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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 74–1). As a consequence, the number of children in the United States killed by pertussis decreased from 8,000 each year in the early twentieth century to less 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 25,000 to less 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, 50,000 developed severe hepatitis 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; 40,000 developed mild polio, 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 (OPV),[21] anaphylaxis following receipt of vaccines containing egg proteins (i.e., influenza and yellow fever vaccines)[22,23] or gelatin (i.e., MMR and varicella vaccines)[24] are problems that are associated with the use of vaccines, albeit rarely. As vaccine usage increases, and the incidence of vaccine vaccine-preventable diseases is reduced, vaccine-related adverse events become more frequent and prominent (Fig. 74–1).

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 (e.g., vaccines, contraceptives) given to healthy people—especially healthy infants and toddlers—to prevent certain conditions is substantially lower than to products (e.g., antibiotics, insulin) to treat people who are sick.[25] 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 on high-dose aspirin therapy experience gastrointestinal symptoms.[26]

Safety monitoring can be carried out both before and after vaccine licensure, with slightly different goals based on the methodologic strengths and weaknesses of each step. Although the general principles are similar irrespective of each country, the specific approaches may differ because of factors such as how immunization services are organized and the level of resources available.[27]

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.[28,29] Phase I trials usually include fewer than 20 participants and can detect only extremely common adverse events. Phase II 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,[30] 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 III trials.[31,32] Sample sizes for Phase III vaccine trials are based principally on efficacy considerations, with safety inferences drawn to the extent possible based on the sample size (approximately 10^2 to 10^5) and the duration of observation (often <30 days).[31] Typically only observations of common local and systemic reactions (e.g., injection site swelling, fever, fussiness) have been feasible. The experimental design of most Phase I to III clinical trials includes 1) a control group (either a placebo or an alternative vaccine) and 2) detection of adverse events by researchers in a consistent manner 'blinded' to which vaccine

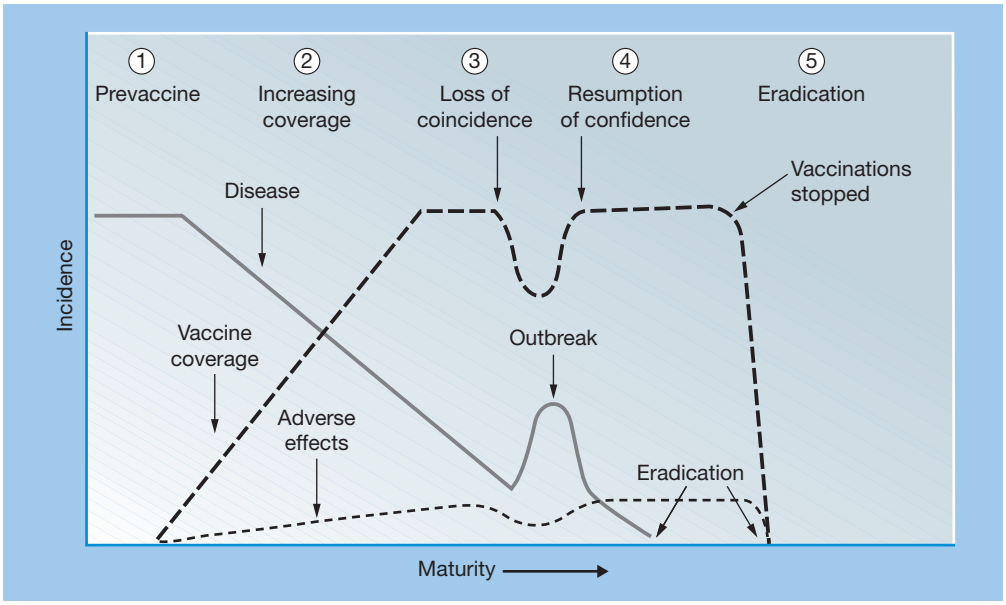

Figure 74–1 Evolution of immunization program and prominence of vaccine safety.

Table 74–1 Maximum and Current Reported Morbidity from Vaccine-Preventable Diseases Events, United States

Disease	Maximum Cases (Year)	2004	Percent Change
Smallpox	206,939 (1921)	0	–100
Diphtheria	894,134 (1941)	1	>–99.9
Measles	152,209 (1968)	37	>–99.9
Mumps	265,269 (1934)	238	–99.8
Polio (paralytic)	57,686 (1952)	0	–100
Congenital rubella syndrome	20,000† (1964–65)	14	>–99.9
H. influenzae type b	25,000†	282	–98.6

†Estimated because no national reporting existed in pre-vaccine era.

the patient received. This allows relatively straightforward inferences on the causal relationship between most adverse events and vaccination.[33]

Several ways of enhancing pre-licensure 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 both pre- and post-licensure settings.[34] 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 multi-site Phase III infant DTaP trials, definitions of high fever across trials varied by temperature (39.5°C vs. 40.5°C), measurement (oral vs. rectal), and time (measured at 48 vs. 72 hours).[35] 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.[36,37] 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 less resources (e.g., studies in less developed settings or post-licensure surveillance).

Another of the recent advances to pre-licensure 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 pre-licensure 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.[38] Thus to be able to detect an attributable risk of 1 per 10,000 vaccinees (e.g., such as the approximate risk found for intussusception in the post-licensure evaluation of RotaShield vaccine), a pre-licensure trial of at least 30,000 vaccinees and 30,000 controls is needed. Both second generation rotavirus vaccines (RotaTeq and RotaRix) were subjected to Phase III trials that included at least 60,000 infants.[39,40] 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.[41]

Nevertheless, given the need to appreciate better the safety of vaccines administered universally to healthy infants in a timely manner, there has been a call for larger studies to assess vaccine risks. This could be done either with larger pre-licensure trials, as has been done for RotaTeq and RotaRix in children, or in some organized manner post-licensure prior to scale-up to universal recommendations (e.g., rapidly and routinely performed active surveillance analysis using large-linked databases such as the Vaccine Safety DataLink).[42] Even with these measures, separate large-scale, long-term, randomized intervention trials would theoretically be the only way to study unforeseen delayed adverse effects,[42] for example, as seen with killed or high-titer measles vaccines.[43,44] Therefore, a more likely way forward probably lies in maximizing the existing pre-licensure assessment process and the post-licensure infrastructure for monitoring.

