CHAPTER 26
Pharmacoepidemiologic Studies of Vaccine Safety

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Introduction

Vaccines are among the most cost effective and prevalent public health interventions.[1,2] Where immunization is widely practiced, rates of targeted vaccine-preventable disease (VPD) have declined considerably.[3,4] However, no vaccine is perfectly safe or effective.[5] With high rates of vaccinations and a low incidence of VPD, adverse events following immunizations (AEFIs) are understandably of concern, and have received increasing attention.[6–10] Unfortunately, this concern has often negatively affected the stability of immunization programs.[11]

For example, questions about the safety of pertussis vaccine in Japan and elsewhere during the 1970s reduced the coverage rate for this vaccine, resulting in resurgence of pertussis.[12] Similar concerns in the United States led to lawsuits, substantial vaccine price increases, loss of vaccine manufacturers,[13] and were a potential deterrent to the development of new vaccines.[14] More recently, concerns about the safety of mercury-based thimerosal preservative used in vaccines[15,16] and the safety of anthrax[17] and smallpox vaccines[18,19] have affected the stability of US civilian and military immunization programs, respectively. In the United Kingdom, a case series report of autism following MMR vaccination in a small number of patients (n = 12; subsequently retracted) precipitated widespread vaccine safety concerns, leading to reduced MMR vaccination rates and subsequent measles outbreaks.[20,21] Similarly, vaccine safety concerns have affected public acceptance of hepatitis B vaccine in France,[22] oral polio vaccine (OPV) in Nigeria,[23,24] and 2009 H1N1 vaccine in several countries.[25,26]

In the early 1990s, a review by the Institute of Medicine (IOM) in the United States[27,28] noted that vaccine safety knowledge and research capacity had been limited by several factors: (i) inadequate understanding of biologic mechanisms underlying adverse events; (ii) insufficient or inconsistent information from case reports and case series; (iii) inadequate size or length of follow-up of many population-based epidemiologic studies; (iv) limitations of existing surveillance systems in providing persuasive evidence of causation; and (v) few experimental studies published relative to the total number of epidemiologic studies published. IOM concluded that, "if research capacity and accomplishments [are] not improved, future reviews of vaccine safety [will be] similarly handicapped."

Pharmacoepidemiology has played a vital role in providing the scientific methods for assessing vaccine safety in the United States,[29] Europe,[30] and globally.[11,31–33] Many research and knowledge gaps continue to be identified in each IOM review of specific immunization safety controversies since

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2001, ranging from autism to unexpected infant deaths.[17,34–40a] In this chapter, we discuss the major differences in how epidemiology is applied to vaccines and other pharmaceutical products, giving consideration to both policy and methodology.

Clinical problems to be addressed using pharmacoepidemiologic research

Policy issues

Vaccines share many characteristics with other pharmaceuticals, such as their phased development and licensure, but differ fundamentally in many ways. Understanding these differences is important to appreciate the policy context of vaccine safety and the role of pharmacoepidemiology. Vaccines, for example, are biological products that are inherently more complex than most small-molecule drugs in terms of both constituent components and the production process.[41,42] Each component of the vaccine formulation—the immunogen, conjugated protein,[43] preservative,[15] adjuvant,[44,45] stabilizer,[46–49] diluent,[50] and other excipients—has its respective safety considerations (e.g., sourcing, production, quality assurance, safety profile), individually as well as combined.[51] Programmatic errors such as mixing up vaccine vials and administration errors such as unsafe injections can also be a concern, especially in low-income countries.[50,52]

A higher standard of safety is also expected of vaccines. In contrast to pharmaceuticals, most of which are administered to people who are ill, for curative or therapeutic purposes, vaccines are generally given to healthy people to prevent disease. Tolerance of adverse reactions to products given to healthy people—especially healthy babies—is substantially lower than to products administered to people who are already sick. This lower risk tolerance for vaccines translates into a need to investigate the possible causes of much rarer adverse events following vaccinations than would be acceptable for other pharmaceuticals. Events that occur at approximately 1/100 000 to 1/1 000 000 doses, such as acute encephalopathy after whole-cell pertussis vaccine,[27,53] Guillain–Barré syndrome (GBS) after swine[54] or 2009 H1N1[55] influenza vaccines, and oral polio vaccine-associated paralytic polio (VAPP),[56] are of concern for vaccines. In contrast, side effects are essentially universal for cancer chemotherapy, and gastrointestinal side effects are very common (10–30%) among people on high-dose aspirin therapy.[57]

The cost and the difficulty of studying events increase with their rarity, however (see Chapter 3). Furthermore, the ability to provide definitive conclusions from epidemiologic studies of rare events is poor. Attributable risks in the order of 1/10 000–1/100 000 are on the margin of resolution for epidemiologic methods.[27,58] This challenge was illustrated during the whole-cell pertussis vaccine safety concern in the late 1970s.[12] All British children 2 to 35 months of age hospitalized for several neurological illnesses over 3 years (n = 1167) were enrolled in a very large case–control study.[59] The finding of a significant association between vaccine and permanent brain damage was based on only seven exposed cases.[53] Whether or not this study finding was valid, it generated much controversy in and out of the courts.[27,60] Interestingly, a recent study suggests a possible *de novo* genetic mutation predisposing risk factor for the cases.[61]

Despite considerably more robust data linking GBS with the swine influenza vaccine,[54] subsequent controversy[62,63] resulted in a court-ordered independent re-examination of the data[64] and ultimately to a partial repetition of the study, confirming the initial findings.[65] Robust results from two studies on rhesus rotavirus vaccine and intussusception[66,67] have also been challenged.[68,69]

Perhaps not surprisingly, but adding to the confusion, much of the published literature on vaccine safety historically has been in the form of case reports and case series (e.g., a subsequently retracted *Lancet* article alleging links between measles vaccination and autism[20]) rather than controlled studies with adequate statistical power.[27,28] This problem has been ameliorated recently with the advent of carefully controlled, large, linked database studies in the United States, United Kingdom, and Denmark.[33,70]

A higher standard of safety is also required for vaccines because of the large number of people

who are exposed, some of whom are compelled to do so by law or regulation for public health reasons.[71] Such requirements have been implemented by public health authorities because many VPD (e.g., measles) are highly contagious. When a high proportion of the population is immunized, it creates "herd immunity" so that some of the remaining unimmunized people will still be protected.[72] Without such mandates, a "tragedy of the commons" may occur where high vaccine coverage is reached and the individual risk–benefit ratio diverges from the societal risk–benefit ratio.[73,74] Persons may try to avoid the risks of vaccination while being protected by the herd immunity resulting from others being vaccinated. However, this "commons" provided by herd immunity may disappear if too many people avoid vaccination, with the resulting tragedy that outbreaks return,[75,76] as was experienced in the United Kingdom with pertussis[12] and measles.[21] A similar policy consideration occurs for some mandatory military vaccinations such as anthrax[17] and smallpox,[18] where a higher vaccine reaction rate may be accepted in exchange for battlefield readiness.

Because of the need for almost universal exposure to many vaccines, the medical maxim "first do no harm" applies even more in public health than in clinical medicine (where decisions usually affect fewer people). Inadequately inactivated polio vaccine was administered to about 400 000 people in the "Cutter Incident", resulting in 260 polio cases.[77,78] The following incidents have fortuitously not resulted in any documented harm to date. Nevertheless, they highlight the importance of ensuring the safety of a relatively universal human-directed "exposure" such as immunizations: (i) polio vaccine contaminated by simian virus 40 may have been received by millions of people during the 1950s;[79] (ii) some vaccines may have contained gelatin stabilizers produced in cattle infected with bovine spongiform encephalopathy;[80] (iii) some US children were exposed to high levels of ethyl mercury from thimerosal preservatives in vaccines;[15] and (iv) two of the new rotavirus vaccines were contaminated by a porcine circo virus.[81] These concerns are the basis for strict regulatory control and other oversight of vaccines by National regulatory authorities such as the Food and Drug Administration (FDA), European Medicines Agency (EMA),[41] and the World Health Organization (WHO).[82] Modern technology will continue to improve the ability to detect contaminants in vaccines and influence regulatory decisions during manufacturing; postlicensure monitoring will continue to be important should such findings raise safety concerns.[81]

Very high standards of accuracy and timeliness are needed because vaccine safety studies have extremely narrow margins for error. Unlike many classes of drugs for which other effective therapy may be substituted, vaccines generally have few alternative strains or types (oral and inactivated poliovirus vaccines being the best known exception). The decision to withdraw a vaccine[62] or switch between strains may also have wide ramifications.[56,83] In 1992, the United Kingdom withdrew the license of mumps vaccines containing the Urabe strain after studies suggested a high rate of vaccine-associated meningitis.[84] The manufacturers subsequently withdrew this product worldwide, leaving countries without an alternative vaccine if the Urabe strain was the sole mumps vaccine licensed.[85,86] Safety concerns led to the withdrawal in the early 2000s of what were then the only licensed vaccines against rotavirus[68] and Lyme disease,[87] rendering these vaccines unavailable anywhere. Establishing associations of adverse events with vaccines and timely measurement of the attributable risk are critical in placing adverse events in the proper risk–benefit perspective. An erroneous association or attributable risk, especially with misinformed media or websites,[88,89] can undermine confidence in a vaccine and have disastrous consequences for vaccine acceptance and disease incidence.[21] On the other hand, denials of association despite accumulating evidence can erode public confidence and compromise vaccination programs. For example, public dismay with delayed action on Urabe mumps vaccine-associated aseptic meningitis in Japan forced the Ministry of Health to rescind compulsory school MMR vaccination requirements in 1993.[90,91]

