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Vaccine safety

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During the past 100 years, pharmaceutical companies have made vaccines against pertussis, polio, measles, rubella, and *Haemophilus influenzae* type B (Hib), among others (Table 76-1). As a consequence, the number of children in the United States killed by pertussis decreased from 8,000 each year in the early 20th century to fewer than 20; the number paralyzed by polio from 15,000 to 0; the number killed by measles from 3,000 to 0; the number with severe birth defects caused by rubella from 20,000 to 0; and the number with meningitis and bloodstream infections caused by Hib from 20,000 to fewer than 300.

Vaccines have been among the most powerful forces in determining how long we live.¹ But 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 (such as animal brains and spinal cords); the vaccine prevented a uniformly fatal infection, but the rabies vaccine 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, severe hepatitis 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 problem, 120,000 children were inadvertently injected with live, dangerous poliovirus; in 40,000, mild polio developed, 200 were permanently paralyzed, and 10 were killed. 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 errors. For example, acute encephalopathy after whole-cell pertussis vaccine,^{11,12} acute arthropathy following rubella vaccine,¹³⁻¹⁷ thrombocytopenia following measles-containing vaccine,^{18,19} Guillain-Barré syndrome (GBS) after swine flu vaccine,²⁰ paralytic polio following live attenuated oral polio vaccine,²¹ anaphylaxis following receipt of vaccines containing egg proteins (ie, influenza and yellow fever vaccines),^{22,23} severe or fatal viscerotropic disease following yellow fever vaccine,²⁴ possible narcolepsy following a squalene-adjuvanted influenza vaccine,²⁵ and severe allergic reactions associated with gelatin contained in the measles-mumps-rubella vaccine²⁶ are problems associated with the use of vaccines, albeit rarely. As vaccine use increases and the incidence of vaccine-preventable diseases is reduced, vaccine-related adverse events become more prominent in

vaccination decisions (Figure 76-1). 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 and brain damage (Figure 76-1). 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.²⁷⁻³⁰

Methods of monitoring immunization safety

Because vaccines are given to healthy children and adults, a higher standard of safety is generally expected of immunizations compared with other medical interventions. Tolerance of adverse reactions to pharmaceutical products (eg, vaccines, contraceptives) given to healthy people—especially healthy infants and toddlers—to prevent certain conditions is substantially lower than to products (eg, antibiotics, insulin) used to treat people who are sick.³¹ This lower tolerance for risks from vaccines 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, side effects are essentially universal for cancer chemotherapy, and 10% to 30% of people receiving high-dose aspirin therapy experience gastrointestinal symptoms.³²

Safety monitoring can be done before and after vaccine licensure, with slightly different goals based on the methodological strengths and weaknesses of each step.³³⁻³⁶ Although the general principles are similar irrespective of country, the specific approaches may differ because of factors such as how immunization services are organized and the level of resources available.³⁷

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.^{38,39} Phase 1 trials usually include fewer than 20 participants and can detect only extremely common adverse events. Phase 2 trials generally enroll 50 to several hundred people. When carefully coordinated, as in the comparative infant diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine trials,⁴⁰ important insight into the relationship between concentration of antigen, number of vaccine components, formulation, effect of successive doses, and profile of common reactions can be drawn and can affect the choice of the candidate vaccines for phase 3 trials.^{41,42} Sample sizes for

Table 76-1 Maximum and Current Reported Morbidity From Vaccine-Preventable Disease Events, United States*

Disease	Maximum cases (year)	2011	Percent decrease
Smallpox	206,939 (1921)	0	100
Diphtheria	894,134 (1941)	0	100
Measles	152,209 (1968)	212	> 99.9
Mumps	265,269 (1934)	370	99.9
Polio (paralytic)	57,686 (1952)	0	100
Congenital rubella syndrome	20,000† (1964-1965)	0	100
<i>Haemophilus influenzae</i> type b	20,000†	8	99.9†

*Data from National Center for Health Statistics: Health, United States, 2009: With Special Feature on Medical Technology. Hyattsville, MD: National Center for Health Statistics; 2010 (<http://www.cdc.gov/nchs/data/abus/abus09.pdf#047>) and Centers for Disease Control and Prevention (CDC): *Haemophilus influenzae* type b. (<http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hib.pdf>).

†Estimated because no national reporting existed in the prevaccine era.

phase 3 vaccine trials are based principally on efficacy considerations, with safety inferences drawn to the extent possible based on the sample size (approximately 10^3 to 10^5) and the duration of observation (often <30 days).⁴¹ Typically only observations of common local and systemic reactions (eg, injection site swelling, fever, fussiness) have been feasible. The experimental design of most phase 1 to 3 clinical trials includes a control group (a placebo or an alternative vaccine) and detection of adverse events by researchers in a consistent manner “blinded” to which vaccine the patient received. This allows relatively straightforward inferences on the causal relationship between most adverse events and vaccination.⁴³

Several ways of enhancing prelicensure safety assessment of vaccines have been developed. One of these ways includes the Brighton Collaboration (www.brightoncollaboration.org), established to develop and implement globally accepted standard case definitions for assessing adverse events following

immunizations in prelicensure and postlicensure settings.⁴⁴ Without such standards, it was difficult if not impossible to compare and collate safety data across trials in a valid manner. For example, in the large multisite phase 3 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).⁴⁵ 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.^{46,47} 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 (eg, studies in less developed settings or postlicensure surveillance).

Another of the recent advances to prelicensure safety assessments of vaccines has stemmed from the recognition of the need for much larger safety and efficacy trials 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 1 in 3,333 vaccinees.⁴⁸ Thus, to be able to detect an attributable risk of 1 per 10,000 vaccinees (eg, such as the approximate risk found for intussusception in the postlicensure evaluation of RotaShield vaccine), a prelicensure trial of at least 30,000 vaccinees and 30,000 control subjects is needed. Both second-generation rotavirus vaccines (RotaTeq and RotaRix) were subjected to phase 3 trials that included at least 60,000 infants.^{49,50} While these trials were adequately powered to detect the problem with intussusception found following RotaShield, in general, the cost of such large trials might limit the number of vaccine candidates that go through this process in the future.⁵¹

Postlicensure evaluations of vaccine safety

Because rare reactions, reactions with delayed onset, or reactions in subpopulations may not be detected before vaccines are licensed, postlicensure evaluation of vaccine safety is critical. Historically, this evaluation has relied on passive surveillance

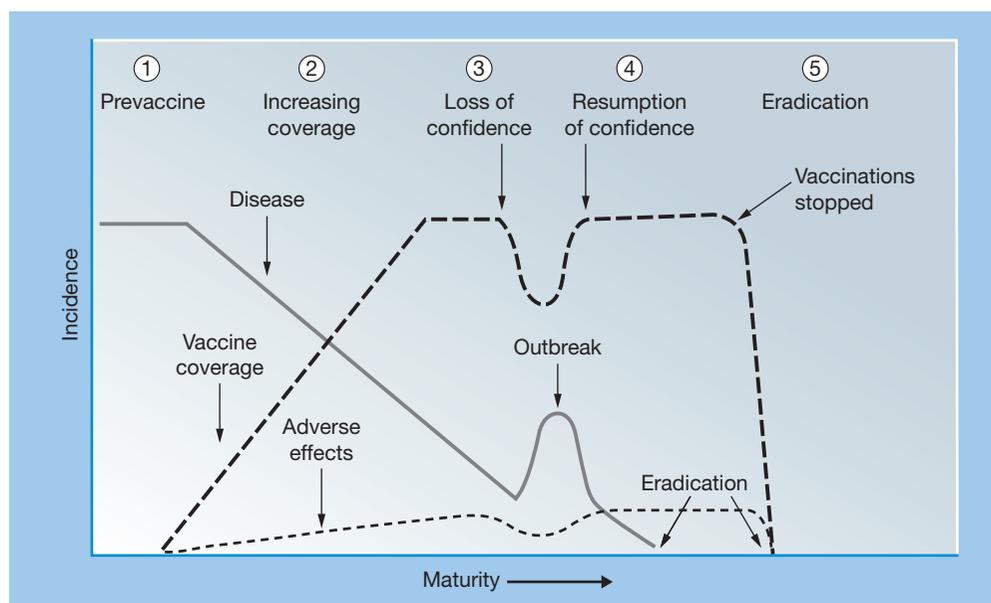


Figure 76-1 Evolution of immunization program and prominence of vaccine safety.

and ad hoc epidemiologic studies, but, more recently, phase 4 trials and preestablished large linked databases have improved the methodological capabilities to study rare risks of specific immunizations.⁴³ Such systems may detect variation in rates of adverse events by manufacturer^{52,53} or specific lot.⁵⁴ More recently, clinical centers for the study of immunization safety have emerged as another useful infrastructure to advance our knowledge about safety.⁵⁵

In contrast with the methodological strengths of prelicensure randomized trials, however, postlicensure observational studies of vaccine safety pose a formidable set of methodological difficulties.⁵⁶ Confounding by contraindication is especially problematic for nonexperimental designs. Specifically, persons who do not receive vaccine (eg, because of a chronic or transient medical contraindication or low socioeconomic group) may have a different risk for an adverse event than vaccinated persons (eg, background rates of seizures or sudden infant death syndrome (SIDS) may be higher in unvaccinated people). Therefore, direct comparisons of vaccinated and unvaccinated children are often inherently confounded, and teasing this issue out requires understanding of the complex interactions of multiple, poorly quantified factors.