Post-licensure evaluations of vaccine safety

Because rare reactions, reactions with delayed onset, or reactions in subpopulations may not be detected before vaccines are licensed, post-licensure evaluation of vaccine safety is critical. Historically, this evaluation has relied on passive surveillance and ad hoc epidemiologic studies, but, more recently, Phase IV trials and pre-established large linked databases (LLDBs) have improved the methodologic capabilities to study rare risks of specific immunizations.[45] Such systems may detect variation in rates of adverse events by manufacturer[46,47] or specific lot.[48] More recently, clinical centers for the study of immunization safety have emerged as another useful infrastructure to advance our knowledge about safety.[49]

In contrast to the elegance of pre-licensure randomized trials, however, post-licensure observational studies of vaccine safety pose a formidable set of methodologic difficulties.[50] Confounding by contraindication is especially problematic for non-experimental designs. Specifically, individuals who do not receive vaccine (e.g., because of a chronic or transient medical contraindication or low socioeconomic group) may have a different risk for an adverse event than vaccinated individuals (e.g., background rates of seizures or sudden infant death syndrome may be higher in the unvaccinated). Therefore, direct comparisons of vaccinated and unvaccinated children is 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 event reporting system

Informal or formal passive surveillance or spontaneous reporting systems (SRSs) have been the cornerstone of most post-licensure safety monitoring systems because of their relative low cost of operations.[51–53] The national reporting of adverse events following immunizations can be done through the same reporting channels as those used for other adverse drug reactions,[53] as is the practice in France,[54] Japan,[55] New Zealand,[56] Sweden,[57] and the United Kingdom,[58] or with reporting forms or surveillance systems different from the drug safety monitoring systems, as done by Australia,[59] Canada,[60,61] Cuba,[62] Denmark,[63] India,[64] Italy,[65] Germany,[66] Mexico,[67] the Netherlands,[68] Brazil[69] and the United States.[70] Vaccine manufacturers also maintain SRSs for their products, which are usually forwarded subsequently to appropriate national regulatory authorities.[28,67]

In the United States, the National Childhood Vaccine Injury Act (NCVIA) of 1986 mandated for the first time that health care providers report certain adverse events after immunizations.[71] The Vaccine Adverse Events Reporting System (VAERS) was implemented jointly by the Centers for Disease Control and Prevention (CDC) and the 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,[70] replacing its predecessors.[72]

The VAERS form permits narrative descriptions of adverse events (Fig. 74–2). Patients and their parents—not just health care professionals—are permitted to report to the VAERS, and there is no restriction on the interval between vaccination and symptoms that can be reported. Annual reminders about VAERS are mailed to physicians likely to administer vaccines. The form is pre-addressed and postage paid so that, after completion, it can be folded and mailed. Report forms, assistance in completing the form, or answers to other questions about the VAERS are available by calling a 24-hour toll-free telephone number (1-800-822-7967). Beginning in 2002, web-based reporting and simple data analyses were also available (www.vaers.org).

A contractor, under CDC and FDA supervision, distributes, collects, codes (currently using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)[73]), and enters VAERS reports in a database. Reporters of selected serious events receive medical follow-up from trained nurses at 60 days after vaccination and one year after vaccination in order to provide additional information about the VAERS report, including the patient's recovery. Both CDC and FDA have on-line access to the VAERS database and focus their efforts on analytic tasks of interest to the respective agencies. Approximately 13,000 VAERS reports are now received annually and these data (without personal identifiers) are also available to the public.

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,[61,74] which is supplemented by an active, pediatric hospital-based surveillance system that searches all admissions for possible relationships to immunizations (Immunization Monitoring Program-Active [IMPACT]).[75] Serious VAAE reports are reviewed by an Advisory Committee on Causality Assessment consisting of a panel of experts.[76] The Netherlands also convenes an annual panel to categorize their reports, that are then published.[68] 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.[52,57] Data on adverse drug (including vaccine) events from about 40 nations are compiled by the WHO Collaborating Center for International Drug Monitoring in Uppsala.[77]

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,[69] Canada,[61] India[64] and the Netherlands.[68] However, real progress in implementation of similar standards across national boundaries is only beginning to be realized with the advent of the International Conference on Harmonization[78] and the Brighton Collaboration.[34]

VAERS often first identifies potential new vaccine safety problems because of clusters of unusual clinical features in time or space. For example, Gullian–Barré syndrome (GBS), a rare but serious neurological disease, was the only illness reported more commonly in the second and third week than in the first week after swine influenza vaccination in 1976. This unusual finding led to the initiation of special validation studies that confirmed an increased risk for GBS following influenza vaccination.[20,79] Later, in 1999, passive reports to the VAERS of intussusception among children vaccinated with RotaShield was the first post-licensure signal of a problem,[80] leading to several studies that verified these findings.[81,82] Further analysis of adverse events following RotaShield that were reported to the VAERS suggested that intussusception might have been the tip of an iceberg, and that other gastrointestinal problems (notably bloody stool, vomiting, diarrhea, abdominal pain and gastroenteritis) might also have been increased following vaccination.[83] Similarly, initial reports to the VAERS of a previously unrecognized serious yellow fever vaccine-associated neurotropic disease[84] and viscerotropic disease[85,86] have since been confirmed elsewhere.[87] 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.[88]

Several lessons are beginning to emerge from VAERS.[89–91] VAERS has successfully detected unrecognized potential reactions and obtained data to evaluate whether these events are causally linked to vaccines.[92] VAERS has also successfully served as a source of cases for further investigation of idiopathic thrombocytopenic purpura after measles–mumps–rubella

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-free information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name: _____ Last First M.I.
Address
_____ City State Zip
Telephone no. (_____)_____

Vaccine administered by (Name): _____
Responsible Physician _____
Facility Name/Address
_____ City State Zip
Telephone no. (_____)_____

Form completed by (Name): _____
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
_____ City State Zip
Telephone no. (_____)_____

1. State	2. County where administered	3. Date of birth mm / dd / yy	4. Patient age	5. Sex ☐ M ☐ F	6. Date form completed mm / dd / yy

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date ___/___/___ mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm / dd / yy
Time _____ AM PM

11. Adverse event onset mm / dd / yy
Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other /unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr. / imm. proj. report no.
25. Date received by mfr. / imm. proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS -1

Figure 74–2 The Vaccine Adverse Event Reporting System (VAERS) form.