Because many vaccinations are mandated for public health reasons and no vaccine is perfectly

safe, several countries have established compensation programs for people who may have been injured by vaccination.[92] Accurate assessment of whether adverse events can be caused by specific vaccines is essential to a fair and efficient vaccine injury compensation program.[93] In the United States, for example, the Vaccine Injury Table contains the vaccines, adverse events, and intervals after which no-fault decisions are made in favor of the claimants.[92] Periodic revisions of the Vaccine Injury Table are necessary to reflect the best scientific information on associations between vaccines and adverse events, especially following introduction of new vaccines.[94]

Finally, recommendations for use of vaccines represent a dynamic balancing of risks and benefits. Vaccine safety monitoring is necessary to weigh this balance accurately. In the face of a meningococcal B epidemic in New Zealand, it was prudent to fast track the licensure of a new vaccine with limited prelicensure safety data but assurances of good postmarketing surveillance.[95] When the target diseases are close to eradication, high vaccine complication rates relative to that of the target wild disease may lead to discontinuation or decreased use of the vaccine, as was done with smallpox vaccine.[96] Another example was oral polio vaccines, where there was a shift to either inactivated polio vaccine (IPV)[83,97] or sequential IPV/oral polio vaccine (OPV),[56] in order to control OPV-associated paralytic polio and circulation of OPV-derived polio virus.[98] There may be a tradeoff between safety and cost, however. Some countries continue to use Urabe mumps vaccine, despite its higher risk for aseptic meningitis, after the manufacturer lowered the price.[99]

With the renewed fears of bioterrorism, stopping immunizations and allowing formation of lacunae in herd immunity no longer seems advisable.[32,100] Almost all immunizations will therefore be needed indefinitely, with their attendant adverse reactions and potential for loss of public confidence. Because of the success of immunizations in the near elimination of their target diseases, most health-care providers (let alone parents) have not ever seen a case of the wild VPD. Each future generation must therefore be convinced of the need to be immunized despite an increasingly ancient experience of wild disease but contemporary fear of vaccine adverse events.

Research in vaccine safety—while applying pharmacoepidemiologic principles—can help to distinguish true vaccine reactions from coincidental events,[33,101,102] estimate their attributable risk,[53,54,67,103–107] identify risk factors that may permit development of valid contraindications,[53,108] and, if the pathophysiologic mechanism becomes known, develop safer vaccines.[109,110] Equally importantly, such research demonstrates a commitment to reducing disease from all causes, vaccine-preventable and vaccine-induced, and may help to maintain public confidence in immunizations and the credibility of immunization programs.

Clinical issues

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in phased human clinical trials before licensure[111] (see Chapter 1). Phase I trials usually number their subjects in the tens and can only detect extremely common adverse events. Phase II trials generally enroll hundreds of subjects. When they are carefully coordinated, important conclusions such as the relationship between concentration of antigen, number of vaccine components, formulation technique, effect of successive doses, and profile of common reactions can be drawn from such trials.[112] Such studies can also affect the choice of the candidate vaccine for Phase III.[113]

Sample sizes for Phase III vaccine trials generally range between 5000 and 10 000 people, which is larger than most drug trials. In extremis, more than 600 000 schoolchildren were enrolled in the famous Francis field trial of inactivated Salk poliovirus vaccine.[114] To help rule out links with a rarer outcome such as intussusceptions (background rate ~ 5 per 1000 infant years), the second generation rotavirus vaccine trials enrolled approximately 70 000 infants.[115,116] Traditionally, however, sample sizes for Phase III vaccine trials have been based primarily on efficacy considerations; inferences on safety are drawn to the extent possible based on the sample size (~100–100 000) and the duration

of observation (often <30 days).[113] This usually means that observations of the common local and systemic reactions (e.g., injection site swelling, fever, fussiness) have been possible. Because of the experimental randomized, double-blind, placebo-controlled design of clinical trials, inferences on the causal relationship of an adverse event with the vaccine are relatively straightforward.[27,28] Brazilian investigators also used such a design to compare the risk of aseptic meningitis among three mumps vaccine strains.[117]

Better standardization of safety evaluations in prelicensure clinical trials is needed so that safety data across trials and vaccines can be compared (see also Classifications and Case Definitions, below). In the Phase III trials for infant DTaP, a standard case definition was developed for efficacy, but ironically not for safety—the main reason for the development of DTaP.[118] For example, definitions of high fever across trials varied by the temperature (39.5° versus 40.5°C), the mode of measurement (oral versus rectal), and time after vaccination measured (48 versus 72 hours).[119] However, for rarer events, it may be difficult to have standardized assessments across cultures and health systems, as illustrated in the Swedish and Italian trials in which major differences were detected in rates of hypotonic–hyporesponsive episodes after the same whole-cell pertussis vaccine.[120]

The finding of delayed excess mortality in some recipients of high-titer measles vaccine in developing countries,[121] now believed by some to be due to a change in vaccine sequence[122] or non-specific effects of vaccinations,[123] has also led to a call for increasing the current limited duration of follow-up for AEFI in most trials.[124,125] Furthermore, many of the new vaccines under development (e.g., malaria, tuberculosis) or recently licensed (e.g., rotavirus) are targeted for initial introduction in resource-limited settings. Both pre- and postlicensure safety studies will therefore need to be done in settings where the pharmacovigilance infrastructure is limited or non-existent.[126,127]

Ideally, pharmacogenomics (see Chapter 34) and biobanking can be integrated into prelicensure trials (continuing through to postlicensure) to begin improving our understanding of the biologic/genetic basis for why some persons under-respond and others over-respond to an immunization with respect to immunogenicity and reactogenicity. Historically, the strategy to deal with vaccine recipients with insufficient immune response was straightforward, consisting of a multidose schedule. Those with overly vigorous reactions on the other hand were more problematic; and were at risk of being unfairly labeled as "antivaccine" if they questioned the safety of receipt of subsequent doses.

Despite over 200 years since Jenner first pioneered the smallpox vaccine, the medical science of diagnosing, managing, preventing, or treating rare, serious vaccine reactions remain relatively rudimentary. The reasons are multifold and the challenges are as much logistical as scientific. Modern medicine cannot make progress on rare disorders such as leukemia (or rare serious vaccine reactions) by relying on primary care providers alone. Instead, tertiary subspecialties with adequate referral base and research funds (e.g., hematology/oncology) are needed. With the exception of certain regions in Italy,[128] Australia,[129,130] and six civilian Clinical Immunization Safety Assessment (CISA) sites[130a] and four military Vaccine Research Centers (VHC) in the United States,[131] a similar well-organized, well-identified subspecialty infrastructure has been missing for the study of rare vaccine reactions in most countries. Such centers can also potentially play a role for studying newly hypothesized vaccine adverse event syndromes.[20,132] The diversity of vaccine exposures (active/ passive, live/ killed, single/ combined, etc.), combined with the range of adverse event outcomes (in essence the entire medical textbook, including some not yet defined), means that the new subspecialty will need to play a "case manager" role of drawing upon other subspecialty expertise as needed. But most importantly, such CISA-type centers could potentially prevent outliers (for example, based on genetic susceptibility) in reactogenicity response from becoming antivaccine activists by recruiting them into "win–win" opportunity to improve our scientific understanding and hopefully eventual prevention of vaccine reactions, as done recently in a clinical trial of safer booster dose

in children with extensive limb swelling after pertussis vaccination.[133]

Methodologic problems to be addressed using pharmacoepidemiologic research

Signal detection

Because biologics such as vaccines are generally manufactured in living systems rather than through chemical synthesis as for drugs, variation in rate of adverse reactions by manufacturer or even lot might be expected.[134–136] Surveillance systems need to detect such potential aberrations in the expected number and type of adverse events in a timely manner. Some factors make identification of true signals difficult. Many vaccines are administered early in life, at a time when the baseline risk is constantly changing and may be affected by other infant events. Furthermore, by definition, if vaccination rates are high, most people with adverse medical events will have had a history of vaccination. Distinguishing causal from coincidental events on a case-by-case basis is rarely possible (see Chapter 33), particularly for events where the pathophysiologic mechanisms are not known, regardless of vaccination. Since many vaccinations are administered to individuals either simultaneously or as a combination vaccine, unless the number of people who also receive that exact permutation of vaccine exposures (including manufacturer and lot number) is known so adverse event rates can be calculated, it may be difficult or impossible to know if an aberration has occurred.[137] Similarly, when vaccine coverage rates are high and multiple vaccinations are administered concurrently, it can be difficult to disentangle the individual effects of each component, since simultaneous vaccination patterns are likely to be uniform across the population.

Unlike most public health surveillance systems, which focus on either a single exposure (e.g., lead) or single disease outcome (e.g., measles), vaccine safety surveillance systems need to examine multiple exposures (e.g., different vaccine antigens, manufacturers, lot numbers) and multiple disease outcomes. Until the recent advent of data mining methods (see Chapter 46), detection of a vaccine safety signal occurred as much due to a persistent patient[138] as due to data analysis.[139] The trade-off between sensitivity and specificity depends critically on whether the goal of the surveillance is the detection of a previously unknown illness or syndrome (sensitivity > specificity) or tracking a known disease (specificity > sensitivity). Vaccine safety surveillance systems are asked to monitor *both* previously known and previously unknown adverse events in the same system, however.[140] Nevertheless, the goal of early detection of an aberrant cluster of new adverse events remains identical to other pharmacovigilance and public health surveillance systems.

Standard definitions and evaluative protocols

Case definitions can be used at the time of reporting or at the time of analysis to improve specificity. Applying definitions at the time of reporting may reduce the number of reports processed and lower the operating cost.[141] The sensitivity of surveillance may be lower and the difficulty of assessing misclassification greater, however. Alternatively, if the reporting form is open-ended,[142] this may increase the sensitivity of surveillance but only at the cost of sorting through many non-specific reports. Definitions can then be applied at the time of analysis. But substantial variation in diagnostic workup and description of events makes *post hoc* classification difficult without additional follow-up information, which in turn is usually costly.