Passive reporting systems, including the Vaccine Adverse Events 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.^{57–59} The national reporting of adverse events following immunizations can be done through the same reporting channels as those used for other adverse drug reactions,⁵⁹ as is the practice in France,⁶⁰ Japan,⁶¹ New Zealand,⁶² Sweden,⁶³ and the United Kingdom,⁶⁴ or with reporting forms or surveillance systems different from the drug safety monitoring systems, as done by Australia,⁶⁵ Canada,^{66,67} Cuba,⁶⁸ Denmark,⁶⁹ India,⁷⁰ Italy,⁷¹ Germany,⁷² Mexico,⁷³ the Netherlands,⁷⁴ Brazil,⁷⁵ and the United States.⁷⁶ Vaccine manufacturers also maintain SRSs for their products, which are usually forwarded subsequently to appropriate national regulatory authorities.^{38,73}

In the United States, the National Childhood Vaccine Injury Act of 1986 mandated that health care providers report certain adverse events after immunizations.⁷⁷ The Vaccine Adverse Events Reporting System (VAERS) was implemented jointly by the Centers for Disease Control and Prevention (CDC) and the US 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.⁷⁶

The VAERS form permits narrative descriptions of adverse events. Patients and their parents—not just health care 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, and answers to other questions about VAERS are available on the VAERS Web site (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 (www.meddramsso.com/index.asp), and enters VAERS reports in 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 (VAAE) reporting system,^{67,78} which is supplemented by an active, pediatric hospital-based surveillance system that searches all admissions for possible relationships to immunizations (Immunization Monitoring Program-Active, or IMPACT).⁷⁹ Serious VAAE reports are reviewed by the Advisory Committee on Causality Assessment consisting of a panel of experts.⁸⁰ The Netherlands also convenes an annual panel to categorize reports, which are then published.⁷⁴ 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.^{58,63} Data on adverse drug (including vaccine) events from several countries are compiled by the World Health Organization (WHO) Collaborating Center for International Drug Monitoring in Uppsala.⁸¹

With so many different passive surveillance systems that collect information on various medical events following vaccination, standardized definitions of vaccine-related adverse events are necessary. In the past, different definitions were developed in Brazil,⁷⁵ Canada,⁶⁷ India,⁷⁰ and the Netherlands.⁷⁴ However, implementation of similar standards across national boundaries has been advanced by the International Conference on Harmonization⁸² and the Brighton Collaboration.⁴⁴

VAERS often first identifies potential new vaccine safety problems because of clusters of cases in time or space, often with unusual clinical features. For example, in 1999, passive reports to VAERS of intussusception among children vaccinated with RotaShield was the first postlicensure signal of a problem,⁸³ leading to epidemiologic studies that verified these findings.^{84,85} Similarly, initial reports to VAERS of a previously unrecognized serious yellow fever vaccine-associated neurotropic disease⁸⁶ and viscerotropic disease^{87,88} have since been confirmed elsewhere.⁸⁹ 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.⁹⁰ These include empirical Bayesian data mining to identify unexpectedly frequent vaccine-event combinations.⁹¹

VAERS has provided some of the first safety data after the introduction of a number of vaccines.^{92–95} VAERS has also successfully served as a source of cases for further investigation of idiopathic thrombocytopenic purpura after measles-mumps-rubella (MMR) vaccine,⁹⁶ encephalopathy after MMR,^{67,97} and syncope after immunization.⁹⁸ When denominator data on vaccine doses distributed or administered are available from other sources, VAERS can be used to evaluate changes in reporting rates over time or when new vaccines replace old vaccines. For example, VAERS showed that after millions of doses had been distributed, reporting rates for serious events such as hospitalization and seizures after DTaP in toddlers were one third of those after diphtheria and tetanus toxoids and whole-cell pertussis (DTP).⁹⁹ Because VAERS is the only surveillance system covering the entire US population with data available on a relatively timely basis, it is the major means available currently to detect possible new, unusual, or extremely rare adverse events.

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 systems, and potential safety concerns may be missed.^{100–102} Aseptic meningitis associated with the Urabe mumps vaccine strain, for example, was not detected by SRSs in most countries.^{103,104} Some increases in adverse events detected by VAERS may not be true increases, but instead may be due to increases in reporting efficiency or vaccine coverage. For example, an increase in GBS reports after influenza vaccination during the 1993 to 1994 season was found to be largely

due to improvements in vaccine coverage and increases in GBS independent of vaccination.¹⁰⁵ An increased reporting rate of an adverse event after one hepatitis B vaccine compared with a second brand was likely due to differential distribution of brands in the public vs private sectors, which have differential VAERS reporting rates (higher in the public sector).¹⁰⁶ Finally, pending litigation resulted in the filing of a large number of VAERS reports claiming that vaccines caused autism.¹⁰⁷

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, however, 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 MMR vaccination.¹⁰⁰ The reporting efficiency or sensitivity of SRSSs can sometimes be estimated if an independent source of cases of specific adverse events following immunization is available to conduct capture-recapture analyses. Such an analysis was conducted to estimate that VAERS reporting completeness for intussusception following Rotashield vaccine was 47%.¹⁰⁸

Formal evaluation has been limited by the quality of diagnostic information on VAERS reports, especially the probability that 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 to 1991 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 22 (85%).¹⁰⁹ Intussusception was verified in 88% of VAERS reports filed after Rotashield vaccination.⁸³ 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.¹¹⁰ Clinical review verification rates were similar for VAERS reports following human papillomavirus vaccination: 57% for GBS and 38% for anaphylaxis.⁹⁵

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 4 surveillance studies

Vaccines may undergo clinical trials after licensure to assess the effects of changes in vaccine formulation,¹¹¹ vaccine strain,¹¹² age at vaccination,¹¹³ number and timing of vaccine doses,¹¹⁴

simultaneous administration,¹¹⁵ and interchangeability of vaccines from different manufacturers on vaccine safety and immunogenicity.¹¹⁶ Unanticipated differential mortality among recipients of high- and regular-titered measles vaccine in developing countries (albeit lower than among unvaccinated children)¹¹⁷ led to a change in recommendations by the WHO for the use of such vaccines.¹¹⁸

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 4 surveillance studies on populations with sample sizes that have included as many as 100,000 people. These studies usually have used 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.^{119–121} Large postlicensure studies on safety and efficacy have also been conducted for several other vaccines, including those for DTaP,⁴⁶ varicella, and herpes zoster.^{122,123} Requirements for phase 4 evaluation have even been extended to less frequently used vaccines, such as Japanese encephalitis vaccine.¹²⁴

Large linked databases, including the Vaccine Safety Datalink project

Historically, ad hoc epidemiologic studies have been used to assess signals of potential adverse events detected by SRSSs, the medical literature, or other mechanisms. Some examples of such studies include the investigations of poliomyelitis after inactivated^{10,125} and oral¹²⁶ polio vaccines, SIDS after DTP vaccination,^{127–130} encephalopathy after DTP vaccination,^{131,132} meningoencephalitis after mumps vaccination,¹³³ injection site abscesses after vaccination,¹³⁴ and GBS after influenza vaccination.^{20,105,109} The Institute of Medicine (IOM) has compiled and reviewed many of these studies.^{11,135}