(MMR) vaccine,[93] encephalopathy after MMR,[61,94] and syncope after immunization.[95] The VAERS has been of great value for answering routine public queries (e.g., Has adverse event X ever been reported after vaccine Y?). When denominator data on doses are available from other sources, the 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 those after diphtheria and tetanus toxoids and whole-cell pertussis (DTP).[96] Because VAERS is the only surveillance system covering the entire U.S. population with data available on a relatively timely basis, it is the major means available currently to detect possible new, unusual, or extremely rare adverse events.[89]

The reporting efficiency or sensitivity of SRSs can be estimated if expected rates of adverse events generated from carefully executed studies are available. A higher proportion of serious events, such as seizures, that follow vaccinations are likely to be reported to the VAERS than milder events, such as rash, or delayed events requiring laboratory assessment, such as thrombocytopenic purpura after MMR vaccination.[97] The estimate of VAERS reporting completeness for intussusception using capture-recapture methods was 47%.[98] Although formal evaluation has been limited, the probability that a serious event reported to the VAERS has been diagnosed accurately is likely to be high. Of 26 patients reported to VAERS who developed GBS after influenza vaccination during the 1990 to 1991 season, and whose hospital charts were reviewed by an independent panel of neurologists blinded to immunization status, the diagnosis of GBS was confirmed in 22 (85%).[99]

Despite the aforementioned uses, SRSs for drug and vaccine safety have a number of major methodologic weaknesses. Under-reporting, biased reporting, and incomplete reporting are inherent to all such systems, and potential safety concerns may be missed.[97,100,101] Aseptic meningitis associated with the Urabe mumps vaccine strain, for example, was not detected by SRSs in most countries.[102,103] Some increases in adverse events detected by the 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.[104] 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 versus private sectors, which have differential VAERS reporting rates (higher in the public sector).[105] Finally, there was probably no greater threat to the ability of VAERS to generate useful information than the recent realization that a large percentage of reports claiming that vaccines caused autism were made related to pending litigation.[106]

Perhaps the most important methodologic weakness of the VAERS, however, is that such signals do not contain the information necessary for formal epidemiologic analyses. Such analyses require calculation of the rate of the adverse events after vaccination (a/[a + b]) 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 (Table 74–2). These rates are compared with the background rate of the same adverse event in the absence of vaccination if available (c/[c + d]). Because VAERS databases provide data only for cell 'a' in Table 74–2, and, even then, only in a biased and under-reported manner, they fundamentally lack the data in the other three cells needed to calculate rates and 1) generate accurate signals of potential vaccine safety problems or 2) make a rigorous epidemiologic assessment of the role of vaccine in causation.

Table 74–2 Epidemiologic Analysis of Causality Between a Vaccine and an Adverse Event

	Adverse Event	
Vaccinated	**Yes**	**No**
Yes	a	b
No	c	d

Rate of adverse event after vaccination = a/(a + b).
Rate of adverse event in the absence of vaccination = c/(c + d).
Reports to passive surveillance systems for vaccine adverse events (e.g., Vaccine Adverse Event Reporting System) represent just partial information because of under-reporting and biased reporting for cell 'a'. Epidemiologic studies aim to gather information for all four cells in an unbiased manner.

These studies highlight the often crude nature of signals generated by VAERS, and the difficulty in ascertaining which 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 ascertaining vaccine safety.

Post-licensure clinical trials and phase IV surveillance studies

Vaccines may undergo clinical trials after licensure to assess the effects of changes in vaccine formulation,[107] vaccine strain,[108] age at vaccination,[109] number and timing of vaccine doses,[110] simultaneous administration[111] and interchangeability of vaccines from different manufacturers on vaccine safety and immunogenicity.[112] Unanticipated differential mortality among recipients of high- and regular-titered measles vaccine in developing countries[44] (albeit lower than among unvaccinated children)[113] led to a change in recommendations by the WHO for the use of such vaccines.[114]

To improve the ability to detect adverse events that are not detected during pre-licensure trials, some recently licensed vaccines in developed countries have undergone formal Phase IV surveillance studies on populations with sample sizes that have included as many as 100,000 people. These studies usually have used cohorts in health maintenance organizations (HMOs) supplemented by diary or phone interviews. These methods were first used extensively after the licensure of polysaccharide and conjugated *Haemophilus influenzae* type b vaccines.[115–117] Post-licensure studies on safety and efficacy of infant DTaP are also continuing.[36] Extensive Phase IV evaluation of varicella vaccine includes multiyear evaluation for disease incidence and for herpes zoster, and a pregnancy registry.[118,119] Requirements for Phase IV evaluation have even been extended to less frequently used vaccines, such as Japanese encephalitis vaccine.[120]

Large linked databases, including the Vaccine Safety Datalink (VSD) project

Historically, ad hoc epidemiologic studies have been employed to assess signals of potential adverse events detected by SRSs, the medical literature, or other mechanisms. Some examples of such studies include the investigations of poliomyelitis after inactivated[10,121] and oral[122] polio vaccines, sudden infant death syndrome after DTP vaccination,[123–126] encephalopathy after DTP vaccination,[127,128] meningoencephalitis after mumps vaccination,[129] injection site abscesses post-vaccination,[130] and Gullian–Barré syndrome after influenza vaccination.[20,99,104] The IOM has compiled and reviewed many of these studies.[11,131]

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 methodologic limitations of passive surveillance systems (such as described for VAERS), pharmacoepidemiologists began to turn to large databases linking computerized pharmacy prescription (and later immunization) and medical outcome records.[101] These databases derive from defined populations such as members of HMOs, single-provider health care systems, and Medicaid programs. Such databases cover enrollee populations numbering from thousands to millions, good for examining relatively infrequent adverse events, and, because the data are generated from the routine administration of the full range of medical care, under-reporting and recall bias are reduced. With denominator data on doses administered and the ready availability of appropriate comparison (i.e., unvaccinated) groups, these large databases provide an economical and rapid means of conducting post-licensure studies of safety of drugs and vaccines.[102,132–135]

The CDC participated in two pilot vaccine safety studies using large-linked databases in Medicaid and HMO populations during the late 1980s.[136,137] These projects validated this approach for vaccine safety studies and provided scientifically rigorous results but were limited by relatively small sample sizes, retrospective design, and a focus on the most severe reactions after vaccination.[11] To overcome these limitations, the CDC initiated the VSD project in 1990,[132] with the goal of gathering vaccination, medical outcome (e.g., hospital discharge, outpatient visits, emergency department visits, and deaths), and covariate (e.g., birth certificates, census) data under joint protocol at multiple HMOs. Selection of staff-model prepaid health plans also minimized potential biases for more severe outcomes resulting from data generated from fee-for-service claims. Originally, the VSD project conducted active surveillance on approximately 500,000 children from birth through 6 years of age (with a birth cohort of 75,000, approximately 2% of the U.S. population in this age group),[132] but it expanded in 1999 to include seven HMOs (covering eight different health plans), with three HMOs also contributing information on adolescents and adults and now covers about 3% of the population.[135] Proposals for studies are initiated by scientists at the CDC or at the participating HMOs, and study protocols are reviewed and critiqued using a standardized process. There is rigorous attention to the maintenance of patient confidentiality, and each study undergoes Institutional Review Board review.