Historically, it was difficult if not impossible to compare and collate vaccine safety data across clinical trials or surveillance systems in a valid manner because of lack of standard case definitions. We can advance our scientific knowledge of immunization safety by using a common vocabulary, particularly helpful in the prelicensure setting where maximizing the yield of safety data may help with limited sample sizes. The Brighton Collaboration (see Classifications and Case Definitions, below) is addressing this gap.[143]

Assessment of causality

Aside from events such as local reaction or anaphylaxis, assessing whether any adverse event was actually caused by vaccine is generally not possible unless a vaccine-specific clinical syndrome (e.g., myopericarditis in healthy young adult recipients of smallpox vaccine[19]), or repeat exposures resulting in the same adverse event (e.g., alopecia and hepatitis B vaccination[138]), or a vaccine-specific laboratory finding (e.g., Urabe mumps vaccine virus isolation[144]) can be identified. Whenever the adverse event can also occur in the absence of vaccination (e.g., seizure), a very large clinical trial or more affordable epidemiologic studies are necessary to assess whether vaccinated people are at higher risk than unvaccinated people. As noted earlier, when multiple vaccinations are administered simultaneously, determining whether events are attributable to particular components or one of several combinations is frequently difficult or impossible.

Exposure

Misclassification of exposure status may occur if there is poor documentation of vaccinations. Unlike children of school age where vaccination documentation is often required, ascertaining vaccination status in older people may be particularly difficult. In the United States, recent and likely future increases in the number of licensed vaccines, the relative lack of combination vaccines, plus historically, the high mobility among immunization providers (up to 25% annually) because of changes in health insurance plans, have led to a potential confusing maze of vaccination history misclassifications.[137,145]

For example, even though only the acellular pertussis vaccine is available in the United States, adverse event reports of the old whole-cell pertussis "DTP" vaccine continue to be received—presumably due to errors in recording by immunization providers due to old habits. An infant may have started their immunization series with one provider who uses DTaP combination vaccine from manufacturer A, but switched to another provider to complete the series with DTaP combination vaccine from manufacturer B. Add in the complexity of whether other vaccines such as polio or hepatitis B vaccines are administered simultaneously, at different dose series in the schedule, at different ages, using different lots of vaccine, and the number of permutations of vaccine exposures that need assessment for potential safety concerns quickly becomes formidable.[146] The near-unique availability of complete documentation of vaccine exposure on a large cohort of children in the Vaccine Safety Datalink (VSD) project allowed the evaluation of the safety of thimerosal preservatives.[147,148]

Outcome

Because of the higher standard required for vaccine safety (as discussed previously), events being assessed are frequently extremely rare (e.g., encephalopathy, GBS), and identifying enough cases for a meaningful interpretation of study findings can be a major challenge. Even when technically feasible, a study may be logistically infeasible or the findings likely to be too inconclusive to justify the resources. This was the conclusion of a 1989 Institute of Medicine committee that evaluated whether the United Kingdom's National Childhood Encephalopathy Study should be replicated in the United States.[58]

The difficulty in achieving adequate statistical power is further compounded in assessing rare events in populations less frequently exposed (e.g., early use soon after introduction on the market, vaccines given to travelers or subpopulations with special indications). This challenge is well illustrated in studies of the potential association between GBS, which occurs at a background rate of about one per 100 000 person years, and various vaccines. Study of GBS after newly introduced meningococcal conjugate vaccine (MCV) required assembling data from 9 million adolescents.[149] A retrospective study of GBS after the 1992–1994 influenza vaccinations required assessing hospital records of over 20 million people for 2 years.[150] Recently, active GBS case finding among a population of 45 million may have detected an attributable risk of one additional case of GBS per million H1N1 vaccinations.[55]

Whenever both the rarity of the adverse outcome and the number of exposures limits the ability to assess a small potential increased risk, identifying risk factors of such rare associations imposes an additional (and possibly prohibitive) level of sample size requirements—unless multinational collaborations are organized.[49]

Many adverse events hypothesized to be caused by vaccines have poorly defined etiologies (e.g., encephalopathy,[151] GBS,[54] chronic fatigue syndrome,[152] narcolepsy,[152a] sudden infant death syndrome [SIDS][153]) and attributing the outcome to vaccination can only be done after all other potential etiologies have been ruled out, and even then causality cannot be certain. Our scientific understanding of some diseases is frequently limited in the absence of vaccination, let alone with vaccination. This poor understanding severely limits clinical and epidemiologic studies of these illnesses. Furthermore, in highly vaccinated populations, risk-interval analyses (where a specific risk/exposure period is assigned) may be the only epidemiologic study design possible (see Study designs, analyses, confounding, and bias, below). Predicting the onset of illness is critical in calculating the risk interval. For certain hypothesized vaccine adverse events, there is no known biological mechanism to allow prediction of the risk interval. Diseases with insidious or delayed onset like autism,[20] inflammatory bowel disease,[154] and multiple sclerosis[155] do not permit prediction of the risk interval and are therefore also difficult to study.

Study designs, analyses, confounding, and bias

Analyzing observational studies of vaccine safety poses several methodologic challenges. Traditional epidemiologic study designs, such as the cohort and case–control designs, are limited because a large percentage of the population tends to be vaccinated. This implies that few unvaccinated individuals are available for analysis, and the unvaccinated tend to differ from the vaccinated by several potential confounding variables, including ethnicity, socioeconomic status, and underlying health disorders.[121]

Another challenge is that serious vaccine adverse events are rare. Cohort studies typically require hundreds of thousands or even millions of study subjects to be able to detect an association between vaccination and the suspected adverse event.[156–159] Such studies can be prohibitively expensive, unless all requisite information is automated and linkable.

A possible alternative to the cohort design is the case–control study design, in which cases are sampled from the source population and compared to a group of randomly selected event-free controls. This design is well-suited for rare events, and has been used for several studies of vaccine safety.[66,106,160–162] It is, however, particularly difficult to choose an appropriate control group without introducing selection bias if the study is not population based. Moreover, because childhood vaccines are generally administered on an age schedule and many childhood illnesses that may be potential AEFIs are age-dependent, age may confound exposure–outcome relations (e.g., diphtheria–tetanus–pertussis [DTP] vaccine and febrile seizures or SIDS[163]). Consequently, such factors must be controlled, generally by matching and subsequent adjustment in the statistical analysis.

To address these limitations, various self-controlled study designs have been developed and implemented.[106,164–172] These designs involve cohorts of vaccinated individuals (risk-interval) or analyses where vaccinated cases are compared to themselves (self-controlled case-series). Such designs have been shown to be efficient and valid alternatives to the traditional epidemiologic study designs.[173,174] For details on these methods see Methodologic Approaches section below.

More difficult to control are factors leading to delayed vaccination or non-vaccination.[121] Such factors (e.g., low socioeconomic status, preceding illness) may confound studies of vaccine adverse events and lead to under-estimates of the true relative risks. The extent of bias introduced by confounding can be examined as a function of six variables (Table 26.1). Relatively little is known about the nature, frequency, and implications of these variables, however.[121]

Table 26.1 Variables determining the extent of bias attributable to confounding in studies of vaccine adverse events (AE)[122]

Variable	Description
S	Risk of AE in unvaccinated children who lack the contraindication*
R	True relative risk of AE associated with vaccination
D	Relative risk of AE associated with the contraindication
C	Proportion of children with the contraindication
V	Proportion vaccinated among children without the contraindication
P	Proportion vaccinated among children with the contraindication

* "Contraindication" used here to mean any factor associated with avoidance or delay of vaccination.

Currently available solutions

Prelicensure

Whenever potentially important safety signals are detected in prelicensure trials (e.g., intussusceptions after rotavirus vaccine),[175] it is critical that they are pursued postlicensure.[176] Given the need for improved understanding of the safety of vaccines administered universally to healthy babies and the methodologic difficulties of assessing safety postlicensure, some have argued that larger experimental trials may be needed to better assess rare but serious vaccine risks.[74,177] This could be done either with larger prelicensure trials, as has been done with antipyretics in children[177–179] and the postrhesus rotavirus vaccine trials,[116] or in some organized step-wise manner postlicensure (e.g., registry of the first million vaccinations), prior to universal recommendation of the vaccine for entire birth cohorts.[178] Even with these measures, separate large-scale, long-term randomized intervention trials would theoretically be the only way to study unforeseen delayed vaccine adverse effects[74] or non-specific effects of immunizations[123] such as those seen with killed[180] or high-titer measles vaccines.[181,182] Such trials would have to overcome major concerns about the ethics of withholding efficacious vaccines from people in need. Therefore, a more likely way forward probably lies in maximizing both the pre-and postlicensure assessment processes as discussed in this Chapter.

In addition to standardized case definitions for adverse outcomes, Data and Safety Monitoring Boards (DSMBs) represent an area of potential improvements in the prelicensure process. Currently, such DSMBs are constituted uniquely for each clinical trial. If instead there is greater overlap across prelicensure trials for the same vaccine, the DSMB may have better ability to oversee the safety data for the experimental vaccine. The Council of International Medical Organizations (CIOMS) has also proposed an internationally harmonized Development Safety Update Report (DSUR) for summarizing the safety experience for a clinical trial (or entire development program). When aligned with the postapproval Periodic Safety Update Report (PSUR) for marketed products, these could be integrated into a single harmonized safety report that would cover a product throughout its lifecycle.[183]

Furthermore, despite its name, there is currently no requirement for the DSMB to include someone with drug/ vaccine safety experience. For vaccine trials, someone with rare disease (versus infectious disease) epidemiology skills, usually fine-tuned from postlicensure safety monitoring experience, should be considered for the DSMB.