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 began to turn to large databases linking computerized pharmacy prescription (and later immunization records) and medical outcome records.¹⁰² These databases derive from defined populations such as members of MCOs, single-provider health care 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 (ie, unvaccinated) groups, these large databases provide an economical and rapid means of conducting postlicensure studies of safety of drugs and vaccines.^{103,136–139}

The CDC initiated the Vaccine Safety Datalink (VSD) project in 1990¹³⁶ to conduct postmarketing evaluations of vaccine safety and to establish an infrastructure allowing for high-quality research and surveillance. Selection of staff-model pre-paid health plans minimized potential biases for more severe outcomes resulting from data generated from fee-for-service claims. Currently, eight MCOs in the United States participate in the VSD. The eight participating MCOs comprise a population of more than 9 million members. Each MCO 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 (eg, 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,^{11,135} from VAERS,^{85,106} from changes in immunization schedules,¹⁴⁰ or from introduction of new vaccines.^{120,121} The creation of near real-time data files has enabled the development of near real-time postmarketing surveillance for newly licensed vaccines and changes in vaccine recommendations. The size of the VSD population also permits separation of the risks associated with individual vaccines from those associated with vaccine combinations, whether given in the same syringe or simultaneously at different body sites. For example, VSD safety monitoring found that the combined MMRV vaccine carried an increased risk of febrile seizures compared with giving MMR and varicella vaccines simultaneously as separate injections.¹⁴¹ Such studies are especially valuable in view of combined pediatric vaccines.¹⁴² More than 130 studies have been or are being performed within the VSD project,¹³⁹ including general screening studies of the safety of inactivated influenza vaccines among children and of thimerosal-containing vaccines. Disease- or syndrome-specific investigations have been or are being performed, including studies investigating autism, multiple sclerosis, thyroid disease, acute ataxia, alopecia, rheumatoid arthritis, asthma, diabetes, and idiopathic thrombocytopenic purpura following vaccination.

Amid these promises, 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 (eg, to study the question of whether outcome "x" is more common in period "y" following vaccination compared with other periods) (Table 76-2).¹⁴³ 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 (eg, autism). The VSD project also cannot easily assess mild adverse events (such as fever) that do not always come to medical attention.¹³⁶ Finally, because vac-

cines 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,¹⁴⁴ and inferences on causality may be limited.¹⁴⁵

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.^{139,139} In view of the methodological and logistic advantages offered by large linked databases, the United Kingdom and Canada also have developed systems linking immunization registries with medical files.^{79,103} Because of the relatively limited number of vaccines used worldwide and the costs associated with establishing and operating these large databases, it is unlikely that all countries will be able to or need to establish their own. These countries should be able to draw on the scientific base established by the existing large linked databases for vaccine safety and, if the need arises, conduct ad hoc epidemiologic studies.

Clinical centers, including the Clinical Immunization Safety Assessment centers

More recently, there has been an increasing awareness that the usefulness of SRSs as potential disease registries and the immunization safety infrastructure can be usefully augmented by tertiary clinical centers. Well-organized, well-identified clinical infrastructures for the study of rare vaccine safety outcomes were first developed in certain regions in Italy¹⁴⁶ and Australia.^{147,148}

In the United States, the CDC established the Clinical Immunization Safety Assessment (CISA) network in 2001 with the following primary goals: (1) to develop research protocols for clinical evaluation, diagnosis, and management of adverse events following immunization (AEFI); (2) to improve the understanding of AEFI at the individual level, including determining possible genetic and other risk factors for predisposed persons and high-risk subpopulations; (3) to develop evidence-based algorithms for vaccination of persons at risk of serious adverse events following immunization; and (4) to provide a resource of subject matter experts for clinical vaccine safety inquiries.³⁶ The CISA investigators bring in-depth clinical, pathophysiologic, and epidemiologic expertise to assessing causal relationships between vaccines and adverse events and to understanding the pathogenesis of adverse

Table 76-2 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 (eg, 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 (eg, for a child observed for 365 days during which three doses of vaccine were received, total risk interval time = 3 × 30 person-days = 90 person-days; total nonrisk interval time = 365 – 90 = 275 person-days).			
0-----x=====x=====x=====//----> Birth Dose 1 Dose 2 Dose 3 365 days			
3. Add (a) total risk interval and nonrisk interval observation times for each child in the study (person-time observed; for mathematical convenience, the following example uses 100 and 1,000 person-months of observation) and (b) adverse events occurring in each period to complete a 2 × 2 table (for illustration, the example 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	1,000	0.01
Total	13	1,100	

Incidence rate for adverse event in vaccinated persons = 3/100 = 0.03.

Incidence rate for adverse event in unvaccinated persons = 10/1,000 = 0.01.

Relative rate vaccinated/unvaccinated = 0.03/0.01 = 3.0.

Probability finding is due to chance: < 5/100.

Conclusion: There is a threefold increase in risk for developing the adverse event within the 30-day interval after vaccination compared with other periods.

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.¹⁴⁹ Some of the studies undertaken by CISA include an assessment of extensive limb swelling after DTaP¹⁵⁰ a study of the usefulness of irritant skin test reactions for managing hypersensitivity to vaccines,¹⁵¹ the clinical evaluation of patients with serious adverse events following yellow fever vaccine administration,¹⁵² and evaluation of vaccine safety among children with inborn errors of metabolism.¹⁵³ New understanding of the human genome, pharmacogenomics, and immunology hold promise for future CISA studies and may make it possible to elucidate 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.¹⁵⁴

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. Mass immunization campaigns pose specific safety challenges precisely because large populations are vaccinated during a short time and often they are conducted outside the usual health care setting.¹⁵⁵ Mass immunization campaigns are often conducted in developing countries, which poses a particular challenge of ensuring injection safety.¹⁵⁶ 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-H1N1 vaccines 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.¹⁵⁷ To rapidly detect any unforeseen safety problems, the federal government implemented enhanced postlicensure 2009-H1N1 vaccine safety monitoring.¹⁵⁸ First, VAERS undertook special outreach efforts to encourage providers to report, and daily reviews and follow-up of submitted reports were conducted by medical personnel to rapidly evaluate the reports and obtain any needed additional clinical or other information. Second, a new Web-based active surveillance system was implemented to prospectively follow tens of thousands of vaccinees for medically attended adverse events. Third, large population-based systems that link computerized vaccination data with health care encounter codes were used to conduct rapid ongoing analyses to evaluate possible associations of H1N1 vaccination with selected adverse events, including potential associations suggested by VAERS or other

sources. Such systems included the existing VSD project; a new collaboration involving additional large health plans covering several million people that also performed rapid ongoing analyses similar to VSD; and the databases of the Department of Defense, Medicare, and the Veterans Administration. Fourth, active case finding for GBS was conducted in 10 areas of the United States with a combined population of about 50 million. The findings from the various safety monitoring activities were regularly reviewed by government and other scientists and an independent vaccine safety review panel convened by the Department of Health and Human Services. 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, although the reporting rate was higher after 2009-H1N1 than seasonal influenza vaccines, which may be, at least in part, a reflection of stimulated reporting; death, GBS, and anaphylaxis reports after 2009-H1N1 vaccination were rare (each < 2 per million doses administered).^{110,158} Preliminary results from the large special study of GBS found 0.8 excess cases of GBS per 1 million vaccinations, which is similar to the increased risk found with some seasonal influenza vaccines.¹⁵⁹

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.¹⁶⁰ These countries collaborated in their activities and routinely shared information among themselves and with other countries that have limited vaccine safety monitoring capabilities. 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.

Vaccine fears

Unfortunately, vaccine safety issues have increasingly taken on a life of their own outside of the scientific arena—arguably to society's overall detriment. Liability concerns, for example, have severely limited development of maternal immunizations to protect their newborn infants against diseases such as from group B *Streptococcus*.¹⁶¹ More worrisome, however, are various chronic diseases (and their advocates) in search of a simple cause, for which immunizations—as a relatively universal exposure—make all too convenient a hypothesized link. Case studies of some of these fears are discussed in the following sections.