The VSD project focused its initial efforts on examining potential associations between immunizations and a series of serious neurologic, allergic, hematologic, infectious, inflammatory and metabolic conditions. However, the VSD project also is being used to test new ad hoc vaccine safety concerns that may arise from the medical literature,[11,131] from VAERS,[82,105] from changes in immunization schedules,[138] or from introduction of new vaccines.[116,117] 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. Such studies are especially valuable in view of combined pediatric vaccines.[139] More than 130 studies have been or are being performed within the VSD project,[135] including general screening studies of the safety of inactivated influenza vaccines among children, and of thimerosal-containing vaccines. Disease- or syndrome-specific investigations either have been or are being performed, including ones investigating autism, multiple sclerosis, thyroid disease, acute ataxia, alopecia, rheumatoid arthritis, asthma, diabetes and idiopathic thrombocytopenic purpura following vaccination. In addition, the infrastructure created by the VSD project easily lends itself to a wide range of other vaccine-related studies beyond those for safety.[132,135]

Amid these promises, a few caveats are appropriate. Although diverse, the population in the HMOs currently in the VSD project is not wholly representative of the United States in terms of geography or socioeconomic status. More importantly, because of the high coverage attained in the HMOs for most vaccines, few non-vaccinated controls are available. The VSD project must therefore rely primarily on risk-interval analyses (e.g., to study the question of whether outcome 'x' is more common in time period 'y' following vaccination compared with other time periods) (Table 74–3).[136,140] This approach has limited ability to assess associations between vaccination and adverse events with delayed or insidious onset (e.g., autism). The VSD project also cannot easily assess mild adverse events (such as fever) that do not always come to medical attention.[132] The current VSD project is also not large enough to examine the

Table 74–3 Example of Method for Risk-Interval Analysis of Association Between a Universally Recommended Three-Dose Vaccine and an Adverse Event

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

0----------x====--------x====----------x====-----//----->|

Birth Dose 1 Dose 2 Dose 3 365 days

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

Vaccinated in Risk Interval	Adverse Event: Yes	Person-Time Observed (mo)	Incidence Rate
Yes	3	100	0.03
No	10	1,000	0.01
TOTAL	13	1,100	

Incidence rate adverse event vaccinated = 3/100 = 0.03
Incidence rate adverse event unvaccinated = 10/1,000 = 0.01
Relative rate vaccinated: unvaccinated = 0.03/0.01 = 3.0
Probability finding is 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 to other time periods.

risk of extremely rare events, such as GBS, after each season's influenza vaccine. Finally, because vaccines are not delivered in the context of randomized, controlled trials, the VSD project may not be able to successfully control for confounding and bias in each analysis,[141] and inferences on causality may be limited.[142]

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.[134,135] In view of the methodologic and logistic advantages offered by large linked databases, the United Kingdom and Canada also have developed systems linking immunization registries with medical files.[75,102] 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 (CISA) centers

More recently, there has been an increasing awareness that the utility of SRSs as potential disease registries and the immunization safety infrastructure can be usefully augmented by tertiary clinical centers. With the exception of certain regions in Italy[143] and Australia,[144,145] a similar well-organized, well-identified subspecialty infrastructure has been missing for the study of rare vaccine safety outcomes in most countries.

The United States created its Clinical Immunization Safety Assessment (CISA) network with four sites in 2001, bringing together infectious disease epidemiologists, immunologists, dermatologists, and other subspecialists as needed.[49] Among their tasks will be the standardized assessment of persons who suffered a true vaccine reaction (e.g., anaphylaxis, intussusception) to improve our scientific understanding of the pathophysiology and risk factors of the reaction. Because most persons are vaccinated without such complications, those who suffer such reactions are clearly outliers in a biologic gaussian spectrum. New understanding of the human genome, pharmacogenomics, and immunology may now make it possible for us to truly understand the reaction and to study the safest means of revaccination when indicated.[146] For patients who had an adverse event that is not contraindicating but generates enough concern to interfere with completion of the series, the CISA centers can provide assessment and management under protocols, as was done with hypotonic-hyporesponsive episodes.[144] Some of the studies undertaken by CISA and underway include an assessment of extensive limb swelling after DTaP, a study of the usefulness of irritant skin test reactions for managing hypersensitivity to vaccines, a study of the safety of vaccinating patients with DiGeorge syndrome, an assessment of patients with Guillan–Barré syndrome after conjugate meningococcal vaccination, and the clinical evaluation of patients with serious adverse events following yellow fever vaccine administration.

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 against diseases such as group B streptococcus.[147] 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 coworkers[148] published a series of 22 cases of children with mental retardation and epilepsy following receipt of the whole-cell pertussis vaccine. During the next several years, fear of the pertussis vaccine generated by media coverage of this report caused a decrease in pertussis-immunization rates in British children from 81 to 31% and resulted in more than 100,000 cases and 36 deaths from pertussis.[149] Media coverage of the Kulenkampff report also caused decreased immunization rates and increased pertussis deaths in Japan, Sweden and Wales.[149]

However, many subsequent excellent well-controlled studies found that the incidence of mental retardation and epilepsy following whole-cell pertussis vaccine was similar in children who did not receive the vaccine.[150–156]

Vaccines cause mad-cow disease

By July 2000 at least 73 people in the United Kingdom developed a progressive neurological disease termed variant Creutzfeld–Jakob disease (vCJD) 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.[157] 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 propagated in mammalian brains and not in cell culture used to make vaccines. Fourth, transmission of prions occurs from either eating brains 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 poliovirus vaccines that were administered in the Belgian Congo between 1957 and 1960 was the subject of a popular magazine article[158] and book.[159] The logic behind this assertion was as follows: 1) All poliovirus vaccines were grown in monkey kidney cells; 2) monkey kidney cells used at that time contained simian immunodeficiency virus (SIV); 3) SIV is very closely related to 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.[160–163] First, SIV is not found in monkey kidney cells. Second, monkey, not chimpanzee, kidney cells were used to grow the polio vaccines used in Africa in the late 1950s. Third, SIV and HIV are not very close genetically; mutation to HIV from SIV would likely require decades, not years. Fourth, both

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 either HIV or SIV genomes as determined by the very sensitive reverse-transcription polymerase chain reaction (RT-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 (i.e., mesothelioma, osteosarcoma and non-Hodgkins lymphoma), leading some to hypothesize a link between vaccination and the subsequent development of cancer.[164] However, genetic remnants of SV40 were present in cancers of people who either 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 those who received polio vaccine between 1955 and 1963 and those who did not receive these vaccines.[164] Taken together, these findings do not support the hypothesis that SV40 virus contained in polio vaccines administered before 1963 caused cancers.