Another area of potential improvement is the method used to determine the likelihood of a causal relationship of an adverse event with the experimental exposure (e.g., new vaccine; see Chapter 33). Traditionally, the principal investigator of a clinical trial makes an assessment of the causal relationship; this procedure is difficult to standardize and prone to bias.[184] In an era of increasing automation of medical records and sophistication of methods for detecting non-random clusters or elevated rates, similar approaches to assessing prelicensure safety data are needed. Finally, there is a need to improve clinical trial infrastructure in resource-limited settings for

assessing the safety and efficacy of various preventive and therapeutic products for poverty-related diseases.[126,127,185]

Postlicensure

Passive surveillance or spontaneous reporting systems (SRS)

Informal or formal passive surveillance or spontaneous reporting systems (SRS) have been the cornerstone of most vaccine safety monitoring systems because of their simplicity and relatively low cost.[186] The national reporting of vaccine adverse events can be done through the same reporting channels as those used for other adverse drug reactions,[187] as is the practice in most European countries,[188,189] Japan,[190] and New Zealand.[191] Historically, however, few countries have forwarded their AEFI reports to the Uppsala Monitoring Center[192] (see also Chapter 10). An increasing number of countries are collecting safety data specific to vaccinations either with reporting forms and/or surveillance systems different from the drug safety monitoring systems. These countries include Australia,[193] Brazil,[194] Canada,[195] Cuba,[196] Denmark,[197] India,[198] Italy,[199] Germany,[200] Mexico,[186] Netherlands,[201] New Zealand,[202] Switzerland,[203] and the United States.[142] Vaccine manufacturers also maintain SRS for their products,[204] which are usually forwarded subsequently to appropriate national regulatory authorities.[41]

Because of their importance in infectious disease control, a significant proportion of vaccines in many countries is purchased or administered by national public health authorities. For example, in the United States, the public sector (federal, state, and local governments) purchases over half of the childhood vaccines administered. In many developing countries, the Ministry of Health in conjunction with the WHO's Expanded Program for Immunizations (EPI) administers almost all vaccines. Potential vaccine adverse events commonly are first reported by the health-care providers who administered the vaccine. In many countries, such health-care providers also participate in public health surveillance for other diseases. Public health authorities (e.g., Centers for Disease Control, CDC) therefore commonly lead or collaborate with the vaccine licensure and regulatory agency (e.g., the US FDA) in developing AEFI reporting systems. A similar model for harmonization and avoiding duplication is followed in Canada[205] and six European countries,[189] and is highly recommended for other countries.[206]

The US experience

The US National Childhood Vaccine Injury Act of 1986 mandated for the first time that health-care providers report certain adverse events after immunizations (Table 26.2).[207] The Vaccine Adverse Event Reporting System (VAERS) was implemented jointly by the CDC and 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.[142] To increase sensitivity, the VAERS form is designed to permit narrative descriptions of adverse events. All people, including patients or their parents and not just health-care professionals, are permitted to report to VAERS, especially clinically significant events. As of 2010, 15% of US VAERS reports come directly from consumers. There are no restrictions set on the interval between vaccination and onset of illness or requirements that a patient must have medical care in order for the event to be reported. Web-based reporting became available in 2002; experience to date shows it to be more complete and timely[208] and it was therefore heavily used during the 2003 US smallpox[209] and 2009 H1N1 vaccination campaigns.[210] Future potential enhancements include: (i) integration of VAERS reporting modules with computerized immunization registries that can transfer vaccine exposure and patient identifier information automatically, resulting in more accurate, complete, efficient, and timely transmission of VAERS reports;[211] and (ii) reporting of denominators from the registry to allow calculation of VAERS reporting rates.[212] The latter is especially important to overcome the problem of interpreting VAERS data in the face of increasing heterogeneity of vaccine exposures in the United States.

Enhancements to VAERS passive surveillance since its inception have included capability for near real-time report review by CDC and FDA medical officers, collaborations with professional medical associations, development of a user-friendly public use data query tool, and web-based reporting, in

Table 26.2 Table of reportable events following vaccination, United States*

Vaccine/toxoid	Event	Interval from vaccination
Tetanus in any combination; DTaP, DTP, DTP-HiB, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaPHepB-IPV	A. Anaphylaxis or anaphylactic shock B. Brachial neuritis C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 28 days Not applicable See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, Tdap, P, DTaP-IPV, DTaP-IPV/Hib, DTaPHepB-IPV	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 7 days Not applicable See package insert
Measles, mumps, and rubella in any combination; MMR, MR, M, MMRV, R	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 15 days Not applicable See package insert
Rubella in any combination; MMR, MMRV, MR, R	A. Chronic arthritis B. Any sequela (including death) of above events C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	42 days Not applicable See package insert
Measles in any combination; MMR, MMRV, MR, M	A. Thrombocytopenic purpura B. Vaccine-strain measles viral infection in an immunodeficient recipient C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	30 days 6 months Not applicable See package insert
Oral polio (OPV)	A. Paralytic polio B. Vaccine-strain polio viral infection C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	30 days†/6 months‡ 30 days†/6 months‡ Not applicable See package insert
Inactivated polio (IPV) in any combination; DTaP-IPV, DTaP-IPV/HIB, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hepatitis B in any combination; with HepB, HepAHepB, DTaP-HepB-IPV, Hib-HepB	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hemophilus influenza type b in any combination; (conjugate)-Hib, Hib-HepB, DTP-Hib, DTaPIPV/Hib	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

(*Continued*)

Table 26.2 (*Continued*)

Vaccine/toxoid	Event	Interval from vaccination
Varicella in any combination; VAR, MMRV	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rotavirus (monovalent or pentavalent) RV1, RV5	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pneumococcal conjugate (7-valent or 13-valent) PCV7, PCV13	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis A in any combination; HepA, HepA-HepB	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Influenza – trivalent inactivated influenza, live attenuated influenza – TIV, LAIV	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Meningococcal - MCV4, MPSV4	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Human papillomavirus (Quadrivalent or Bivalent) - HPV4, HPV2	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

* Effective November 10, 2008. The Reportable Events Table (RET) reflects what is reportable by law (42 USC 300aa-25) to the Vaccine Adverse Event Reporting System (VAERS) including conditions found in the manufacturers package insert. In addition, individuals are encouraged to report *any* clinically significant or unexpected events (even if you are not certain the vaccine cause the event) for *any* vaccine, whether or not it is listed on the RET. Manufacturers are also required by regulation (21CFR 600.80) to report to the VAERS program all adverse events made known to them for any vaccine. A list of vaccine abbreviations is located at: http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm

† In a non-immunodeficient recipient.

‡ In an immunodeficient recipient.

addition to more frequent review and dissemination of safety data. "Enhanced passive" surveillance via VAERS has been successfully used to date in safety surveillance for rotavirus,[213] yellow fever,[214] smallpox vaccines,[215] and 2009 H1N1 vaccine,[210] and would likely be implemented in any counter-bioterrorism-related, wide-scale vaccination program.[216]

Among the approximately 27,000 US VAERS reports now received annually, about 9% are classified as serious (reported as resulting in death, life-threatening illness, disability, or hospitalization).[217] A contractor, under CDC and FDA supervision, collects, codes (using the Medical Dictionary for Regulatory Activities, MedDRA),[218] and enters VAERS reports in a database. Trained nurses follow up with the person who reported an event classified as serious to obtain additional medical information and recovery status. CDC and FDA have access to the VAERS database and focus their efforts on analytical tasks of interest to the respective agencies. A database of initial VAERS reports (without personal identifiers) and a user-friendly data query tool are available to the public at www.vaers.hhs.gov.

Other national experiences

Several other countries also have substantial experience with passive surveillance for vaccine safety.

What is now the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) was first developed in 1987.[195] Reporting forms have check-off boxes for specific events with accompanying case definitions. Provision is also made for an "other" category. To supplement the passive system, an active, pediatric hospital-based surveillance system that searches all admissions for possible relationships to immunizations, known as Immunization Monitoring Program–Active (IMPACT), has been operational since 1990.[219,220] An Advisory Committee on Causality Assessment, consisting of a panel of experts, has also been formed to review the serious passive reports.[221] The Netherlands also convenes a panel of experts annually to categorize their reports, which are then published.[222] The United Kingdom and most members of the Commonwealth use the "yellow card" system, where a reporting form is attached to officially issued prescription pads.[223] Data on adverse drug (including vaccine) events from many nations are compiled by the WHO Collaborating Center for International Drug Monitoring in Uppsala (www.who-umc.org) which has also begun a vaccine focus.[192,224]

A field guide for implementation of monitoring of AEFI has been developed by WHO.[225] The primary focus is on detection of correctable programmatic errors such as injection site abscesses (suggestive of inadequate sterilization), and development of a rapid response/ assessment team for clusters of more serious events (e.g., toxic shock syndrome from contamination of vaccine vials[198] or deaths from confusing other medications for vaccines[226]). As more new vaccines are first introduced in low and middle-income countries, there is increasing awareness of the need to improve currently inadequate pharmacovigilance systems in these countries.[11] The decades long delay in discovering serious AEFIs after yellow fever vaccination,[227] and BCG vaccination in human immunodeficiency virus-infected infants[228] further highlight this urgent need.

Classifications and case definitions

Vaccine adverse events can be classified by frequency (common, rare), extent (local, systemic), severity (hospitalization, disability, death), causality (probable, possible, unlikely, etc.),[203] and preventability (intrinsic to vaccine, faulty production, faulty administration). Wilson developed the first classification system with focus on errors of production (e.g., bacterial, viral, toxin contamination) and administration (e.g., non-sterile apparatus).[5] A more recent classification[229,230] divides adverse events after vaccinations into: (i) *vaccine-induced*: due to the intrinsic characteristic of the vaccine preparation and the individual response of the vaccinee, these events would not have occurred without vaccination (e.g., vaccine-associated paralytic poliomyelitis); (ii) *vaccine-potentiated*: may have occurred anyway, but were precipitated by the vaccination (e.g., first febrile seizure in a predisposed child); (iii) *programmatic error*: due to technical errors in vaccine preparation, handling, or administration; or (iv) *coincidental*: associated temporally with vaccination by chance or due to underlying illness. The distinction between vaccine-induced and vaccine-potentiated, as first clarified for DTP and DT vaccine and infantile spasm,[231] has been useful because vaccine-potentiation does not result in excess vaccine-attributable risk over time, whereas vaccine-induced does (Figure 26.1).

