd immunity may disappear if too many people avoid vaccination, resulting in outbreaks of vaccine-preventable diseases.[352,353] Debates in the United States, where such laws are created and enforced at the state level, have focused on whether philosophical (in addition to medical and religious) exemptions to mandatory immunizations for school entry should be more or less restrictive, and what standards for claim of exemption are needed.[349,354,355] For example, in 2015, California removed all nonmedical exemptions to school-entry vaccination requirements beginning in the 2016–17 school year.[356] Thus, vaccine risk communications should not only describe the risks and benefits of vaccines for individuals, but also should include discussion of the impact of individual immunization decisions on the larger community.

Factors That Can Influence Parental Vaccine Acceptance

Vaccination coverage among infants and young children in the United States has been consistently high, suggesting that vaccination as recommended by medical and public health professionals is still the norm.[357] However, high national coverage can mask variation at the local level.[358] Uneven distribution of undervaccinated individuals can mean a greater likelihood of disease outbreaks if exposed. One consequence of the success of vaccines is that an increasing number of parents and clinicians have little or no personal experience with or knowledge of many of the diseases that vaccines prevent. Thus, vaccine-preventable diseases often are not perceived as a real threat by parents.[359,360] Moreover, increasingly parents want to be fully informed about their children's medical care[361]; consequently, merely recommending vaccination may not be sufficient. Stories in the media highlighting adverse events (real or perceived) may also cause some parents to question the safety of vaccines.

Apart from the media attention on vaccine safety issues, several factors can shape parents' vaccine attitudes in the present environment of a low incidence of vaccine-preventable diseases. Some of these factors are: (a) depth of information needed, (b) timing of information given, (c) information sources and social media, (d) personal experience, and (e) general health literacy. An understanding of these factors and a proactive approach to vaccine education may prevent future concerns from escalating into widespread refusal of vaccines, with a consequent increased incidence of vaccine-preventable diseases. Each of these factors is discussed in more detail below.

Depth of Information

There is an association between information and vaccine acceptance. One study found that while 67% of parents agreed that they had access to enough information to make a good decision about immunizing their children, 33% of parents disagreed or were neutral.[362] Parents who disagreed they had enough vaccine information had negative attitudes about immunizations, healthcare providers, immunization requirements and exemptions, and trust in people responsible for immunization policy. Moreover, a larger percentage of parents who reported they did not have access to enough information about vaccines also had several specific vaccine concerns compared with parents who were neutral or agreed they had access to enough information.[362] It may be that when there is a void of accurate, trusted information, doubts about vaccines arise and misinformation is more readily accepted.

By using the principle of audience segmentation (partitioning a population into segments with shared characteristics), a survey study identified five parent groups that varied on health and immunization attitudes, behaviors, information sources, and demographics: Immunization Advocates (33.0%), Go Along to Get Alongs (26.4%), Health Advocates (24.8%), Fencesitters (13.2%), and Worrieds (2.6%).[363] It is important to recognize that parents vary in the amount and depth of information that they need to make decisions about vaccines, and that health communicators should take this into account when developing educational materials.

Timing of Information

Vaccine Information Statements (VISs) are typically given to parents the day their child is scheduled for immunization.[364–366] This often places the parent in a conflict situation of reviewing the VIS or attending to a frightened or upset child. Not surprisingly, studies have shown that parents would rather receive such information in advance of the first vaccination visit.[364,366–368] Suggested earlier times for vaccine education include prenatal clinic visits and just after delivery in a hospital.[369] A national survey indicated that 80% of providers said that a preimmunization booklet for parents would be useful for communicating risks and benefits to parents.[365]

Information Sources and Social Media

The majority of parents (84%) report receiving immunization information from a physician.[178] Furthermore, most parents,

including those who have concerns about vaccines, consider their child's doctor to be an important influence in their vaccination decision and report a high level of trust in their vaccine advice.[370,371] Thus, having a physician who engenders trust providing immunization information and who is available to listen and answer questions is the optimal situation from the public health perspective. If trust in a child's physician is low, parents may be drawn to other, less-credible sources of information.