Whole-cell pertussis vaccine causes permanent brain damage

In 1974, Kulenkampff and coworkers¹⁶² 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 due to pertussis.¹⁶³ Media coverage of the Kulenkampff report also caused decreased immunization rates and increased pertussis deaths in Japan, Sweden, and Wales.¹⁶³

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 compared with children who did not receive the vaccine and that many of these children actually suffered from Dravet's Syndrome (a neuronal sodium channel transport defect caused by an SCN1A mutation).^{166-171,171a}

Vaccines cause SIDS

In the mid-1980s, the antivaccine group called Dissatisfied Parents Together raised the notion that the whole-cell pertussis vaccine could cause SIDS. Subsequent study of children who did or did not receive DTP vaccine showed that the incidence of SIDS was not greater in the vaccinated group.¹⁴³

In the early 1990s, when the hepatitis B vaccine was recommended for routine use in newborns, a program on ABC's *20/20* raised the question of whether vaccines could cause SIDS. Again, studies failed to find any association between hepatitis B vaccine and SIDS.^{130,170,171} Two recent reviews have confirmed the notion that vaccines do not cause SIDS.^{172,173}

Vaccines cause mad-cow disease

By July 2000, at least 73 people in the United Kingdom developed a progressive neurological disease termed variant Creutzfeldt-Jakob disease that likely resulted from eating meat prepared from cows with "mad-cow" disease, a disease caused by proteinaceous infectious particles (prions). Some vaccines were made with serum or gelatin obtained from cows in England or from countries at risk for mad-cow disease.

Two products obtained from cows may be present in vaccines: trace quantities of fetal bovine serum used to provide growth factors for cell culture and gelatin used to stabilize vaccines. However, the bovine-derived products used in vaccines are not likely to contain prions for several reasons.¹⁷⁴ First, fetal bovine serum and gelatin are obtained from blood and connective tissue respectively; neither are sources that have been found to contain prions. Second, fetal bovine serum is highly diluted and eventually removed from cells during the growth of vaccine viruses. Third, prions are not propagated in cell cultures used to make vaccines. Fourth, transmission of prions occurs from eating meat contaminated with nervous tissue obtained from infected animals or, in experimental studies, from directly inoculating preparations of brains from infected animals into the brains of experimental animals. Transmission of prions has not been documented after inoculation into the muscles or under the skin (routes used to vaccinate). Taken together, the chance that currently licensed vaccines contain prions is essentially zero.

Oral polio vaccine trials in Africa caused AIDS

The notion that the origin of AIDS could be traced to polio-virus vaccines that were administered in the Belgian Congo between 1957 and 1960 was the subject of a popular magazine article¹⁷⁵ and book.¹⁷⁶ The logic behind this assertion was as follows: (1) The polio vaccine used in the Belgian Congo was grown in chimpanzee kidney cells. (2) The chimpanzee kidney cells used at that time contained simian immunodeficiency virus (SIV). (3) SIV is very closely related to human immunodeficiency virus (HIV). (4) People were inadvertently inoculated with SIV that then mutated to HIV and caused the AIDS epidemic.

This reasoning is problematic and based on several false assumptions.¹⁷⁷⁻¹⁸⁰ First, SIV most closely related to HIV has been demonstrated in chimps in the Cameroon, far from the chimps near Stanleyville that were used to make the vaccine. Second, SIV and HIV are not very close genetically; mutation to HIV from SIV would likely require decades, not years. Third, polymerase chain reaction (PCR) analysis showed that the cell substrate used to make the vaccine was monkey, not chimp. Fourth, SIV and HIV are enveloped viruses that are easily disrupted by extremes in pH. If given by mouth (in a manner similar to the oral polio vaccine), both of these viruses would likely be destroyed in the acid environment of the stomach.

Last, and most important, original lots of the polio vaccine (including those used in Africa for the polio vaccine trials) did not contain HIV or SIV genomes as determined by the very sensitive reverse-transcription PCR assay. Unfortunately, the notion that live attenuated polio vaccine could cause AIDS remains an obstacle to eliminating polio in some countries in Africa.

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. Recently, investigators found SV40 DNA in biopsy specimens obtained from patients with certain unusual cancers (ie, mesothelioma, osteosarcoma, and non-Hodgkin lymphoma), leading some to hypothesize a link between vaccination and the subsequent development of cancer.¹⁸¹ 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 and people who did not receive these vaccines.¹⁸¹ Taken together, these findings do not support the hypothesis that the SV40 contained in polio vaccines administered before 1963 caused cancers.

Vaccines overwhelm the immune system

One hundred years ago, children received one vaccine—smallpox. Today, young 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 by 2 years of age, including as many as five shots at one time. The increase in the number of vaccines, and the consequent decline in vaccine-preventable illnesses, has focused attention by parents and health care professionals on vaccine safety. Specific concerns include whether vaccines weaken, overwhelm,^{182,183} or in some way alter the normal balance of the immune system, paving the way for chronic diseases such as diabetes, asthma, multiple sclerosis, and allergies.

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 76-3). 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.

A practical way to determine the capacity of the immune system to respond to vaccines would be to consider the number of B and T cells required to generate adequate levels of binding antibodies per milliliter of blood.¹⁸⁴ Calculations are based on the following assumptions:

- Approximately 10 ng/mL is likely to be an effective concentration of antibody directed against a specific epitope.
- Approximately 10^3 B cells/mL are required to generate 10 ng of antibody/mL.
- Given a doubling time of about 0.75 days for B cells, it would take about 7 days to generate 10^3 B cells/mL from a single B-cell clone.

Table 76-3 Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines

Vaccine	Year of introduction	No. of proteins or polysaccharides or both
Smallpox*	1796	198
Rabies	1885	5
Diphtheria†	1923	1
Pertussis (whole-cell)*	1926	≈ 3,000
Tetanus†	1927	1
Yellow fever	1936	11
Influenza†	1945	10
Polio (inactivated)†	1955	15
Polio (live attenuated)*	1961	15
Measles†	1963	10
Mumps†	1967	9
Rubella†	1969	5
Hepatitis B†	1981	1
H. influenzae type b (conjugate)†	1990	2
Pertussis (acellular)†	1991	2-5
Hepatitis A†	1995	4
Varicella†	1995	69
Pneumococcus (conjugate)†	2000	14
Meningococcus (conjugate)†	2005	5
Rotavirus†	2006	11-16
Human papillomavirus†	2006	2-4

*Formerly in the US routine child and adolescent immunization schedule.

†Currently in the US routine child and adolescent immunization schedule.

- Because vaccine-specific humoral immune responses are first detected about 7 days after immunization, those responses could initially be generated from a single B-cell clone per milliliter.
- One vaccine contains about 10 immunogenic proteins or polysaccharides (Table 76-3).
- Each immunogenic protein or polysaccharide contains about 10 epitopes (ie, 10^2 epitopes per vaccine).
- 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 (approximately 10^7 /ml) by the average number of epitopes per vaccine (10^2). Therefore, a person could theoretically respond to about 10^5 vaccines at one time.

The analysis used to determine the theoretical capacity of a person to respond to as many as 10^5 vaccines at one time, although consistent with the biology and kinetics of vaccine-specific immune responses, is limited by lack of consideration of several factors. First, only vaccine-specific B-cell responses are considered. However, protection against disease by vaccines may also be mediated by vaccine-specific cytotoxic

T lymphocytes (CTLs). For example, virus-specific CTLs are important in the regulation and control of varicella infections.¹⁸⁵ Second, in part because of differences in the capacity of various class I or class II glycoproteins (encoded by the MHC) to present viral or bacterial peptides to the immune system, some people are not capable of responding to certain virus-specific proteins (eg, hepatitis B surface antigen).¹⁸⁶ Third, some proteins are more likely to evoke an immune response than others (ie, immunodominance). Fourth, although most circulating B cells in a neonate are naïve, the child very quickly develops memory B cells that are not available for response to new antigens and, therefore, should not be considered as part of the circulating naïve B-cell pool. Fifth, the immune system is not static. A study of T-cell population dynamics in HIV-infected persons found that adults have the capacity to generate about 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. Primarily because of this fifth reason, the assessment that people can respond to at least 10^5 vaccines at one time might be low.