The Dutch system further classifies a report based on whether single or multiple vaccines were received and single or multiple adverse events were reported.[232] Case definitions of certain vaccine adverse events were first developed in Brazil,[233] Canada,[234] India,[198] and the Netherlands.[232] When case definitions were added to the Canadian form as guidance for what should be reported, the proportion of reports meeting the case definition criteria increased from 69 to 87%.[141] Alternatively, in a more open reporting system such as VAERS, these definitions can be applied to reports to develop a case series for further investigation.[235,236] Real progress in implementation of similar standards across national boundaries are being realized with the advent of the International Conference on Harmonization (ICH)[237] and the Brighton Collaboration.[143]

The Brighton Collaboration was established in 2000 and is an international voluntary effort to facilitate the development, evaluation, and

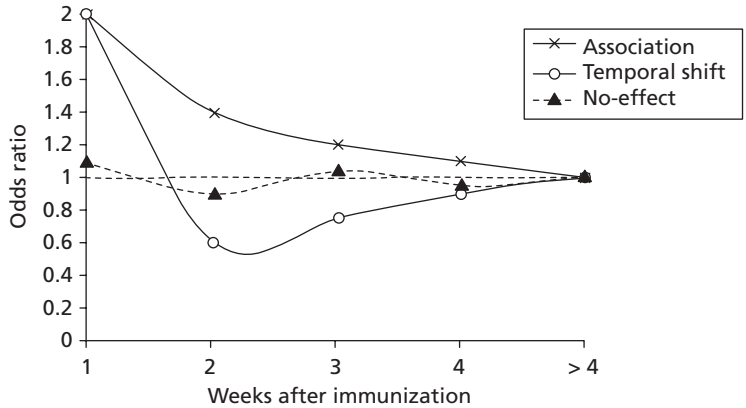

Figure 26.1 Three theoretical models of the temporal relationship between immunization and an adverse effect: (1) Association: the risk exceeds 1 at all time windows postimmunization; (2) temporal shift: the risk exceeds 1 initially but then falls below 1 but coming back to 1 eventually, such that the area under the curve above and below 1 is similar; and (3) no effect: the risk stays around 1.[231]

dissemination of standardized case definitions of Adverse Events Following Immunizations.[143] Global workgroups of experts are convened to develop case definitions that are then reviewed by relevant experts. The Brighton case definitions for each adverse event are arrayed by the level of evidence presented (insufficient, low, intermediate, and highest); therefore they can also be used in settings with a range of resources (e.g., from prelicensure trials to postlicensure surveillance, or from developing to developed country settings). Over 30 Brighton case definitions are now available for use at www.brightoncollaboration.org.

Standardized clinical assessment protocols and centers

There has been an increasing awareness that the utility of a spontaneous reporting system (SRS) as a potential disease registry and the immunization safety infrastructure can be usefully augmented by tertiary clinical centers. The United States initiated its military Vaccine Healthcare Centers (VHC; www.vhcinfo.org) and civilian Clinical Immunization Safety Assessment (CISA) Network in 2001; these bring together infectious disease epidemiologists, immunologists, dermatologists, and other subspecialists from multiple participating sites as needed for various tasks.[32] Among these tasks is the standardized assessment of people who suffered an apparently true vaccine reaction (e.g., hypersensitivity),[48,238] to improve our scientific understanding of the pathophysiology and risk factors of the reaction. New understanding of the human genome, pharmacogenomics, and immunology may now make it possible for us to truly understand these reactions (see also Chapter 34).[129,239] For example, studies of myopericarditis following smallpox vaccination in the VHC suggested increased risk in people with HLA type UD,[19] and a person with a case of yellow fever vaccine-associated viscerotropic disease showed polymorphisms in *CCR5* and *RANTES* genes.[240]

Through these centers, standardized assessment protocols can be developed to examine patients with similar adverse events to see if they constitute a rare or a previously unrecognized clinical syndrome. If so, a case definition can be developed that permits identification of cases for follow-up validation studies examining the potential role of vaccination in causing this syndrome. The diagnosis of a specific epilepsy syndrome was made in 14 cases with alleged pertussis vaccine encephalopathy; genetic mutations of the sodium channel gene were identified in 11 of 14 patients.[61]

For patients who have had adverse events that generate concern but do not contraindicate com-

pletion of a vaccine series, such as hypotonic–hyporesponsive episodes[129] and extensive limb swelling after acellular pertussis vaccination,[133,241] the standardized clinical assessment centers, such as CISA, can provide assessment and management of subsequent vaccinations under protocols.

Finally, standardized clinical assessment centers can provide regional referral and advice services—with the opportunity to follow-up and document compliance with advice provided and outcome so that this rare experience can be added to our scientific knowledge. Ultimately, many AEFI diagnostic or management protocols can be made available on the Internet for other clinicians to use (and to provide a mechanism for them to contribute their experience).[242] Both development and application of standardized case definitions and standardized evaluation of clinical syndromes play a "hypothesis strengthening" role, intermediate between hypothesis generation and hypothesis testing.

Assessment of causality

The formal process of assessing causality in the association of an adverse event and an exposure (e.g., vaccine) is complex and can be considered in terms of the answers to three questions: (i) *Can It?*; (ii) *Did It?*; and (iii) *Will It?*.[243] The answer to *Can It?* was the focus of the Institute of Medicine reviews.[27,28,40a] It is usually based on population-level inferences drawn from epidemiologic studies and the following considerations: (i) strength of association, (ii) analytic bias, (iii) biologic gradient/ dose–response, (iv) statistical significance, (v) consistency, and (vi) biologic plausibility/ coherence.[244]

For individual case reports, the *Did It?* question is more relevant. If the answer is yes, then *Can It?* is also answered in the affirmative. It is natural to suspect a vaccine to be the cause when an adverse event occurs in temporal association following vaccination. To base causal inference purely on temporal association, however, is to fall for the logical fallacy of *post hoc ergo propter hoc* ("after this, therefore because of this").[28] Information useful for assessing causality in individual case reports include: (i) previous general experience with vaccine (e.g., duration of licensure, number of vaccinees, whether similar events have been observed among other vaccinees or non-vaccinees, existence of animal models to test vaccine as a cause); (ii) alternative etiologies; (iii) biologic plausibility; (iv) individual characteristics of the vaccinee that may increase the risk of the adverse event; (v) timing of events; (vi) characteristics of the event (e.g., laboratory findings); and (vii) rechallenge[245,246] (see also Chapter 33).

When a vaccine *can* cause an adverse event, the *Will It?* refers to the probability that an individual will experience the event, or for populations, the proportion that will experience the event as a result of vaccination (i.e., the attributable risk fraction). These data are critical for developing valid contraindications for the individuals and risk–benefit policy decisions for the population. The *Will It?* is usually very difficult to answer, however, as it can only be answered based on epidemiologic studies.[28] Furthermore, the sample sizes of such studies may be large enough to establish whether vaccine can cause a given event but yet inadequate to stratify by subgroups to examine risk factors that can help delineate potential contraindications.

Specific adverse events may be considered to be caused by a specific vaccine if the event is associated with (i) a unique laboratory finding, and/or (ii) a very specific clinical outcome. For example, Urabe mumps vaccine virus was implicated as a cause of aseptic meningitis because mumps virus was isolated from the cerebrospinal fluid (a normally sterile body site) and was shown to be vaccine and not wild strain by genetic sequencing.[144] The detection of IgG antibodies to the stabilizers in vaccine in children with hypersensitivity reactions confirms the etiology.[46,49] Demonstrations that severe local swelling following tetanus toxoid tended to occur in people with extremely high levels of circulating antitoxin (due to excessive tetanus boosters) support the proposed mechanism of an Arthus reaction.[247] Acute flaccid paralysis, especially shortly after receipt (or contact with a recipient) of oral polio vaccine, is almost pathognomonic of vaccine-associated paralytic polio in countries where wild polio virus is unlikely to be

circulating.[56,248] Similarly, acute myopericarditis in otherwise healthy recent smallpox vaccinees also supports a causal relationship.[18,19] Causality can sometimes be inferred if a specific and uncommon clinical finding occurs after each vaccination (i.e., challenge–rechallenge), as in cases of alopecia after hepatitis B vaccination.[138] But unlike drug safety, dechallenge (disappearance of the adverse event by stopping the medication) is usually not feasible with immunizations.

If the adverse event is known to be associated with the wild VPD (e.g., acute arthritis and idiopathic thrombocytopenic purpura (ITP) after rubella), its association with the live, attenuated vaccine at a lesser frequency is not surprising.[27] This relationship is not universal, however, as pregnant women who receive live attenuated rubella vaccine, unlike those exposed to wild rubella, have not been shown to have illness compatible with congenital rubella syndrome.[249] Clustering of events in time after vaccination can also suggest causation if "reporting bias" can be ruled out. Such bias may occur as parents and doctors are most likely to link adverse events with vaccinations the shorter the time interval between the two and the more serious the event. Febrile seizures associated with killed bacterial vaccines tend to occur within a day of vaccination, while those due to live viral vaccines are delayed by about a week due to viral replication.[103,250] Onset of GBS after the swine influenza vaccination was delayed up to 6 weeks, but clustered at 2 to 3 weeks following vaccination, as autoimmune demyelination is a slower process.[54] The pattern of the risk by time since vaccination may suggest that the relationship to vaccination is more one of temporal shift or triggering of an underlying susceptibility (Figure 26.1).[231,251]

Unfortunately, most serious reported vaccine adverse events lack these unique features that permit easy inferences on causality. Adverse events such as autism, chronic fatigue syndrome, SIDS, and GBS either have multiple or as yet unknown etiologies. In a highly vaccinated population, it is not surprising that most cases of any adverse event have a history of prior vaccinations. Epidemiologic studies have to be relied upon to ascertain likelihood of association and if related, the attributable fraction.