Vaccines overwhelm the immune system

One hundred years ago, children received one vaccine—smallpox. Today children receive 14 vaccines routinely. Although some vaccines are given in combination, infants and young children could receive more than 20 shots and three oral doses 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 both parents and health care professionals on vaccine safety. Specific concerns include whether vaccines weaken, overwhelm,[165] or in some way alter the normal balance of the immune system, paving the way for chronic diseases such as diabetes, asthma, multiple sclerosis, or 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 74–4). The decrease in the number of immunogenic proteins and polysaccharides contained in vaccines is attributable to 1) discontinuation of the smallpox vaccine and 2) 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.[166] Calculations are based on the following assumptions:

1. Approximately 10 ng/mL is likely to be an effective concentration of antibody directed against a specific epitope.
2. Approximately 10^3 B cells/mL are required to generate 10 ng of antibody/mL.
3. Given a doubling time of 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.
4. 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.
5. One vaccine contains about 10 immunogenic proteins or polysaccharides (see Table 74–4).
6. Each immunogenic protein or polysaccharide contains about 10 epitopes (i.e., 10^2 epitopes per vaccine).
7. Approximately 10^7 B cells are present per milliliter of blood.

Given these assumptions, the number of vaccines to which an individual could respond would be determined by dividing the number of circulating B cells (~10^7) by the average number of epitopes per vaccine (10^2). Therefore, an individual could theoretically respond to about 10^5 vaccines at one time.

The analysis used to determine the theoretical capacity of an individual to respond to as many as 10^5 vaccines at one time, although consistent with the biology and kinetics of vaccine-

Table 74–4 Year of Introduction and Number of Immunogenic Proteins and Polysaccharides Contained in Selected Vaccines

Vaccine	Year of Introduction	Number of Proteins or Polysaccharides or Both
Smallpox*	1796	198
Rabies	1885	5
Diphtheria**	1923	1
Pertussis (whole-cell)*	1926	~3000
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	8
Meningococcus (conjugate) **	2005	5
Rotavirus**	2006	16
Human papillomavirus (HPV)**	2006	4

*Formerly in the U.S. routine child and adolescent immunization schedule.
**Currently in the U.S. routine child and adolescent immunization schedule.

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.[167] Second, in part because of differences in the capacity of various class I or class II glycoproteins (encoded by the major histocompatibility complex [MHC]) to present viral or bacterial peptides to the immune system, some individuals are not capable of responding to certain virus-specific proteins (e.g., hepatitis B surface antigen).[168] Third, some proteins are more likely to evoke an immune response than others (i.e., immunodominance). Fourth, although most circulating B cells in the 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 human immunodeficiency virus (HIV)-infected individuals found that adults have the capacity to generate about 2×10^9 new T lymphocytes each day.[169] Although the quantity of new B and T cells generated each day in healthy individuals is unknown, studies of HIV-infected persons demonstrate the enormous capacity of the immune system to generate lymphocytes when needed. For this reason, the assessment that individuals can respond to at least 10^5 vaccines at one time might be low.

Babies are too young to be vaccinated

Within hours of birth, cells of the innate and adaptive immune system are actively engaged in responding to challenges in the environment (e.g., colonizing bacterial flora).[170,171] 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).[172–174] Similarly, newborns inoculated with Bacille Calmette–Guérin (BCG) vaccine are protected against severe forms of tuberculosis presumably by activation of bacteria-specific T cells.[175–177] In addition, about 90 to 95% of infants inoculated in the first 6 months of life with multiple vaccines, including diphtheria-tetanus-pertussis, pneumococcus, *Haemophilus influenzae* type b, hepatitis B and polio, develop protective, vaccine-specific immune responses.[178] Conjugation of bacterial polysaccharides (such as *S. pneumoniae* and *H. influenzae* type b) to carrier molecules that elicit helper T cells circumvents the poor immunogenicity of unconjugated polysaccharide vaccines in infants and young children.[179,180]

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.[181,182] Down-regulation of cell-mediated immunity by wild-type measles virus probably results from down-regulation of the production of IL-12 by measles-infected macrophages and dendritic cells.[181] Taken together, the immunosuppressive effects of wild-type measles virus account, in part, for the increase in both morbidity and mortality from measles infection. Similarly, the immunosuppressive effects of infections with wild-type varicella virus[183] or wild-type influenza virus[184] 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,[185–191] measles-containing vaccines can cause a decrease in protective immune responses to varicella vaccine,[192] and high-titered measles vaccine (Edmonston–Zagreb strain) can cause an excess of cases of invasive bacterial infections in developing countries.[193] 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 appear 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.[194–197,197a]

Vaccines cause autoimmunity

Mechanisms are present at birth to prevent the development of immune responses directed against self-antigens (autoimmunity). T-cell 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 (i.e., immunoglobulins) that bind self-antigens strongly are also eliminated. Therefore, the thymus and bone marrow, by expressing antigens from many tissues of the body, enable the removal of the majority of potentially dangerous autoreactive T and B cells before they mature—a process termed central tolerance.[198]

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 individuals 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.[199,200] Mechanisms of peripheral tolerance include 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 co-stimulatory 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.[201–204]

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 below, 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, co-stimulatory 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 is not likely to occur.

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 Bacille Calmette-Guérin (BCG), smallpox, tetanus, pertussis, rubella, or mumps vaccine and diabetes.[205] A study in Canada found no increase in risk for diabetes as a result of receipt of BCG vaccine.[206] In a large 10-year follow-up study among Finnish children enrolled in a *H. influenzae* type b 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 those vaccinated at 2 years only, or with children born prior to 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.[207–209]

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 individuals that was not statistically significant.[210–212] However, the capacity of vaccines to either cause or exacerbate multiple sclerosis has been evaluated in several excellent epidemiologic studies.[213–217] Two large case-control studies showed no association between hepatitis B vaccine and multiple sclerosis[214] and found no evidence that either hepatitis B, tetanus, or influenza vaccines exacerbated symptoms of multiple sclerosis.[215] Other well-controlled studies also found that influenza vaccine did not exacerbate symptoms of multiple sclerosis.[216–218] Indeed, in a retrospective study of 180 patients with relapsing multiple sclerosis, infection with influenza virus was more likely than immunization with influenza vaccine to cause an exacerbation of symtpoms.[218]