Babies are too young to develop adequate immune responses to vaccines

Within hours of birth, cells of the innate and adaptive immune systems are actively engaged in responding to challenges in the environment (eg, colonizing bacterial flora).^{188,189} Similarly, newborn and young infants are quite capable of generating protective immune responses to single and multiple vaccines. For example, children born to mothers infected with hepatitis B virus are protected against infection after inoculation with hepatitis B vaccine (given at birth and 1 month of age).¹⁹⁰⁻¹⁹² Similarly, newborns inoculated with bacille Calmette-Guérin (BCG) vaccine are protected against severe forms of tuberculosis presumably by activation of bacteria-specific T cells.¹⁹³⁻¹⁹⁵ In addition, about 90% to 95% of infants inoculated in the first 6 months of life with multiple vaccines, including diphtheria-tetanus-pertussis, pneumococcus, Hib, hepatitis B and polio, develop protective, vaccine-specific immune responses.¹⁹⁶ Conjugation of bacterial polysaccharides (such as *Streptococcus pneumoniae* and Hib) to carrier molecules that elicit helper T cells circumvents the poor immunogenicity of unconjugated polysaccharide vaccines in infants and young children.^{197,198}

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.^{199,200} 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.¹⁹⁹ 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 virus²⁰¹ or wild-type influenza virus²⁰² 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 weakly mimic events that occur after natural infection. For example, measles, mumps, or rubella vaccines can significantly depress reactivity to the tuberculin skin test,²⁰³⁻²⁰⁹ measles-containing vaccines

can cause a decrease in protective immune responses to varicella vaccine,²¹⁰ and high-titered measles vaccine (Edmonston-Zagreb strain) can cause an excess of cases of invasive bacterial infections in developing countries.²¹¹ All of 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, BCG, measles, mumps, rubella, or live attenuated poliovirus vaccines was not greater than that found in unimmunized children.²¹²⁻²¹⁶

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-MHC 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-MHC. In the fetal liver, and later in the bone marrow, B-cell receptors (ie, 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*.²¹⁷

However, it is not simply the presence of autoreactive T and B cells 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.^{218,219} Mechanisms of peripheral tolerance include the following: (1) antigen sequestration (Antigens of the central nervous system, eyes, and testes are not regularly exposed to the immune system unless injury or infection occurs.); (2) anergy (Lymphocytes partially triggered by antigen but without costimulatory signals are unable to respond to subsequent antigen exposure.); (3) activation-induced cell death (a self-limiting mechanism involved in terminating immune responses after antigen is cleared); and (4) inhibition of immune responses by specific regulatory cells.²²⁰⁻²²³

Therefore, 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 of 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 of these conditions are not met, the activation of self-reactive lymphocytes and progression to autoimmune disease are not likely.²²⁴

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.²²⁵ A study in Canada found no increase in risk for diabetes as a result of receipt of BCG vaccine.²²⁶ 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.²²⁷⁻²²⁹

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.²³⁰⁻²³² However, the capacity of vaccines to cause or exacerbate multiple sclerosis has been evaluated in several excellent epidemiologic studies.²³³⁻²³⁷ Two large case-control studies showed no association between hepatitis B vaccine and multiple sclerosis²³⁴ and found no evidence that hepatitis B, tetanus, or influenza vaccines exacerbated symptoms of multiple sclerosis.²³⁵ Other well-controlled studies also found that influenza vaccine did not exacerbate symptoms of multiple sclerosis.²³⁶⁻²³⁸ 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 symptoms.²³⁸

A recent review also showed that the novel H1N1 2009 vaccine had an attributable risk for Guillain-Barré Syndrome of 1-2 cases per million doses administered, not higher than that found following the 2009-2010 seasonal influenza vaccine.²³⁹

Vaccines cause allergies and asthma

Allergic symptoms are caused by soluble factors (eg, IgE) that mediate immediate-type hypersensitivity; production of IgE by B cells is dependent on release of cytokines such as interleukin-4 by Th2 cells. Two theories have been advanced to explain how vaccines could enhance IgE-mediated, Th2-dependent allergic responses. First, vaccines could shift immune responses to potential allergens from Th1-like to Th2-like.²⁴⁰ Second, by preventing common prevalent infections (the “hygiene hypothesis”), vaccines could prolong the length or increase the frequency of Th2-type responses.^{241,242}

Although all factors that cause changes in the balance of Th1 and Th2 responses are not fully known,²⁴³ it is clear that dendritic cells have a critical role. For example, adjuvants (eg, aluminum hydroxide or aluminum phosphate [“alum”] contained in some vaccines) promote dendritic cells to stimulate Th2-type responses.^{244,245} 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.²⁴⁶ Furthermore, local inoculation of adjuvant does not cause a global shift of immune responses to Th1 or Th2 type.^{247,248}

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.^{241,242} 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.²⁴⁹ 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 despite the fact that they are commonly infected with helminths and worms—organisms that induce strong Th2-type responses.²⁵⁰ Finally, the incidence of diseases that are mediated by Th1-type responses, such as multiple sclerosis and type 1 diabetes, have increased in the same populations as those that experienced an increase in allergies and asthma.

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,²⁵¹ more recent studies have suggested otherwise. A large clinical trial performed in Sweden found no increased risk,²⁵² 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.²⁵³ Two studies from the VSD project have also lent data to this controversy. In one study of 1,366 infants with wheezing during infancy, vaccination with DTP and other vaccines was not related to the risk of wheezing in full-term infants,²⁵⁴ and, in another study of more than 165,000 children, childhood vaccinations were not associated with an increased risk for developing asthma.²⁵⁵ Finally, a study from Finland also suggested that children with a history of natural measles were at increased risk for atopic illness. Such findings would run contrary to the hypothesis that the increase in atopic illnesses seen in several countries is due to the reduction in wild measles resulting from immunizations.²⁵⁶

Another separate concern is whether inactivated influenza vaccination may induce asthma exacerbations 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.²⁵⁷ In fact, after controlling for asthma severity, acute asthma exacerbations were less common after inactivated influenza vaccination than before,²⁵⁸ and inactivated influenza vaccination seems to be associated with a decreased risk for asthma exacerbations throughout influenza seasons.²⁵⁹ Several more recent studies have also shown a lack of correlation between receipt of vaccines and the development of asthma.^{260–263}

MMR vaccine causes 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.²⁶⁴ 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.²⁶⁵ 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 a study based on 12 children proposed an association between the vaccine and the development of ileonodular hyperplasia, nonspecific colitis, and regressive developmental disorders (later termed by some as “autistic enterocolitis”).²⁶⁶ Among the proposed mechanisms was that MMR vaccine 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.²⁶⁷

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.²⁶⁸ 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.^{269,270} A study in the United States in the VSD project investigated whether measles-containing vaccine was associated with inflammatory bowel disease and found no relationship between receiving MMR vaccine and inflammatory bowel disease or between the timing of the vaccine and risk for disease.²⁷¹ Soon after *The Lancet* published the article that ignited the controversy,²⁶⁶ two ecologic analyses found no evidence that MMR vaccination was the cause of apparent increased trends in autism over time,^{272,273} while two other studies found no evidence of a new variant form of autism associated with bowel disorders secondary to vaccination.^{274,275} Several more recent studies have also refuted the notion that MMR vaccine caused autism.^{276–281} In February 2010, *The Lancet* retracted the original article claiming an association.

Because of the level of concern surrounding this issue, the CDC and the National Institutes of Health requested an independent review by the IOM.²⁸² 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 good evidence of biological mechanisms that would support or explain such a link.

Thimerosal causes autism

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.²⁸³ Consequently, the routine neonatal dose of hepatitis B vaccine in infants born to hepatitis B surface antigen–negative mothers was suspended in the United States until preservative-free vaccines became available, and transitioning to a vaccine schedule free of thimerosal began as a precautionary measure.²⁸⁴ Currently, some multidose influenza vaccines contain preservative quantities (ie, 25 µg per dose) of thimerosal although thimerosal-free vaccines are available.