Because of these challenges, some vaccine injury compensation programs simplify their administrative proceedings by making a blanket assumption that all adverse events occurring within particular periods after vaccination are "caused" by the vaccine, irrespective of whether they were truly causal or just coincidental. This, unfortunately, may lead some individuals to imply inaccurately that all such compensated cases are caused by vaccinations.[92] Despite these caveats, the timing of the onset interval after vaccination plays a major role in most causality assessment algorithms, as AEFIs after live viral vaccines usually occur later than those of killed vaccines. The WHO classifies a clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals as *Very Likely/ Certain* to be caused by vaccination; a clinical event with a reasonable time relationship to vaccine administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals as *Probable*; and that which could also be explained by concurrent disease or other drugs or chemicals as *Possible*.[203,252]

In some countries, expert committees of specialists in relevant disciplines (e.g., pediatrics, infectious disease, neurology) review reports. This "global introspection" approach[253] has been used in both Canada[221] and the Netherlands[222] to classify reports of adverse events in gradations of probable association to vaccination (see also Chapter 33). The CISA network used a standardized protocol for individual case reviews of reported H1N1 vaccine adverse events,[222a] building on the lessons of the Canadian Advisory Committee on Causality Assessment (ACCA). Classifications are based on the reported symptoms, the interval between vaccination and onset of symptoms, and a set of case definitions. Because opinions of experts play such a major role in this form of causality assessment, the results are less satisfying than results obtained from rigorously conducted scientific studies. After a review of available approaches, the European Vaccine Adverse Event, Surveillance and Communication (VAESCO) project (www.vaesco.net) recently concluded: "the usefulness of individual causality assessment of AEFI remains to be demonstrated. Well documented cases and proper case definitions may be more important than causality

assessment especially for signal detection and evaluation."

Signal detection

Identifying a potential new vaccine safety problem ("signal") requires a mix of clinical intuition, epidemiologic expertise, the application of statistical data mining tools, and, frequently, a large increase in vaccine exposure.[254] As indicated above, unusual clinical features and/or clustering in time or space usually suggest that something may be awry. No illness other than GBS was reported more commonly in the second and third week than in the first week after swine influenza vaccination, leading to further validation studies.[54,255,256] Traditionally, a signal occurs when an observed number of events exceeds the number of events expected by chance alone for the specific data source. In general, an acceptable false positive rate is set at 5%, with 80% statistical power to detect a signal. Once a signal has been detected, additional methods such as a temporal scan statistic can be used to detect nonrandom clustering of onset intervals.[257,258]

Several recent examples in the United States and elsewhere highlight the importance of rapidly identifying and responding to serious AEFIs identified following new vaccines or newly reintroduced vaccines. After a prelicensure signal,[259] passive reports to VAERS of intussusception among children vaccinated with rhesus rotavirus vaccine were the first postlicensure signal of a problem,[213] leading to several studies to verify these findings.[66,67] Similarly, initial reports to VAERS of a previously unrecognized serious yellow fever vaccine-associated viscerotropic disease,[260,261] and neurotropic disease[214] have since been confirmed elsewhere[227] and as early as 1973, based upon retrospective review.[262] Acute myopericarditis has been a relatively unexpected finding among people vaccinated against smallpox in the United States for bioterrorism preparedness.[19,215] Oculorespiratory syndrome was found among influenza vaccines from one Canadian manufacturer in one season.[132] Bell's palsy was detected in recipients of a new Swiss intranasal influenza vaccine.[106] While several GBS cases were reported to VAERS after introduction of MCV4 in adolescents in the United States,[263] subsequent large controlled studies found no association.[264] Most recently, febrile seizures in young children were observed more than expected in passive reporting in Australia following administration of one formulation of trivalent inactivated influenza vaccine (TIV).[265] A febrile seizure signal was also identified in VAERS after receipt of a different US TIV; after evaluation in the VSD project, the signal was verified and it found that simultaneous administration of another vaccine with TIV contributed to the increased risk.[265a]

Because of the success in detecting these signals, there have been various attempts to automate screening for signals using SRS reports. Historically, this has been relatively unsuccessful,[266] largely because of inherent methodologic problems of spontaneous reports (see above and Chapter 10). For example, automated signal generation will not flag events that are not uniquely coded (e.g., the coding system may lack a specific term for Sjögren's disease or other rare conditions). However, new tools developed for pattern recognition in extremely large databases are increasingly being applied.[267–270] VAERS is one of the largest registries for rare vaccine adverse events in the world, with approximately 300 000 reports. Because of its continuously increasing size and the need to monitor a large number of vaccine–symptom combinations, there has been a substantial effort made to apply various computer-assisted techniques for automated detection of unusual trends and patterns. Several different "data mining" methods that have been evaluated in VAERS to date, include Empirical Bayesian,[271] Association Rule Discovery,[272] multi-item gamma Poisson shrinkage (MGPS),[273] proportional morbidity distribution,[274] and proportional reporting rate ratio.[268,275] No single method appears to be superior.[276] Rational approaches to prioritizing the large numbers of potential signals generated using automated algorithms on large passive AEFI report databases may involve utilization of complementary approaches, such as data visualization and an array of different data mining methods (each with pros and cons), where cumulative higher score might signal cause for greater concern. Ultimately, these methods do represent a useful adjunct to, but not a substitute for, traditional methods of scrutinizing spontaneous reports in increasingly complex databases such as VAERS.[268]

A "rapid cycle" analytic approach has been developed by the CDC VSD project (see Automated Large, Linked Databases, below) to rapidly analyze safety data on new vaccines,[277] existing vaccines with new recommendations or indications, and the annual influenza vaccine strain.[278] This initiative utilizes the strengths of the VSD with its ability to gather automated vaccination and medical care utilization data from enrolled members in ten managed care organizations, and incorporates new data management to collect and analyze the safety profile of each successive week's cohort of vaccinated people. To date, the project has not only successfully simulated,[278–280] but also detected an observed increase in febrile seizures after combination MMRV vaccines.[281] The VSD covers a population of about 9 million people, which while large, may still not be able to detect associations between rare exposures and very rare outcomes, or more common exposures or outcomes among a specific subpopulation, such as pregnant women. Furthermore, rapid cycle analysis requires *a priori* specification of the adverse events to be studied, and therefore is not a true source of *de novo* signals. New information theory approaches may provide a way of detecting previously unexpected associations after vaccination.[282] Until then, a large national passive surveillance system such as VAERS is still necessary as an early harbinger of potential vaccine safety signals for very rare or unusual events.

Large immunization campaigns

Whenever very large numbers of vaccine doses are administered over a short time interval, this can result either in more prominent clusters of vaccine adverse events, or, by their absence, can demonstrate their safety. Note that this occurs irrespective of whether the vaccine exposure is part of a planned mass immunization campaign or not. For example, the link drawn between hepatitis B vaccine and demyelinating disease in France was due in part to increased vaccinations beyond the intended adolescent age group.[283] Surveillance of vaccine adverse events around the time of mass immunization campaigns have been extremely useful in generating signals, either positive (e.g., allergic reaction after dextran-stabilized measles vaccine,[49] viscerotropic disease following yellow fever vaccine,[284] aseptic meningitis after mumps vaccine,[104,285] GBS with swine influenza vaccine,[54] GBS after oral polio vaccine,[286] allergic reactions after Japanese encephalitis vaccine,[287] neuropathy after rubella vaccine[288]) or absent (e.g., events after meningococcal vaccine,[289,290] GBS after measles[291]). Such signals still require validation, however, since some, after more careful scientific studies, are not confirmed to represent a true association.[292,293] Mass psychogenic illness can plague mass vaccination campaigns, especially among adolescents in school settings.[294,295]

Preparation in advance of mass vaccination campaigns is critical. During mass campaigns with group B meningococcal vaccine in New Zealand[296] and during the large vaccination effort for 2009 H1N1 influenza vaccine in the United States and elsewhere,[55,297,298] several systems were put in place to identify signals early. For the latter, in the United States, VAERS offered the earliest available data to determine if there was a safety concern. An active GBS case finding project among a population of 45 million was also able to determine rapidly if there was an increased risk of GBS following H1N1vaccination. Both systems had strength in the population size and the rapid review of reports.[55] Assessing and having background rates for likely AEFIs during mass campaigns is also very helpful.[298,299] Special registries or studies will be needed, however, to monitor the outcome for subpopulations such as pregnant women, who may need to be vaccinated with limited safety data during such campaigns.[300]

Lessons learned to date

Several lessons are beginning to emerge from spontaneous reporting systems such as VAERS.[217,301–303] Such systems worldwide have successfully detected previously unrecognized reactions and helped to obtain data to evaluate whether AEFIs are causally linked to vaccines.[106,132,138,213–215] VAERS has also successfully served as a source of cases for further investigations of idiopathic thrombocytopenic purpura after MMR,[304] anaphylaxis after MMR,[46] and syncope after immunization.[305] VAERS has been of great value for answering routine public queries such as "has adverse event X ever been

reported after vaccine Y?" and describing the postlicensure safety profile of new vaccines.[306,307]