Vaccines cause allergies and asthma

Allergic symptoms are caused by soluble factors (e.g., IgE) that mediate immediate-type hypersensitivity; production of IgE by B cells is dependent on release of cytokines such as IL-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.[219] Second, by preventing common prevalent infections (the 'hygiene hypothesis'), vaccines could prolong the length or increase the frequency of Th2-type responses.[220,221]

Although all factors that cause changes in the balance of Th1 and Th2 responses are not fully known,[222] it is clear that dendritic cells play a critical role. For example, adjuvants (e.g., aluminum hydroxide or aluminum phosphate ['alum'] contained in some vaccines) promote dendritic cells to stimulate Th2-type responses.[223,224] 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.[225] Furthermore, local inoculation of adjuvant does not cause a global shift of immune responses to Th1- or Th2-type.[226,227]

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.[220,221] However, the diseases that are prevented by vaccines constitute only a small fraction of the total number of illnesses to which the 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.[228] Also at variance with the hygiene hypothesis is the fact that children in developing countries have lower rates of allergies and asthma than those in developed countries despite the fact that these children are commonly infected with helminths and worms—organisms that induce strong Th2-type responses.[229] Finally, the incidence of diseases that are mediated by Th1-type responses, such as multiple sclerosis or 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,[230] more recent studies have suggested otherwise. A large clinical trial performed in Sweden found no increased risk,[231] 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.[232] 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,[233] and, in another study of more than 165,000 children, childhood vaccinations were not associated with an increased risk for developing asthma.[234] Finally, a study from Finland also suggested that children with 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.[235]

Another separate concern is whether inactivated influenza vaccination may induce asthma exacerbations in children with pre-existing 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.[236] In fact, after controlling for asthma severity, acute asthma exacerbations were less common after inactivated influenza vaccination than before,[237] and inactivated influenza vaccination appears to be associated with a decreased risk for asthma exacerbations throughout influenza seasons.[238]

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 plays a fundamental role.[239] 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 play a more important role than postnatal insults.[240] 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 over 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').[241] 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.[242]

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.[243] 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.[244,245] A study in the United States within 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.[246] Soon after publication of the Lancet paper that ignited the controversy,[241] two ecologic analyses found no evidence that MMR vaccination was the cause of apparent increased trends in autism over time,[247,248] while two other studies found no evidence of a new variant form of autism associated with bowel disorders secondary to vaccination.[249,250] Several more recent studies have also refuted the notion that MMR vaccine caused autism.[251–256]

Because of the level of concern surrounding this issue, the CDC and the National Institutes of Health requested an independent review by the IOM.[257] 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 biologic 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 six months of age could receive as much as 187.5 ug of ethylmercury (thimerosal) from vaccines: a level that exceeded recommended safety guidelines for methylmercury from the Environmental Protection Agency, but not those recommended by the Food and Drug Administration or the Agency for Toxic Substance Disease Registry.[258] Consequently, the routine neonatal dose of hepatitis B vaccine in infants born to hepatitis B surface antigen (HBsAg)-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.[259] Currently, only the multi-dose influenza vaccine contains preservative quantities (i.e., 25 μg per dose) of thimerosal.

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.

Evidence that thimerosal does not cause autism

Several pieces of biological and epidemiological evidence support the notion that thimerosal does not cause autism. First, in 1971 Iraq imported grain that had been fumigated with methylmercury.[260] 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 babies with epilepsy and mental retardation. However, there was no evidence that these babies had an increased incidence of autism. Second, five large studies have now compared the risk of autism in children who received vaccines containing thimerosal to those who received vaccines without thimerosal or vaccines with lesser quantities of thimerosal; the incidence of autism was similar in all groups.[261–264a,264b] The Institute of Medicine 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.[264c] 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.[265] Fourth, methylmercury is found in low levels in water, infant formula and breast milk.[266] 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 breast-fed for six months will ingest more than twice the quantity of mercury that was ever contained in vaccines and fifteen 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.[267] 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.

Vaccine risk communication

Disease prevention, especially if it requires continuous near-universal compliance, is a formidable task. In the pre-immunization era, vaccine-preventable diseases such as measles and pertussis were so prevalent that the risks and benefits of disease versus vaccination were readily evident. As immunization programs successfully reduced the incidence of vaccine-preventable diseases, however, an increasing proportion of 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.[268,269] Similarly, the media may sensationalize vaccine safety issues or, in an effort to present 'both sides' of an argument, fail to provide perspective.[270,271] 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.[272] 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,[273] has only recently been formally applied to immunizations.[274] 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.[275] In contrast, research has shown that laypersons may have subjective, multidimensional, and value-laden conceptualizations of risk.[276] Among the key principles and lessons learned about public perceptions of risk are the following:

1. Individuals differ in their perceptions of risk depending on their personality, education, life experience, and personal values;[277,278] educational materials tiered for different needs are therefore likely to be more effective than a single tier.
2. Perceptions of risk may differ dramatically among various stakeholders, such as members of government agencies, industry, or activist groups.[279] The level of trust between stakeholders has an impact on all other aspects of risk communication.[280] Trust is generally reinforced by open communication regarding 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.[281]
3. Certain hazard characteristics, including involuntariness, uncertainty, lack of control, high level of dread, and low level of equity, lead to higher perceived risk[276]; only risks with similar characteristics should be compared in risk communication efforts.[282]
4. For quantitatively equivalent risk that is due to action (e.g., vaccination reaction) versus inaction (e.g., vaccine-preventable disease caused by non-vaccination), many people prefer the consequences of inaction to action.[283]
5. 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.[272]
6. Finally, different ways of presenting, or framing, the same risk information (e.g., using survival rates versus mortality rates) can lead to different risk perceptions, decisions, and behaviors.[284,285]

Risk communication can be used for the purposes of advocacy, public education, or decision-making partnership.[273] 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.[286] In medical decision making, this has resulted in a transition from more paternalistic models to increasing degrees of informed consent.[287] Some have argued that a similar transition to informed consent also should occur with immunizations.[288] However, immunization is unlike most other medical procedures (e.g., surgery) in that the consequences of the decision affect not only the individual, but also others in the society. Because of this important distinction, many countries have enacted public-health (e.g., immunization) laws that severely limit an individual's right to infect others. Without such mandates, individuals may attempt to avoid the risks of vaccination while being protected by the herd immunity resulting from others being vaccinated.[289] Unfortunately, the protection provided by herd immunity may disappear if too many people avoid vaccination, resulting in outbreaks of vaccine-preventable diseases.[290,291] 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.[288,292,293] Thus vaccine risk communications not only should describe the risks and benefits of vaccines for individuals, but also should include discussion of the impact of individual immunization decisions on the larger community.