Even though parents may have a number of sources of vaccine information other than a physician (e.g., family, friends), it is also important to consider the rise in social media use when discussing sources of information and influence regarding vaccine decisions. Online social media platforms, such as Facebook and Twitter, promote the two-way exchange of information and ideas, as opposed to the one-way information presentation of traditional Internet sites.[372] Although it remains to be seen how much of an influence social media interactions will have on parents' vaccine beliefs and behaviors, research to date points to both the potential importance of new technologies for engaging parents with accurate and timely information, as well as the potential for dissemination of myths and misinformation among parents' online social networks.[373]

Personal Experience

When a child experiences an adverse event following receipt of a vaccine, it often raises the question, "Was this vaccine necessary?" To the parent, it may seem that the risks of the vaccine are greater than the risks of not getting the vaccine. Parents who sought medical attention for any of their children owing to an apparent adverse event following immunizations (6.9%) not only expressed more concern about immunizations, but also were more likely to have a child who lacked one or more doses of three high-profile vaccines compared with parents who reported that none of their children had experienced an adverse event following immunization.[374] Two scenarios were seen as plausible. It may be that parents who were already concerned about vaccines before their child began the vaccination schedule sought medical attention for minor side effects (e.g., fever) or nonrelated problems. It is also possible that an apparent adverse event following immunization that resulted in parents seeking medical attention for their child caused the parents' perception of vaccines to become more negative. Both possibilities may result in parents declining future vaccines for their children. It is also important to note, however, that a physician's personal experience, with both vaccinations and vaccine-preventable diseases, can also be influential in helping reluctant parents understand the importance of on-time vaccination.[375] Education and descriptions of vaccine-preventable diseases may also help parents balance the perceived risks of vaccines with the risks of vaccine-preventable diseases.[376]

Health Literacy

There is a wide gap in the level of health literacy across the U.S. population, and this gap emphasizes the need for tailored information. The need for tailored information applies to all areas of health, including childhood immunizations. Immunization educational materials aimed at a "one-size-fits-all" audience are not likely to satisfy all parents' needs.[377] Tailoring should also take into account the need to avoid technical jargon and instead use a plain language approach to communication, regardless of the literacy level of the intended audience. Resources such as CDC's Clear Communication Index[378] can help assess the clarity of educational materials.

Evaluating and Addressing Vaccine Safety Concerns: Role of Healthcare Practitioners and Public Health Professionals

Empathy, patience, scientific curiosity, and substantial resources are needed to address concerns about vaccine safety. Although each evaluation of a vaccine safety concern is in some ways unique, some general principles may apply to most cases. As with all investigations, the first step is objective and comprehensive data gathering.[43] It is also important to gather and weigh evidence for causes other than vaccination. For individual cases or clusters of cases, a field investigation to gather data firsthand may be necessary.[108,379] Advice and review from a panel of independent experts also may be needed.[90,380,381] Causality assessment at the individual level is difficult at best; further evaluation via epidemiologic or laboratory studies may be required.[382] Even if the investigation is inconclusive, such studies can often help maintain public trust in immunization programs.[383]

In the United States, written information about the risks and benefits of immunizations developed by the CDC has been required to be provided to all people vaccinated in the public sector since 1978.[384] The National Childhood Vaccine Injury Act requires every healthcare provider—public or private—who administers a vaccine that is covered by the Act to provide a copy of the most current VIS to the adult vaccinee or, in the case of a minor, to the parent or legal representative, each time a dose of vaccine is administered.[385] Healthcare providers must note in each patient's permanent medical record the date printed on the VIS and the date the VIS was given to the vaccine recipient or the recipient's legal representative. VISs are the cornerstone of provider–patient vaccine risk–benefit communication. Each VIS contains information on the disease(s) that the vaccine prevents, who should receive the vaccine and when, contraindications, vaccine risks, what to do if a side effect occurs, and where to go for more information. Current VISs can be obtained from the CDC's National Center for Immunization and Respiratory Diseases[386] and are available in a number of languages other than English from the Immunization Action Coalition (www.immunize.org). An increasing number of resources that address vaccine safety misconceptions and allegations also have become available, including websites, brochures, resource kits, and videos (Table 82.5). Some studies have been conducted to assess the use and effectiveness of such materials[364,365,387–389]; however, more research in this area is needed.