When denominator data on doses are available from other sources (e.g., net doses distributed, vaccine coverage surveys, immunization registries), VAERS can be used to evaluate changes in reporting rates over time or when new vaccines replace old vaccines. However, reported rates may be susceptible to biases from media attention, systems enhancement efforts, or other environmental changes that can increase reporting, making comparison over time difficult. Comparing the proportion of reports for specific events may be helpful to minimize this type of bias. For example, analysis of VAERS data showed that after millions of doses of DTaP had been distributed, the reported rate for serious events such as hospitalization and seizures after DTaP in toddlers was one-third that after DTP.[274] Reports to VAERS of vaccine-associated paralytic polio disappeared after the shift away from oral polio vaccine in the United States.[217] The proportion of GBS reports following inactivated influenza vaccines over several seasons did not vary including following 2009 H1N1 vaccines even though the reporting rates for GBS were higher following 2009 H1N1 which was likely attributed to heightened media attention.[217a] VAERS is also currently the only surveillance system that covers the entire US population, and the data are available on a relatively timely basis. It is, therefore, the major means available currently to detect possible new, unusual, or extremely rare adverse events, including whether certain lots of vaccines are associated with unusually high rates of adverse events,[308,309] especially when combined with estimates of lot use denominator obtained from statistical models.[310]

Data from passive spontaneous reporting systems, such as VAERS, have helped to inform potential clinical management[311] of vaccine adverse events and to identify potential risk factors for such events, such as advanced age[261] and thymic dysfunction[312] associated with yellow fever vaccine complications, concurrent zoster infection in varicella vaccinees resulting in meningitis,[313] personal and family history of convulsions in pertussis vaccinees,[108] and factors associated with postvaccinial syncope-related injuries.[305,314]

The reporting efficiency or sensitivity of a spontaneous reporting system can be estimated if the expected rates of adverse events generated from carefully executed studies are available. A study using this method showed a higher proportion of serious events such as seizures that follow vaccinations are likely to be reported to VAERS (or its predecessor, Monitoring System for Adverse Events Following Immunizations, MSAEFI) than milder events such as rash, or delayed events requiring laboratory assessment, such as thrombocytopenic purpura after measles–mumps–rubella vaccination (Table 26.3).[315] "Capture–recapture" methods, when at least two independent sources are available to ascertain incident adverse event cases in the same population and enough identifying data on the cases are also available to identify individuals ascertained in both datasets sources, can help assess the sensitivity of the reporting systems. Using this method, only an estimated 47% of rhesus rotavirus vaccine attributable cases of intussusception were reported to VAERS despite the substantial associated media publicity.[316] Although formal evaluation has been limited, the probability that a serious event reported to VAERS has been accurately diagnosed (i.e., predictive value positive) is likely to be high. Of 26 patients reported to VAERS who developed GBS after influenza vaccination during the 1990–1991 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%).[317] In general, the validity of diagnoses reported to VAERS is highly variable, depending on the condition.

Despite the above uses, spontaneous reporting systems for drug and vaccine safety have a number of major methodologic weaknesses (see also Chapter 10) and pitfalls for the unwary use of public-use datasets.[303] Biased and incomplete reporting are inherent to all such spontaneous reporting systems and potential safety concerns may be missed.[315,318] Aseptic meningitis associated with the Urabe mumps vaccine strain, for example, was not detected by spontaneous reporting systems in most countries until eight cases with vaccine-specific virus isolation were published in 1989, 7

Table 26.3 Reporting efficiencies for selected outcomes, two passive surveillance systems for vaccine adverse events, United States[311]

Adverse event	Vaccine	Reporting efficiency(%)		
		MSAEFI*	*VAERS** (overall)	VAERS* (public sector)
Vaccine-associated polio	Oral polio vaccine (OPV)	72	68	†
Seizures	Diphtheria–tetanus–pertussis (DTP)	42	24	36
Seizures	Measles–mumps–rubella (MMR)	23	37	49
Hypotonic–hyporesponsive episodes	DTP	4	3	4
Rash	MMR	<1	<1	5
Thrombocytopenia	MMR	<1	4	<1

*MSAEFI, Monitoring System for Adverse Events Following Immunizations; VAERS, Vaccine Adverse Event Reporting System.
†Public and private sector information is missing on these cases.

Box 26.1 "2 × 2" table necessary for epidemiological analysis of causality between vaccine and an adverse event

		Adverse event	
		Yes	No
Vaccinated	**Yes**	"a"	"b"
	No	"c"	"d"

- Rate of adverse event following 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 (due to under- and biased reporting) for cell "a" of the table. Epidemiologic studies aim to gather information for all four cells of this table in an unbiased manner.

years after licensure.[319] Most importantly, however, the information content of such spontaneous reports represent just cell "a" of a two-by-two table of vaccination versus adverse event (Box 26.1), and an incomplete and biased content at that.[32]

Use of data from spontaneous reporting systems is further complicated by heterogeneity in reported clinical syndromes, absence of laboratory confirmation of many of the events, and simultaneous vaccinations that make proper attribution of the causal vaccine difficult. Since much of "signal detection" relies on specific diagnoses and their coding into databases, new adverse event clinical syndromes may not be "recognized" and analyzed as such until hypothesis strengthening procedures such as development of standardized case definitions and/or clinical/laboratory evaluation are undertaken. Researchers in Canada did a series of such studies to characterize then "new" oculorespiratory syndrome (ORS) after 2000–2001 influenza vaccination;[132,320] which, in retrospect, probably also occurred in other influenza seasons[321] and other countries with other influenza vaccine manufacturers.[322]

Current spontaneous reporting systems are also prone to detecting increases in adverse event rates that are not true increases. Instead, they may be due to an increase in: (i) reporting efficiency, (ii) vaccine coverage, or (iii) increases in the incidence of known or unknown etiologies for a particular adverse event. Spontaneous reporting systems are usually unable to sort out causally related from coincidentally related adverse events because of inherent methodologic weaknesses. For example, an increase in GBS reports to VAERS in 1993–1994 influenza vaccinees compared to 1992–1993 influenza vaccinees was found to be due to improvements in vaccine coverage and increases in GBS background incidence, while the vaccination-

associated risk remained unchanged.[150] An increased reporting rate of an adverse event following one hepatitis B vaccine brand compared to another 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).[323] A signal of venous thromboembolic events in human papillomavirus vaccinees in VAERS was probably due to confounding from concurrent use of oral contraceptives.[324] Finally, an approximately two- to threefold increase in 2009 H1N1 reports to VAERS as compared to 2009–2010 seasonal influenza vaccine occurred, most likely due to heightened public awareness and enhancements made to VAERS for safety monitoring efforts of the 2009 H1N1 vaccine.[325]

These studies highlight the crude nature of the "signal" generated by VAERS, and the difficulty in ascertaining which vaccine safety concerns warrant further investigation. Not only are there problems with reporting efficiency and potentially biased reporting, but precise denominators for calculating true rates are usually not available. Instead, crude measures such as *doses distributed* must often be used as surrogates for *doses administered*. Because of these difficulties, the requirement for manufacturers to notify FDA whenever they receive increased number of reports has been dropped.[326]

Historically, most (especially resource-limited) countries have relied on spontaneous reporting systems alone for postlicensure vaccine safety monitoring. The inadequacy of scientific information on vaccine safety found by the Institute of Medicine is related to the methodologic weaknesses inherent to spontaneous reporting systems. The establishment of new population-based immunization information systems in which all vaccines administered are entered, may provide more timely submission of spontaneous reports as well as more accurate and specific denominators for doses administered, providing information necessary to calculate more accurate adverse event rates.[327,328]

Clinical trials

Prelicensure clinical trials

To demonstrate that a new vaccine candidate is safer than a previous vaccine, the two products can be compared head to head in a randomized trial, as was done for acellular and whole-cell pertussis vaccine.[329] Alternatively, active surveillance in a large trial can be done to show the attributable risk for a specific adverse event (e.g., intussusception) was lower for a new rotavirus vaccine compared to the old.[115] When new adverse events such as myopericarditis are detected after smallpox vaccination, trials of new vaccine candidates using a similar viral vector may require more safety assessment (e.g., electrocardiogram).[330]

Postlicensure clinical trials

To optimize vaccine use, clinical trials may be conducted after vaccine licensure to assess the effects of changes in vaccine formulation,[331] vaccine strain,[117,332] age at vaccination,[333] the number and timing of vaccine doses,[334] simultaneous administration,[335] and interchangeability of vaccines from different manufacturers[336] on vaccine safety and immunogenicity. The importance of such trials was demonstrated when studies showed an unanticipated differential mortality among recipients of high and regular titer measles vaccine in developing countries,[337] albeit lower than among unvaccinated children.[338] This finding resulted in a change in recommendations by WHO for the use of such vaccines.[339] The development of automated large, linked databases (see below) may permit improved ability to monitor the safety of such postlicensure changes in vaccine use without necessarily conducting such clinical trials.