Mercury in the environment

Mercury is a naturally occurring element found in the earth's crust, air, soil, and water. Since the earth's formation, volcanic eruptions, weathering of rocks, and burning of coal have caused mercury to be released into the environment. Once released, certain types of bacteria in the environment can change inorganic mercury to organic (methylmercury). Methylmercury makes its way through the food chain in fish, animals, and

humans. At high levels, it can be neurotoxic. Thimerosal 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.^{284a}

Evidence that thimerosal does not cause autism

Several pieces of biological and epidemiologic evidence support the notion that thimerosal does not cause autism. First, in 1971 Iraq imported grain that had been fumigated with methylmercury.²⁸⁵ Farmers ate bread made from this grain. The result was one of the worst, single-source, mercury poisonings in history. Methylmercury in the grain caused the hospitalization of 6,500 Iraqis and killed 450. Pregnant women also ate the bread and delivered infants with epilepsy and mental retardation. However, there was no evidence that these infants had an increased incidence of autism. Second, several large studies have now 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; the incidence of autism was similar in all groups.^{286–291} The IOM has reviewed these studies and concluded that evidence favored rejection of a causal association between vaccines and autism and that autism research should shift away from vaccines.²⁹² Denmark, a country that abandoned thimerosal as a preservative in 1991, actually saw an increase in the disease beginning several years later. Third, studies of the head size, speech patterns, vision, coordination, and sensation of children poisoned by mercury show that the symptoms of mercury poisoning are distinguishable from the symptoms of autism.²⁹³ Fourth, methylmercury is found in low levels in water, infant formula, and breast milk.²⁹⁴ Although it is clear that large quantities of mercury can damage the nervous system, there is no evidence that the small quantities contained in water, infant formula, and breast milk do. An infant who is exclusively breastfed for 6 months will ingest more than twice the quantity of mercury that was ever contained in vaccines and 15 times the quantity of mercury contained in the influenza vaccine.

One known and unfortunate sequela from the uncertainty surrounding the safety of thimerosal was confusion surrounding administration of the birth dose of hepatitis B vaccine. Following the suspension of the routine use of hepatitis B vaccine for low-risk newborns in 1999, there was a marked increase in the number of hospitals that no longer routinely vaccinated all infants at high risk of hepatitis B.²⁹⁵ As a result, there have been cases of neonatal hepatitis B that could have been prevented but were not because of many hospitals suspending their routine neonatal hepatitis B vaccination program.²⁹⁶

Too many vaccines cause autism

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, Michael Smith and Charles Woods mined data from a previous study that had been performed by CDC researchers to determine whether thimerosal in vaccines was associated with an increased risk of autism or neurodevelopmental delays.²⁹⁷ Smith and Woods compared children who had received vaccines according to the CDC/American Academy of Pediatrics schedule with children for whom a decision was

made to delay, withhold, separate, or space out vaccines, noting no difference between the two groups in neurodevelopmental outcomes.²⁹⁸

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 local inflammatory reactions, 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 (eg, antacids).²⁹⁹ Studies have shown that children who receive aluminum-containing vaccines have serum levels of aluminum that are well below the toxic range.^{300–302}

Formaldehyde in vaccines is harmful

Formaldehyde has been used in vaccines to detoxify bacterial toxins (ie, diphtheria toxin, tetanus toxin, pertussis toxins) and to inactivate viruses (ie, poliovirus). Because formaldehyde at high concentrations can cause mutational changes in cellular DNA in vitro,³⁰³ 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 detectable in serum.³⁰⁴ Indeed, the level of formaldehyde in the circulation is about 10-fold more than would be contained in any vaccine.³⁰⁵ Also, people exposed to high levels of formaldehyde in the workplace (eg, morticians) are not at greater risk of cancer than people who are not exposed to formaldehyde.³⁰⁶ Finally, the quantity of formaldehyde present in vaccines is at least 600-fold lower than that necessary to induce toxicity in experimental animals.³⁰⁷

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 Pontifical Academy of Life of the Catholic Church has deemed vaccines made using these cells worthy of continued use, despite their origins.³⁰⁸

Vaccine risk communication

Disease prevention, 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 vs vaccination were readily evident. As immunization programs successfully reduced the incidence of vaccine-preventable diseases, however, an increasing proportion of health care providers and parents have little or no personal experience with vaccine-preventable diseases. For their risk-benefit analysis, they are forced to rely on historical and other more distant descriptions of vaccine-preventable diseases in textbooks or educational brochures. 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 World Wide Web are likely to encounter Web sites that encourage vaccine refusal or emphasize the dangers of vaccines.^{309,310} Similarly, the media may sensationalize vaccine safety issues or, in an effort to present “both sides” of an argument, fail to provide perspective.^{311,312} 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. Therefore, 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 have an impact on parental beliefs about immunizations. A national survey found that although the majority of parents support immunizations, 20% to 25% have misconceptions that could erode their confidence in vaccines.¹⁸² 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 health care providers who administer vaccines.

Risk communication principles

The science of risk perceptions and risk communications, developed initially for technology and environmental arenas,³¹³ has only recently been formally applied to immunizations.³¹⁴ 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.³¹⁵ In contrast, research has shown that laypersons may have subjective, multidimensional, and value-laden conceptualizations of risk.³¹⁶ Among the key principles and lessons learned about public perceptions of risk are the following:

- Individual people differ in their perceptions of risk depending on their personality, education, life experience, and personal values;^{317,318} educational materials tiered for different needs are therefore likely to be more effective than a single tier.
- Perceptions of risk may differ dramatically among various stakeholders, such as members of government agencies, industry, or activist groups.³¹⁹ The level of trust between stakeholders has an impact on all other aspects of risk communication.³²⁰ Trust is generally reinforced by open communication about what is known and unknown about risks and by providing candid accounts of the evidence and how it was used in the decision-making process.³²¹
- Certain hazard characteristics, including involuntariness, uncertainty, lack of control, high level of dread, and low level of equity, lead to higher perceived risk;³¹⁶ only risks with similar characteristics should be compared in risk communication efforts.³²²
- For quantitatively equivalent risk that is due to action (eg, vaccination reaction) vs inaction (eg, vaccine-preventable disease caused by nonvaccination), many people prefer the consequences of inaction to action.³²³
- When there is uncertainty about risks, patients frequently rely on the advice of their physician or other health care professionals; continuing education of health care professionals on vaccine risk issues is key.¹⁸²
- Finally, different ways of presenting, or framing, the same risk information (eg, using survival rates vs mortality rates) can lead to different risk perceptions, decisions, and behaviors.^{324,325}

Risk communication can be used for the purposes of advocacy, public education, or decision-making partnership.³¹³ People care not only about the magnitude of risks, but also how risks are managed and whether they participate in the risk-management process, especially in a democratic society.³²⁶ In medical decision making, this has resulted in a transition from more paternalistic models to increasing degrees of informed consent.³²⁷ Some have argued that a similar transition to informed consent also should occur with immunizations.³²⁸ However, immunization is unlike most other medical procedures (eg, surgery) in that the consequences of the decision affect not only the individual person, but also others in the society. Because of this important distinction, many countries have enacted public health (eg, immunization) laws that severely 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.³²⁹ Unfortunately, the protection provided by herd immunity may disappear if too many people avoid vaccination, resulting in outbreaks of vaccine-preventable diseases.^{330,331} Debates in the United States have focused on whether philosophical (in addition to medical and religious) exemptions to mandatory immunizations should be allowed more universally and, if so, what standards for claim of exemption are needed.^{328,332,333} Thus, vaccine risk communications should not only describe the risks and benefits of vaccines for individual people, but also should include discussion of the impact of individual immunization decisions on the larger community.