Immunization programs and healthcare providers should anticipate that some members of the public may have deep concerns about the need for and safety of vaccines. Some may refuse certain vaccines and a few may reject all vaccinations. In the United States, less than 1% of young children have received no vaccines; a number that has been consistent for the past several years according to the National Immunization Survey.[357] However, surveys have estimated that anywhere from 13% to 39%[181,390,391] of parents have intentionally delayed or refused one or more recommended vaccines, depending on the population studied and the definition of delay and refusal used. Acceptance of this practice among physicians is associated with younger physician age, highlighting the importance of physicians' understanding of the risks of vaccine delay and refusal among their patients.[392] An understanding of vaccine risk perceptions and effective vaccine risk communication are essential in responding to misinformation and concerns. Healthcare professionals are also in the best position to help all parents provide evidence-based comfort measures to children to reduce acute pain and anxiety associated with vaccines.[393] It is also important to convey to those who refuse recommended vaccines that their decision is not without risk,

TABLE 82.5 Websites Containing Reliable, Up-to-Date, and Accurate Information About Vaccines

Source	Website
GOVERNMENT	
Centers for Disease Control and Prevention (main)	www.cdc.gov/vaccines
CDC (flu)	www.cdc.gov/flu
CDC (HPV)	cdc.gov/hpv
CDC (childhood vaccines)	www.cdc.gov/vaccines/conversations
Advisory Committee on Immunization Practices	http://www.cdc.gov/vaccines/acip
PROFESSIONAL ASSOCIATIONS	
American Academy of Pediatrics (AAP)	www.aap.org/immunization
American College of Obstetricians and Gynecologists (ACOG)	www.immunizationforwomen.org
SCHOOLS, HOSPITALS, AND EXPERT GROUPS	
The Albert B. Sabin Vaccine Organization	www.sabin.org
Every Child by Two	www.ecbt.org
Immunization Action Coalition	www.immunize.org
Institute for Vaccine Safety	www.vaccinesafety.edu
Parents PACK (provided by the Vaccine Education Center at The Children's Hospital of Philadelphia)	www.vaccine.chop.edu/parents
Vaccine Education Center at The Children's Hospital of Philadelphia	http://www.chop.edu/centers-programs/vaccine-education-center
Immunization Action Coalition	www.vaccineinformation.org
The Vaccine Page	www.vaccines.org
Vaccinate Your Baby	www.vaccinateyourbaby.org
California Immunization Coalition	www.whyichoose.org
National Foundation of Infectious Diseases	www.adultvaccination.com
PATH Vaccine Resource Library	http://www.path.org/vaccineresources/
PARENT AND FAMILY ORGANIZATIONS	
Families Fighting Flu	www.familiesfightingflu.org
The National Meningitis Association	www.nmaus.org
Meningitis Angels	www.meningitis-angels.org
Parents of Kids with Infectious Diseases	www.pkids.org
Voices for Vaccines	www.voicesforvaccines.org

and that they (or their children) are vulnerable to a vaccine-preventable disease and its possible consequences.

Importance of Educating Parents Concerned About Vaccines

It is important not to assume that just because most parents are having their children immunized that they will continue to do so.[394] While the host of factors contributing to parents' decisions to have their children immunized (e.g., need for information, experience with adverse events) might remain stable for some time, it is possible that one or more factors may change so that some parents perceive the risks of vaccines to be greater than the risk of disease. This would then push the parents above a theoretical "unacceptability threshold" in which they would choose not to have their children immunized with one or more vaccines. One study[181] found that many parents whose children were fully vaccinated were "at risk" for vaccine delay or refusal based on their concerns about the safety or necessity of vaccines. Furthermore, vaccination is not a one-time, all-or-nothing decision, but rather an ongoing series of choices over time.

Averting the future possibility of outbreaks of vaccine-preventable diseases will take a concerted effort by healthcare and public health professionals to educate and better communicate with parents concerned about immunizations. In guidance for clinicians, the American Academy of Pediatrics does not recommend physicians remove nonvaccinating families from their practice, but it does give them permission to do so.[394a] Instead, American Academy of Pediatrics suggests that pediatricians should listen carefully and respectfully to parents' immunization concerns, factually communicate the risks and benefits of vaccines, and work with parents who may be concerned about a specific vaccine or having their child receive multiple vaccines in one visit.[395] Providers can make a huge impact on vaccine acceptance, resulting in a cascading effect in which providing information can increase trust and increasing trust can lead to greater acceptance of and confidence in vaccines. For healthcare providers to be able to optimally fill this important role, however, two related issues need to be addressed. The first is the need for quality communication courses and training in medical schools and residencies and training programs for medical and public health professionals regarding vaccine safety.[396–398] The second is for MCOs and medical insurance companies to adequately reimburse physicians for health education. Lack of reimbursement to physicians has been noted as a barrier to implementation of behavioral treatments for health issues such as heart disease[399] and smoking.[400] It is important to note that studies show that education programs can be a cost savings to healthcare systems.[401,402] We live in a world already benefiting from vaccines that exist, and there is the promise of more vaccines to come. The challenge we have now is to make sure that the promise is not lost because we did not present the benefits and risks of vaccines in a meaningful way acceptable to the public.