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.[41] 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.[130,294] Advice and review from a panel of independent experts also may be needed.[99,295,296] Causality assessment at the individual level is difficult at best; further evaluation via epidemiologic or laboratory studies may be required.[297] Even if the investigation is inconclusive, such studies can often help to maintain public trust in immunization programs.[298]

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.[299] Such groups have been increasingly successful in airing their views in both electronic and print media, frequently with poignant individual stories.[268,269] Because the media frequently raise controversies without resolution and choose 'balance' over perspective, one challenge is to establish credibility and trust with the audience.[300,301] 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.[302] 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 (e.g., whether such rare vaccine reactions exist at all) should be acknowledged, but what is certain also should be noted (e.g., 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 to 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.[303] The National Childhood Vaccine Injury Act (NCVIA) 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 either the adult vaccinee or, in the case of a minor, to the parent or legal representative each time a dose of vaccine is administered.[304] 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 over 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 74–5). Some studies have been conducted to assess the use and effectiveness of such materials;[305–309] 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 regarding 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.

Table 74–5 Websites 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.cispimmunize.org
Schools, Hospitals and Expert Groups	
The Albert B. Sabin Vaccine Organization	www.sabin.org
Allied Vaccine Group	www.vaccine.org
Every Child by Two	www.ecbt.org
Immunization Action Coalition	www.immunize.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
Vaccine Information for the Public (provided by Immunization Action Coalition)	www.vaccineinformation.org
The Vaccine Page	www.vaccines.org
Parent and Family Organizations	
Families Fighting Flu	www.familiesfightingflu.org
The National Meningitis Association	www.nmaus.org
Parents of Kids with Infectious Diseases	www.pkids.org

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 as well as 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.[310,311] Moreover, increasingly parents want to be fully informed about their children's medical care,[312] 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 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 healthcare providers for educating patients and parents.[313] Nonetheless, it is important for us to try to meet the challenge because an understanding of the above 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.[312] 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.[314] 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 2006.

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.[315] 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 percent of parents who reported they did not have access to enough information about vaccines also had several specific vaccine concerns compared to parents who were neutral or agreed they had access to enough information.[315] 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 wellbeing of patients. For example, information is one factor that has been shown to positively influence a sense of control in patients with rheumatoid arthritis[316] and perceived lack of information among mothers was one reason contributing to non-immunization of children in India.[317]

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.[318] 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 healthcare providers in busy office settings to address questions from these two groups of parents. Presentation of these tailored brochures by children's healthcare providers to parents in an empathetic and respectful manner could aid in improving the healthcare provider-parent relationship, increasing vaccine acceptance, and ultimately preventing vaccine-preventable diseases (Table 74–6).

Table 74–6 Physician Guidance for Discussions With Parents About Childhood Immunizations

What can physicians do in this new era of immunizations to keep parental confidence in vaccines high?
1. Be respectful—solicit questions 'What questions do you have about childhood immunizations?'
2. Be empathetic if parents have concerns— 'I understand your concern' 'I know your child is the most important thing in the world to you' 'Immunizations can be confusing'
3. Educate the parent before the day of the child's immunization. 'Here is a brochure describing the immunization process that may be helpful. If you have questions please let me know at your next visit.'
4. Give information tailored to the parent's concerns if possible.
5. Be informed about current vaccine allegations and misinformation so that you can address them with confidence. 'Oh yes, I heard about the 60 Minutes segment on vaccines and autism. But you know, the Institute of Medicine, an independent and highly respected organization, reviewed the evidence and concluded that based on the current evidence, the MMR vaccine does not cause autism.'
6. Strongly recommend vaccines. 'I believe in immunizations, my children are immunized (or nieces or nephews).'

Timing of information

VISs are typically given to parents the day the child is scheduled for their immunization.[319-321] This often places the parent in a conflict situation of either 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.[320–323]

Suggested earlier times for vaccine education include prenatal clinic visits and just after delivery in a hospital.[324] A national survey indicated that 80% of providers said that a pre-immunization booklet for parents would be useful for communicating risks and benefits to parents.[319]

Contrary information

The use of complementary and alternative medicine (CAM) has been increasing over the past 50 years in the US.[325] Part of this increase is due to managed-care organizations providing coverage for some CAM therapies.[326] Chiropractic care is among the top 10 most commonly used CAM therapies.[327] It is of note that some chiropractic colleges teach a negative view of immunizations.[328] In one study, one-third of chiropractors agreed that there is no scientific proof that immunizations prevent disease.[328] The basis for the negative views of vaccine effectiveness may lie in 1) the chiropractic doctrine that disease is the result of spinal nerve dysfunction caused by subluxation coupled with 2) the rejection of the germ theory of disease.[328,329] 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.[330] This emphasizes the importance of a trusting doctor-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.[331] In another study, 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, compared to parents of vaccinated children. These parents were less likely to believe that medical and public health professionals are good or excellent sources of immunization information.[332] The majority of parents (84%), however, report receiving immunization information from a doctor.[165] Thus having a doctor 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 doctor 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 a vaccine, it often raises the question 'Was this vaccine necessary?' To the parent, it may appear 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 due to an apparent adverse event following immunizations (6.9%) not only expressed more concern about immunizations, but 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.[333] Two scenarios were seen as plausible. It may be that parents who were already concerned about vaccines before their child began their vaccination schedule were more reactive and thus sought medical attention for minor side effects (e.g., fever) or non-related problems. It is also possible that an apparent adverse event following immunization that resulted in a parent seeking medical attention for their child caused the parent's perception of vaccines to become more negative. Both possibilities may result in the parent declining future vaccines for their children.

Negative attitudes could be addressed by improving communication between clinician and parent (Table 74–7). Benefit-cost analysis research has shown that physician advice can produce benefits for health issues (e.g., problem drinking).[334] Moreover, positive communication behaviors such as humor and soliciting questions are associated with a lowered physician's risk of a malpractice suit.[335] 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 non-serious adverse events following immunization) and an improved physician-patient relationship (more trust and fewer malpractice suits).