Evaluating and addressing vaccine safety concerns

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.⁵¹ 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.^{134,334} Advice and review from a panel of independent experts also may be needed.^{109,335,336} Causality assessment at the individual level is difficult at best; further evaluation via epidemiologic or laboratory studies may be required.³³⁷ Even if the investigation is inconclusive, such studies can often help to maintain public trust in immunization programs.³³⁸

Scientific investigations are only the beginning of addressing vaccine safety concerns. In many countries, people who believe they or their children have been injured by vaccines have organized and produced information highlighting the risks of and alternatives to immunizations. From the consumer activist perspective, even if vaccine risks are rare, this low risk does not reassure the person who experiences the reaction.³³⁹ Such groups have been increasingly successful in airing their views in electronic and print media, frequently with poignant individual stories.^{309,310} Because the media frequently raise controversies without resolution and choose “balance” over perspective, one challenge is to establish credibility and trust with the audience.^{340,341} Factors that aid in enhancing credibility include demonstrating scientific expertise, establishing relationships with members of the media, expressing empathy, and distilling scientific facts and figures down to simple lay concepts. However, statistics and facts compete poorly with dramatic pictures and stories of disabled children. Emotional reactions to messages are often dominant, influencing subsequent cognitive processing.³⁴² Therefore, equally compelling firsthand accounts of people with vaccine-preventable diseases may be needed to communicate the risks associated with not vaccinating. Clarifying the distinction between perceived and real risk for the concerned public is critical. If further research is

needed, the degree of uncertainty (eg, whether such rare vaccine reactions exist at all) should be acknowledged, but what is certain also should be noted (eg, millions of people have received vaccine X and have not developed syndrome Y; even if the vaccine causes Y, it is likely to be of magnitude Z, compared with the magnitude of known risks associated with vaccine-preventable diseases).

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 1978.³⁴³ The National Childhood Vaccine Injury Act requires every health care provider, public or private, who administers a vaccine that is covered by the act to provide a copy of the most current CDC Vaccine Information Statement (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.³⁴⁴ Health care 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 his or her 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 at www.cdc.gov/vaccines and are available in more than 20 languages from the Immunization Action Coalition at www.immunize.org. An increasing number of resources that address vaccine safety misconceptions and allegations also have become available, including Web sites, brochures, resource kits, and videos (Table 76-4). Some studies have been conducted to assess the use and effectiveness of such materials;³⁴⁵⁻³⁴⁹ however, more research in this area is needed.

Immunization programs and health care providers should anticipate that some members of the public may have deep concerns about the need for and safety of vaccines. A few may refuse certain vaccines or even reject all vaccinations. An understanding of vaccine risk perceptions and effective vaccine risk communication are essential in responding to misinformation and concerns. Toward this end, CDC's vaccine safety website (<http://www.cdc.gov/vaccinesafety/index.html>) provides basic information on the safety of routinely administered vaccines, as well as responses to frequently asked questions. The website also provides more detailed information on how vaccines are tested and monitored for safety; CDC's specific projects for monitoring, evaluation, and research on vaccine safety (VAERS, VSD, and CISA); detailed sections addressing common concerns (eg, autism, thimerosal); and a resource library with articles, fact sheets, and other related materials on immunization safety.

Parental vaccine acceptance in a new era: the role of health care providers and public health professionals

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.^{350,351} Moreover, increasingly parents want to be fully informed about their children's medical care,³⁵² thus merely recommending vaccination may not be sufficient. Also in this new era, stories in the media highlighting adverse events (real or perceived) may cause some parents to question the safety of vaccines.

Apart from the media attention on vaccine safety issues, a confluence of factors has an influence on parents' vaccine attitudes in the present environment of a low incidence of vaccine-preventable diseases. These factors would be relatively unimportant in an environment where diseases such as polio and measles were common and people lived in fear of their

Table 76-4 Web Sites Containing Reliable, Up-to-Date, and Accurate Information About Vaccines

Source	Web site
Government	
Centers for Disease Control and Prevention	www.cdc.gov/vaccines
Professional associations	
American Academy of Pediatrics	www.aap.org/immunization
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 www.vaccineinformation.org
Institute for Vaccine Safety	www.vaccinesafety.edu
National Network for Immunization Information	www.immunizationinfo.org
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	www.vaccine.chop.edu
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	www.path.org/vaccine resources
Parent and family organizations	
Families Fighting Flu	www.familiesfightingflu.org
Faces of Influenza	www.facesofinfluenza.org
The National Meningitis Association	www.nmaus.org
Meningitis Angels	www.meningitis-angels.org
Parents of Kids with Infectious Diseases	www.pkids.org

children contracting disease; however, they have become predominant in the current climate for some parents. Some of these factors are: (1) lack of appropriately tailored information about the benefits of vaccines and contrary information from alternative health practitioners, (2) mistrust of the source of the information, (3) perceived serious side effects, (4) not perceiving the risks of vaccines accurately, and (5) insufficient biomedical literacy. Addressing these issues is a challenge for medical and public health professionals because the typical arrangement for providing medical care does not allow full reimbursement of health care providers for educating patients and parents.³⁵³ Nevertheless, it is important for us to try to meet the challenge

because an understanding of the aforementioned 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.

Information

Most people today want to be thoroughly informed about their health care.³⁵² The desire for more information also applies to parents with regard to medical issues for their children. Parents want to be part of the decision-making process when it comes to immunizations for their children.³⁵⁴ Providing the appropriate information at the appropriate time is especially important now with the increased questioning of vaccines and with 20 states allowing philosophical exemptions in 2011.

There is an association between information and vaccine acceptance. A recent 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.³⁵⁵ Parents who disagreed they had enough vaccine information had negative attitudes about immunizations, health care 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.³⁵⁵ It may be that when there is a void of accurate, trusted information, doubts about vaccines arise and misinformation is more readily accepted. Other studies have demonstrated the effect of providing information on the well-being of patients. For example, information is one factor that has been shown to positively influence a sense of control in patients with rheumatoid arthritis,³⁵⁶ and perceived lack of information among mothers was one reason contributing to nonimmunization of children in India.³⁵⁷

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 and beliefs.³⁵⁸ The two audience segments identified as most concerned about immunizations ("worrieds" and "fencesitters") were chosen as the focus of a follow-up study to obtain the input of mothers in these segments in the development of evidence-based, tailored educational materials. The purpose of these materials would be to assist health care providers in busy office settings to address questions from these two groups of parents. Presentation of these tailored brochures by children's health care providers to parents in an empathetic and respectful manner could aid in improving the health care provider–parent relationship, increasing vaccine acceptance, and ultimately preventing vaccine-preventable diseases.

Timing of information

The VISs are typically given to parents the day the child is scheduled for immunization.^{345,348,359} This often places the parent in a conflict situation of attending to the VIS or attending to a frightened or upset child. Not surprisingly, studies have shown that parents would rather receive the information in advance of the first vaccination visit.^{345,359–361}

Suggested earlier times for vaccine education include prenatal clinic visits and just after delivery in a hospital.³⁶² 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.³⁴⁸

Contrary information

The use of complementary and alternative medicine (CAM) has been increasing during the past 50 years in the United States.³⁶³ Part of this increase is due to MCOs providing coverage for some

CAM therapies.³⁶⁴ Chiropractic care is among the top 10 most commonly used CAM therapies.³⁶⁵ It is of note that some chiropractic colleges teach a negative view of immunizations.³⁶⁶ In one study, one third of chiropractors agreed that there is no scientific proof that immunizations prevent disease.³⁶⁶ The basis for the negative views of vaccine effectiveness may lie in the chiropractic doctrine that disease is the result of spinal nerve dysfunction caused by subluxation coupled with the rejection of the germ theory of disease.^{366,367} It may be that some chiropractors who adhere to this belief influence parents against immunizing their children. In one study, parents who requested immunization exemptions for their children were more likely to report CAM use in their families than parents who did not request these exemptions.³⁶⁸ This emphasizes the importance of a trusting physician-patient relationship and providing parents with tailored information in advance of their child's immunizations; in this manner their questions are answered and they are prepared with the facts when they encounter contrary information from other sources. Reaching out to chiropractic organizations to foster a better understanding of the benefits of immunizations may be advantageous to medical and public health professionals.

Mistrust of the source of information

Parental concern about immunizations has been associated with a lack of trust. For example, one of the factors influencing parents who choose not to vaccinate their children for pertussis is doubt about the reliability of the vaccine information.³⁶⁹ In another study, compared with parents of vaccinated children, parents of children with an immunization exemption were more likely to express a low level of trust in the government, in addition to other factors such as low perceived susceptibility to and severity of vaccine-preventable diseases and low perceived efficacy and safety. These parents were less likely to believe that medical and public health professionals are good or excellent sources of immunization information.³⁶⁸ The majority of parents (84%), however, report receiving immunization information from a physician.¹⁸² 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.

Perceived serious side effects

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.³⁷⁰ Two scenarios were seen as plausible. It may be that parents who were already concerned about vaccines before their child began the vaccination schedule were more reactive and thus sought medical attention for minor side effects (eg, 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.