FUTURE CONSIDERATIONS

An optimal immunization safety system requires rigorous attention to safety during prelicensure research and development; active monitoring for potential safety problems after licensure; and clinical research and risk-management activities, including risk communication, focused on minimizing potential vaccine adverse reactions. Prelicensure activities form the foundation of vaccine safety. Rapid advances in biotechnology are leading to the development of new vaccines,[403] and novel delivery technologies, such as DNA vaccines and new adjuvants, are being developed to permit more antigens to be combined, reducing the number of injections.[404,405]

In the prelicensure evaluation of new vaccines, the trend is likely to continue to conduct larger Phase III trials enrolling tens of thousands of participants. Although such larger trials are helpful in identifying more rare adverse events, even these larger trials may not be large enough to detect increased risks of rare events. For example, the RotaTeq and Rotarix preclinical trials identified no increased risk of intussusception in studies that enrolled more than 60,000 infants.[41,42] Subsequent much larger postlicensure safety monitoring studies, however, identified statistically significant increased risks on the order of approximately one to five per 100,000.[18,19,406,407]

The attributable risks were less than that found for RotaShield (approximately one per 10,000), and, because the benefits of rotavirus vaccines clearly outweighed the small risk of intussusception, no changes were made to the vaccine recommendations.

Although technological advances and more thorough evaluation of safety before vaccines are licensed should lead to the development of safer vaccines, there will continue to be a need for comprehensive postlicensure safety monitoring systems. Combined with the difficulties associated with identifying rare, delayed, or insidious vaccine safety problems in prelicensure studies,[35] the well-organized consumer activist organizations,[408] Internet information of questionable accuracy,[337,338] media eagerness for controversy,[339,409] and relatively rare individual encounters with vaccine-preventable diseases virtually ensure that vaccine safety concerns are unlikely to go away. The existence of a robust vaccine safety monitoring system is essential for providing assurance of the safety of currently marketed vaccines and for rapidly identifying and responding to potential safety problems. Currently, SRSs, such as VAERS, serve as the frontline systems for the early identification of vaccine safety problems. Such systems could be improved if reporting were more complete. Application of web-based and text messaging technologies could make reporting easier and more accurate and also enable more active follow-up of vaccinated persons.[410] Alerts built into electronic medical record systems[411] could also improve reporting to VAERS, as could linkages with immunization registries. Some of these advances will be particularly important to enable monitoring vaccine safety in mass vaccination campaigns during which vaccinations may be administered primarily outside of the traditional healthcare system.

An optimal vaccine safety monitoring system must also include a mechanism or infrastructure to rapidly conduct formal epidemiologic evaluations of potential safety problems identified from SRSs or other sources. In the United States, this function is primarily served by the VSD project. The diffusion of electronic health records and the capability to link records across data systems (such as large health insurance claims databases and immunization registries) may allow the expansion of the population that could be included in postlicensure epidemiologic evaluations of vaccine safety. For example, the FDA Sentinel Initiative has a goal to develop a national electronic system covering 100 million people for monitoring the postlicensure safety of drugs and other medical products, including vaccines.[412]

For adverse reactions that are established as caused by vaccines, clinical and laboratory research is essential for determining the biological mechanisms of the adverse reaction, which, in turn, could lead to the development of safer vaccines. Clinical research is also essential for the development of protocols for safer vaccination, including revaccination of persons who have previously experienced an adverse reaction. Advances in genomics and immunology hold particular promise for elucidating biological mechanisms of vaccine adverse reactions and the development of possible screening strategies for persons who may be at high risk for an adverse reaction.