Risk perception

Individuals can vary in their perception of the magnitude of vaccine risks. Studies have shown that various factors such as gender, race, political worldviews, emotional affect and trust are associated with risk perception.[336] 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.[337] All of which 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.[337]

It can be difficult to communicate the risk of many vaccine-preventable diseases given their low prevalence in the U.S., and difficult to communicate the risks of serious vaccine adverse events because they affect such a small proportion of vaccine recipients.[338,339] 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[340] and thus, comparisons for 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, include risk ladders,[341] stick figures, line graphs, dots, pie charts, and histograms.[342] 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 people[343] and, as discussed above, is developed through listening and ongoing communications.[344]

Table 74–7 Physician Guidance for Parents Who Believe Their Child Experienced an Adverse Event Because of an Immunization

What should physicians do if a parent says their child had an adverse event because of an immunization?
Physicians should pay special attention to parents who believe their child has experienced an adverse event because of an immunization. There are several factors that increase parents' concern in this situation: their child is affected, vaccines are often not voluntary, and the process is not well understood by parents.[1] In addition, parents feel that their child was harmed by someone in whom they have placed their trust, and they sometimes must be treated by the same physician who gave the immunization.[2] This can cause a feeling of conflict, wanting the child to be helped but not trusting the physician because he/she was involved with administering the immunization. In discussing medical adverse events in general, Vincent suggests clinicians should follow some basic principles in order to reduce the trauma to patients harmed by treatment.[2] These suggestions apply equally to parents whose child experienced an adverse event following immunization. First, clinicians should *respect the opinion* of parents who say their child experienced an adverse event. Second, if the adverse event has no basis, the clinician should give the parent *a complete and sympathetic explanation* of why the immunization could not have caused such an effect. In many instances the presence or absence of a causal connection between an adverse event and vaccination is not readily apparent. In such cases clinicians should be honest with patients regarding this uncertainty. Finally, clinicians should be open about the apparent adverse event and *discuss what measures could be taken* to prevent or treat a similar event in the future. Health care providers should report all suspected adverse events following immunization to the Vaccine Adverse Events Reporting System (VAERS) (www.vaers.org), even if a causal relationship to vaccination is uncertain. 1. Covello VT, Peters RG, Wojtecki JG, Hyde RC. Risk communication, the West Nile virus epidemic, and bioterrorism: responding to the communication challenges posed by the intentional or unintentional release of a pathogen in an urban setting. J Urban Health, 78, 382-391, 2001. 2. Vincent C. Understanding and responding to adverse events. N Engl J Med 348, 1051-1056, 2003.

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. Individuals 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.[345] The main factors associated with biomedical literacy are 1) level of formal education, 2) number of college level science courses and 3) age. Some characteristics of scientific literacy include the ability to 1) distinguish experts from the uninformed, 2) recognize gaps, risks, limits and probabilities in making decisions involving a knowledge of science or technology, 3) recognize when a cause and effect relationship cannot be drawn, 4) distinguish 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.[346]

There is a wide gap in the level of biomedical understanding across the U.S. population and this 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.[345]

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 child? We should care because it is not only ethically the right thing to do, it is practically the right thing to do. Vaccine acceptability refers to the factors that go into a parent's decision to have their child immunized. It is important not to assume that just because most parents are having their child immunized that they will continue to do so.[347] While the host of factors contributing to the parent's decision to have their child immunized (e.g., 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 the parent perceives the risks of vaccines to be greater than the risk of disease. This would then push the parent above a theoretical 'unacceptability threshold' where they would choose not to have their child immunized for 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 state philosophical immunization exemption laws or schooling their children at home.[348] 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 the clinician, 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.[349] Providers can make a huge impact on vaccine acceptance by following these suggestions and those listed in Tables 74–6 and 74–7. Following some or all of these suggestions has the potential to improve the quality of the physician-parent relationship, thus resulting in a cascading effect where providing information can increase trust and increasing trust can lead to greater acceptance of and confidence in vaccines. For healthcare providers to be able to optimally fill this important role however, two related issues should be addressed. The first is the need for quality communication courses and training in medical schools and residencies, and training programs for both medical and public health professionals.[350,351] The second is for managed-care organizations and medical insurance companies to adequately reimburse physicians for health education. Lack of reimbursement to physicians has been noted as a barrier to implementation of behavioral treatments for health issues such as heart disease[313] and smoking.[352] It is important to note that studies have shown education programs can be a cost savings to healthcare systems.[353,354] 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 challenges

Many people look to vaccines as the 'magic bullet' solution to a number of public health problems that range from acquired immunodeficiency syndrome to malaria. Rapid advances in biotechnology have brought the promise of these new vaccines closer to reality.[355] Novel delivery technologies, such as DNA vaccines and new adjuvants, are being explored to permit more antigens to be combined, reducing the number of injections.[139,356] These changes in vaccines and vaccine delivery, however, will continue to provide additional challenges in proving their safety to an increasingly skeptical and risk-averse public.[357] Combined with methodologic difficulties associated with studying rare, delayed, or insidious vaccine safety allegations,[33] well-organized consumer activist organizations,[299] Internet information of questionable accuracy,[268,269] media eagerness for controversy,[270,300] and relatively rare individual encounters with vaccine-preventable diseases virtually ensure that vaccine safety concerns are unlikely to go away in mature immunization programs.

Concomitantly, vaccine safety concerns have also emerged as an issue in developing countries.[358] 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.[44,108] Plans to eliminate neonatal tetanus and measles via national immunization days, during which millions of people receive parenteral immunizations over a period of days,[359] pose substantial challenges to ensuring injection safety,[360] 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.[361] The WHO has relatively successfully argued that safer auto-disposable syringes and disposal boxes should be 'bundled' with vaccine donations.[362] These and other new safer administration technologies are urgently needed.[363]

The increasing computerization and centralization of health care services may facilitate epidemiologic studies to reassure the public about the safety of future vaccines.[101,132] Similar to other arenas concerned with safety (e.g., aviation,[364] food[365] and blood[366]), a comprehensive systems design approach to minimize risk and promote vaccine safety is needed.[367] New initiatives to reduce medical errors and improve patient safety are drawing lessons from non-medical systems where an evolution from traditional 'linear' thinking about errors to analyses of multiple causation at the 'systems' level has been effective in developing a culture of safety.[368]

Developments in biotechnology will continue to offer better, safer vaccines.[355,356] The availability of computerized immunization registries[369] will likely permit optimal implementation of immunization policies at the individual level, ensuring receipt of indicated vaccines, avoiding extra vaccination, and appropriate observance of valid contraindications to vaccinations. Vaccine safety research combined with genetic epidemiology may permit better characterization of risk groups for vaccine reactions.[370] Monitoring for strains that have evolved as a consequence of selective pressure from immunizations may be needed.[371] Integrated with immunization registries for both children and adults, this ultimately may offer the possibility for better prevention of both vaccine-preventable[372] and vaccine-induced diseases.

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