Negative attitudes could be addressed by improving communication between clinician and parent. Benefit-cost analysis research has shown that physician advice can produce benefits

for health issues (eg, problem drinking).³⁷¹ Moreover, positive communication behaviors such as humor and soliciting questions are associated with lowered physician's risk of a malpractice suit.³⁷² It may be that in this era of low vaccine-preventable disease incidence and increased public questioning of immunizations, improved provider communication can produce a positive net benefit for parents (reduced anxiety), a cost benefit to the health care system (reduced calls and medical visits for nonserious adverse events following immunization), and an improved physician-patient relationship (more trust and fewer malpractice suits).

Risk perception

Individual people can vary in their perception of the magnitude of vaccine risks. Studies have shown that various factors such as sex, race, political worldviews, emotional affect, and trust are associated with risk perception.³⁷³ In addition, risk perception factors such as involuntariness, uncertainty, lack of control, and high level of dread can lead to a heightened perception of risks.³⁷⁴ All of these can be seen as associated with childhood immunizations. Moreover, these factors have been 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.³⁷⁴

It can be difficult to communicate the risk of many vaccine-preventable diseases given their low prevalence in the United States and difficult to communicate the risks of serious vaccine adverse events because they affect such a small proportion of vaccine recipients.^{375,376} Several factors have been studied that might help people to better understand risk; the first are comparisons. Comparisons that are similar (apples to apples) are reported to be better accepted,³⁷⁷ and, thus, comparisons of vaccines should focus on things that generally prevent harm in children but could pose a small risk (such as bicycle helmets, car seats). The second are visual presentations that help people understand numerical risk, including risk ladders,³⁷⁸ stick figures, line graphs, dots, pie charts, and histograms.³⁷⁹ Unfortunately, there has been little research done in either of these areas. Trust in the source of the risk information is an important factor in its ability to influence people³⁸⁰ and, as discussed, is developed through listening and ongoing communications.³⁸¹

Biomedical literacy

In 1999, American adults had an average score of 51.2 on an Index of Biomedical Literacy designed to measure understanding of biomedical terms and constructs. People with scores less than 50 would likely find it difficult to understand medical stories about why antibiotics are not effective in combating the common cold and the relationship between certain genes and health.³⁸² The main factors associated with biomedical literacy are the following: (1) level of formal education, (2) number of college-level science courses, and (3) age. Some characteristics of scientific literacy include the following abilities: (1) distinguishing experts from the uninformed; (2) recognizing gaps, risks, limits, and probabilities in making decisions involving a knowledge of science or technology; (3) recognizing when a cause-and-effect relationship cannot be drawn; and (4) distinguishing evidence from propaganda, fact from fiction, sense from nonsense, and knowledge from opinion. Unfortunately, parental characteristics of those least motivated to obtain timely immunizations for their children are often characterized by low educational level of either parent.³⁸³

There is a wide gap in the level of biomedical understanding across the US 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 middle level or a "one size fits all" are not likely to satisfy all parents' needs.³⁸²

The importance of educating parents concerned about vaccines

Why should we care about a small number of parents who are worried about vaccines for their children? We should care because it is not only ethically the right thing to do, it is also the right thing to do from a practical viewpoint. Vaccine acceptability refers to the factors that go into parents' decisions to have their children immunized. It is important not to assume that just because most parents are having their children immunized that they will continue to do so.³⁸⁴ While the host of factors contributing to parents' decisions to have their children immunized (eg, need for information, experience with adverse events) might remain stable for some time, it is possible that one or more of the 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. This is especially possible as more vaccines are added to the immunization schedule.

An increasing number of parents have a choice, through religious or philosophical immunization exemption laws or schooling their children at home.³⁸⁵ Averting the future possibility of outbreaks of vaccine-preventable diseases will take a concerted effort by health care and public health professionals to educate and better communicate with parents concerned about immunizations. In guidance for clinicians, the 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.³⁸⁶ 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 health care providers to be able to optimally fill this important role, however, two related issues should 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.^{387,388} 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 disease³⁸³ and smoking.³⁸⁹ It is important to note that studies have shown education programs can be a cost savings to health care systems.^{390,391} 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,³⁹² 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.^{142,393} New

technologies can also be expected to be used to detect potential safety problems throughout the research and development process (eg, adventitious agents). A challenge will be determining the proper role and interpretation of new technologies. For example, a recent study used powerful new metagenomics and panmicrobial microarray technologies to screen for adventitious viral nucleic acid sequences in a number of vaccines.³⁹⁴ The study identified the presence of DNA from porcine circovirus type 1 (PCV1) in Rotarix. This finding led to a temporary suspension of the use of the vaccine while the FDA evaluated the study and its implications. Ultimately, it was determined that the presence of the PCV1 nucleic acid sequences did not represent a health concern, and use of the vaccine was allowed to resume.³⁹⁵

In the prelicensure evaluation of new vaccines, the trend is likely to continue to conduct larger phase 3 trials enrolling tens of thousands of participants. While 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 Rotarix preclinical trial identified no increased risk of intussusception in a study that enrolled more than 60,000 infants.⁴⁹ The manufacturer nevertheless committed to conduct a large postlicensure safety monitoring study. A preliminary analysis of postlicensure monitoring data from Mexico identified a statistically significant increased risk within 30 days of vaccination with an attributable risk of approximately 1 per 100,000.³⁹⁶ The attributable risk was much less than that found for RotaShield (approximately 1 per 10,000), and 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,⁴³ the well-organized consumer activist organizations,³³⁹ Internet information of questionable accuracy,^{309,310} media eagerness for controversy,^{311,340} 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. Alerts built into electronic medical record systems 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 health care 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 post-market safety of drugs and other medical products, including vaccines.³⁹⁷

For adverse reactions that are established to be 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. A challenge for such research will be identifying sufficient numbers of people who may have rare vaccine adverse reactions and enrolling them into studies in which appropriate biological samples can be collected, stored, and analyzed under a standardized protocol.

Scientific data are essential in the monitoring and evaluation of vaccine safety, but scientific evidence alone often is not sufficient for providing reassurance about the safety of a vaccine. Although immunization levels of US 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 health care 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 health care provider. Thus, development of tools and strategies that can assist health care providers in effectively communicating with their patients on the risks and benefits of vaccines will continue to be important.

Vaccine safety has also become an important concern in developing countries.³⁹⁸ The high-titer measles vaccine mortality experience highlighted the importance of improving the quality control and evaluating the safety of vaccines used in developing countries.¹¹² Plans to eliminate neonatal tetanus and measles via national immunization days, during which millions of people receive parenteral immunizations over a period of days,³⁹⁹ pose substantial challenges to ensuring injection safety,⁴⁰⁰ 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.⁴⁰¹ The WHO has promoted the use of safer auto-disposable syringes and disposal boxes.⁴⁰² These and other new, safer administration technologies are urgently needed.⁴⁰³ In addition, 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.

Vaccines are among the most successful and cost-effective public health tools for preventing disease and death. Vaccines, however, 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. Since 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 from vaccines that are universally recommended or mandated. 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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30. Offit PA. *Deadly Choices: How the Anti-Vaccine Movement Threatens Us All*. New York, NY: Basic Books; 2011.
34. Kanesa-thasan N, Shaw A, Stoddard JJ, et al. Ensuring the optimal safety of licensed vaccines: a prospective of the vaccine research, development, and manufacturing companies. *Pediatrics* 127:S16–S22, 2011.
35. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink Project. *Pediatrics* 127:S54–S64, 2011.
36. LaRussa PS, Edwards KM, Dekker CL, et al. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment network. *Pediatrics* 127:S65–S73, 2011.
183. Offit PA, Quarles J, Gerber MA, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics* 109:124–129, 2002.
224. Offit PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 111:653–659, 2003.
282. Stratton K, Gable A, Shetty PMM. Measles-mumps-rubella vaccine and autism. In: Institute of Medicine, Immunization Safety Review Committee. Washington, DC: National Academies Press; 2001.
283. Centers for Disease Control and Prevention. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR Morb Mortal Wkly Rep* 48:563–565, 1999.
296. Offit PA. *Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure*. New York, NY: Columbia University Press; 2008.
305. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, or residuals. *Pediatrics* 112:1394–1401, 2003.