The need for comprehensive postlicensure monitoring of vaccine safety can be expected to grow with the development of new vaccines and as vaccines are increasingly used in populations that may have different susceptibilities to vaccine adverse events, such as immunocompromised individuals and pregnant women. Vaccination in pregnancy is unique in that it can affect the pregnant woman, the developing fetus, and the newborn infant. Pregnant women, however, are usually excluded from prelicensure clinical trials, making postlicensure monitoring key for evaluating safety of maternal immunizations. Currently in the United States, only two vaccines are routinely recommended for all pregnant women, inactivated influenza and combined tetanus, diphtheria and pertussis (Tdap) vaccines,[413,414] although other vaccines recommended for women of reproductive age are sometimes administered during pregnancy when the need arises. Evidence indicates that influenza and Tdap vaccines are safe when administered during pregnancy.[415–418] Safety data, however, are more limited on vaccination in the first trimester of pregnancy and for repeat Tdap vaccination at short intervals. Safety monitoring will also be important when anticipated new vaccines, such as group B streptococcus, respiratory syncytial virus vaccines,[419,420] and possibly meningococcal vaccines are introduced for use in pregnancy.

Scientific data are essential in the monitoring and evaluation of vaccine safety, but scientific evidence alone often is not sufficient to provide reassurance about the safety of a vaccine. Although immunization levels of U.S. children are high, a sizable fraction of parents do not have their children fully immunized, and concern about vaccine safety is the leading reason for underimmunization. These concerns persist despite the scientific evidence that vaccines do not cause autism or a host of other conditions that have been alleged to be caused by vaccines, such as asthma, diabetes, and autoimmune diseases. Thus, it is critically important that public health agencies, medical organizations, and other influential authorities continue to focus on the safety of vaccines and assure public confidence by providing clear, consistent messages on vaccine safety concerns; supporting effective and transparent vaccine safety monitoring systems and research activities; providing review and recommendations by respected independent expert groups on vaccine safety controversies; and engaging advocacy groups in constructive and open dialogue about their vaccine safety concerns. Although the efforts of government, medical, and other authorities are important, it is healthcare providers who have the greatest influence in determining the acceptance of vaccines by individual people. Even among parents who believe that vaccines may not be safe, most will have their children vaccinated if they have a trusting relationship with an influential healthcare provider. Thus, development of tools and strategies that can assist healthcare providers in effectively communicating with their patients on the risks and benefits of vaccines will continue to be important.

In low- and middle-income countries (LMICs) there is a need to establish minimal vaccine safety monitoring capabilities, such as SRSs, and the capability to rapidly investigate vaccine safety problems and effectively communicate the findings of the investigations. Concerns about vaccine safety can adversely impact immunization efforts, as happened in Vietnam and other countries when newly introduced pentavalent vaccines were falsely believed to have caused infant deaths.[157] An increasing number of vaccines are being introduced and used in LMICs, some are primarily for use in these settings.[421–423] A majority of LMICs, however, have nonexistent or limited vaccine safety monitoring capabilities.[424] In 2012, WHO led the development of the Global Vaccine Safety Blueprint[424] to set forth guidance on establishing and strengthening vaccine safety monitoring systems in LMIC settings. The possibilities for conducting enhanced safety monitoring, particularly with the large-scale introduction of new vaccines, was demonstrated with meningococcal A conjugate vaccine in sub-Saharan Africa.[425] Continued development of LMIC vaccine safety monitoring infrastructures will be needed with the introduction of new vaccine products, such as an adjuvanted malaria vaccine,[426] and viral vector dengue[427] and Ebola virus vaccines.[428] Mass immunization campaigns, during which millions of people receive parenteral immunizations over a period of days,[429] pose substantial challenges to ensuring injection safety,[430] especially given concerns about inadequate

sterilization of reusable syringes and needles, recycling of disposable syringes and needles, and cross-contamination resulting from the current generation of jet injectors.[431] The WHO has promoted the use of safer autodisposable syringes and disposal boxes.[432]

Vaccines are among the most successful and cost-effective public health tools for preventing disease and death. However, like all medical interventions, vaccines are not completely without risk of side effects or other adverse outcomes. A timely, credible, and effective monitoring system, coupled with prompt action in response to identified safety problems, is essential to preventing adverse effects of vaccination and to maintaining public confidence in immunizations. Because immunizations are typically administered to healthy people and are often recommended or mandated to provide societal and individual protection, vaccines must be held to a very high standard of safety. Vaccine safety monitoring and research should optimally be able to detect potentially very small levels of increased risk, especially for adverse events that can result in death or permanent disability. The ultimate goal of such research, including the application of new developments in biotechnology, is to develop safer vaccines and vaccination practices.

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