Postapproval surveillance studies

To improve the ability to detect adverse events that are not detected during prelicensure trials, most recently licensed vaccines in developed countries have undergone formal postapproval surveillance studies on populations with sample sizes of 100 000. These studies have usually used computerized data from cohorts in health maintenance organizations supplemented by diary or telephone interview. These methods were first extensively used after the licensure of polysaccharide and conjugated Hib,[340–342] DTaP,[118] and varicella vaccines (including multiyear evaluation for disease incidence, herpes zoster, and a pregnancy registry).[343,344] Postapproval studies are now routine for newly licensed vaccines such as MMRV vaccine,[107] human papillomavirus

vaccine,[345] and second-generation rotavirus vaccines.[346,347] Postapproval studies in Mexico and Brazil have found an increased risk of intussusception in the newer rotavirus vaccines, albeit one-tenth that of the first-generation vaccine.[348] Requirements for postapproval evaluation have even been extended to less frequently used vaccines, such as Japanese encephalitis vaccine.[349] A large postlicensure randomized trial for this vaccine was also completed in China to improve the available data on its short-term safety.[350]

Ad hoc epidemiologic studies

Historically, *ad hoc* epidemiologic studies have been employed to assess signals of potential adverse events generated by spontaneous reporting systems, the medical literature, or other mechanisms. Traditional analyses of secular trends (ecologic studies), cohort studies, and case–control studies have been used to gather information necessary to measure or compare risks of an adverse event following vaccination with risk in the absence of vaccination. Occasionally, data collected for other study outcomes may be reanalyzed to see if vaccine was causally related or not.[351] Examples of *ad hoc* follow-up studies to signals of vaccine safety issues are: the investigations of poliomyelitis after inactivated[77] and oral polio vaccines;[248] SIDS after DTP vaccination;[27,153,352–354] encephalopathy after DTP vaccination;[59,355] meningoencephalitis after mumps vaccination;[144,356] injection site abscesses postvaccination;[357] intussusception after Rotashield vaccine;[66,67,66,67] vaccinations and autism;[358,359] GBS after influenza vaccine;[54,55,150] and GBS after meningococcal conjugate vaccine.[264] Many such studies have been compiled and reviewed by the Institute of Medicine.[27,28,34,36–40] While automated large, linked databases (see below) provide a more cost-effective and flexible framework for hypothesis testing, *ad hoc* epidemiologic studies may still be needed in settings without automated large, linked databases,[106,132] or where the statistical power of the automated large, linked databases may be inadequate to answer a question in a timely manner.[149,150,317]

Automated large, linked databases

Ad hoc epidemiologic studies of vaccine safety, while potentially informative about vaccine causality, are costly, time-consuming, and usually limited to assessment of a single type of event. As with drug safety research (see Chapters 11–21), efforts have increasingly turned to record linkage between automated exposure (immunization records in lieu of pharmacy) files and outcome medical files. The CDC participated during the late 1980s in two pilot vaccine safety studies using automated large, linked databases in Medicaid and Managed Care Organizations (MCO) populations, respectively.[360,361] While validating this approach for vaccine safety studies and providing scientifically rigorous results, these studies were limited by their relatively small sample sizes, inability to prospectively study new hypotheses, and focus on the most severe reactions.[27] These limitations, the constraints of VAERS, and the recognition of the need for improved monitoring of vaccine safety, prompted the CDC to initiate the Vaccine Safety Datalink (VSD) project in 1990.[70,250,362] To help overcome the previously identified shortcomings, the VSD prospectively collects vaccination, medical outcome (e.g., hospital discharge, outpatient visits, emergency room visits, and deaths), and covariate data (e.g., ethnicity and socioeconomic data in birth certificates, census) under joint protocol at multiple MCOs. Selection of staff-model, prepaid health plans also minimized potential biases for more severe outcomes resulting from data generated from fee-for-service claims, a problem prior to implementation of diagnosis-related group (DRG) billing.[363] To increase patient confidentiality, the VSD shifted from annual data tape submissions from the MCOs for data pooling and analysis at CDC to a distributed network data management model; in parallel, VSD is also increasing transparency via public access data sharing and external input.[364]

Originally, the VSD conducted active surveillance on approximately 500 000 children from birth through 6 years of age (75 000 birth cohort, approximately 2% of US population in these age groups).[250] Expansion to eight MCOs (including data on all age groups at three MCOs) was accomplished in 2000.[362] The VSD focused its initial efforts on examining potential associations between immunizations and 34 serious neurologic, allergic, hematologic, infectious, inflammatory, and meta-

bolic conditions. The VSD is also being used to test new *ad hoc* vaccine safety hypotheses that arise from the medical literature,[16,147,148,170,365–367] from VAERS,[67,323] from changes in immunization schedules,[368,369] or introduction of new vaccines.[281,340,342,370] In addition, the VSD databases have been used to conduct influenza vaccine safety studies in which large cohorts of children are screened for evidence of increased medically attended events following vaccination.[167,168] 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.[281,369] At the time of this writing (2010), ongoing surveillance is currently being conducted on the following combination vaccinations: MMR-V, Tdap, DTaP-IPV, and DTaP-IPV/Hib.

When the VSD identifies an adverse event as being associated with vaccine, data on the incidence rate attributable to vaccine are available,[67,170,281] permitting accurate risk–benefit assessment by both the public and policymakers.[371] Subgroup analyses may permit identification of risk factors for adverse events (or vaccine failures), which may be useful in identifying contraindications to vaccinations.[372] Data from VSD have been useful in calculating background rates of illnesses in the absence of vaccination that can serve as expected rates when comparing rates of vaccine-associated events in SRS.[299] Also, incidence rates of vaccine-associated adverse events derived from VSD can be used to evaluate the sensitivity of passive reporting systems. The VSD data also aid the Vaccine Injury Compensation Program in determinations of what events should be compensated as vaccine "injuries."[92]

In addition to *ad hoc* epidemiologic studies, a Rapid Cycle Analysis (RCA) team was formed within the VSD to conduct near-real-time active surveillance on newly licensed vaccines. The RCA relies on analytic data sets that are created weekly from the automated MCO data. The weekly analytic data sets are used to investigate potential associations between vaccines and adverse events that are defined *a priori*. Statistical analysis for signal detection is conducted with methods that account for the multiple testing of accumulating data. The RCA team developed a statistical method known as the maximized sequential ratio probability test (MaxSPRT) to detect safety signals in near-real time, while accurately accounting for repeated testing of the data.[373] The first application of MaxSPRT was in safety assessment of the newly licensed meningococcal conjugate vaccine in 2005.[277] RCA methods also were used to detect a twofold increased risk for febrile seizures following MMRV vaccination compared to MMR and varicella (MMR + V) administered separately.[281] This finding precipitated changes in US immunization policy for MMRV and MMR + V in children.

The VSD has some limitations. While diverse, the population in the MCOs currently in the VSD 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 MCOs for most vaccines, few non-vaccinated controls are available. Therefore, the VSD often relies on some type of "risk-interval" analysis[360,361,374] (Box 26.2). The capability of this approach to assess associations between vaccination and adverse events with delayed or insidious onset (e.g., neurodevelopmental or behavioral outcomes) is limited.[16] The VSD also cannot easily assess adverse events that do not result in a health-care visit, and therefore are not currently captured in existing MCO databases, because they do not result in a health-care consultation (e.g., fever).[250] The current VSD is also not large enough to examine modest increased risks of extremely rare events such as GBS after each season's influenza vaccine. Finally, because the VSD relies on epidemiologic methods, it may not successfully control for confounding and bias in each analysis,[121] and inferences on causality may be limited.[375]

Despite these potential shortcomings, the VSD provides an essential, powerful, and relatively cost-effective complement to ongoing evaluations of vaccine safety in the United States. In view of the methodologic and logistical advantages offered by automated, large, linked databases, Denmark,[33] the United Kingdom,[103,144,376,377] and Canada[378] have also developed large automated databases linking immunization registries with medical files. Europe[30] and Taiwan[298] anticipate they will eventually convert their 2009 H1N1 vaccine safety

Box 26.2 Example of method for risk-interval analysis of association between a universally recommended three-dose vaccine (with few unvaccinated people for comparison) and adverse event

1 Define "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 three 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).

o———————x====———————x====———————x====———//———>
Birth Dose 1 Dose 2 Dose 3 365 days

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

	Adverse event	Person-time observed (months)	Incidence rate
Vaccinated in risk interval: yes	3	100	0.03
Vaccinated in risk interval: no	10	1000	0.01
Total	13	1100	

Incidence rate adverse event$_{vaccinated}$ = 3/100 = 0.03
Incidence rate adverse event$_{unvaccinated}$ = 0/1000 = 0.01
Relative risk vaccinated: unvaccinated = 0.03/0.01 = 3.0
Probability finding due to chance: <5/100
Conclusion: There is a threefold increase in risk for developing the adverse event within the interval following vaccination

surveillance into large, linked databases for routine vaccinations. The first such pilot database in a less developed setting has been established in Vietnam.[379] Given that many vaccines against many poverty related diseases such as rotavirus, malaria, and TB will be introduced first in such countries, there is a need to develop VSD-like infrastructures there, too.[126]

Methodologic approaches for observational epidemiologic studies

Exposures

In countries where vaccinations are required for entry into daycare, kindergarten, schools, and/or colleges, documentation via vaccination cards or medical records is usually available and of good quality for most infants and children. In the United States, documentation of the vaccine type, date of vaccination, manufacturer, lot number, and vaccine provider in a permanent medical record has been required since 1988 for certain routine childhood vaccinations.[207] This requirement, along with improvements in technology, has prompted many organizations to automate their vaccination records.[328]

Although vaccination records can be manually retrieved and reviewed for any study design, automated vaccination records greatly ease the logistics of organizing such studies. Whenever sampling is necessary in the design, automated records also ease the selection of samples that are representative. Assessing the accuracy of such automated data is important in any study.[380,381] When people receive their vaccinations from several providers (not uncommon in the United States), their exposure status may be misclassified.[382] This error could be minimized if a centralized Immunization Information Systems (IIS) were implemented to track all vaccinations from birth. Such an IIS has been implemented in Denmark,[33] most of the

United Kingdom,[327] and state/regional IIS are under development in the United States,[328] Canada,[383] and Australia.[384]

The availability and quality of vaccination records generally decrease as people age. Some vaccines for older people (e.g., tetanus–diphtheria boosters in emergency rooms, hepatitis B vaccinations for health-care personnel) may be administered in settings other than primary health care. In addition to review of primary medical records, interviews or a review of data from secondary vaccination sites may therefore be necessary to accurately ascertain exposure status in adverse event studies of these vaccines in older populations. To increase the accuracy of exposure data in a study of adverse reactions to plasma-derived hepatitis B vaccine among Alaskan natives,[385] medical records from the village, the hospital, and the regional public health nurse, in addition to the automated vaccination record, were reviewed.[385,386] Studies of GBS and H1N1 influenza vaccine relied on patient/family interview, hospital medical record, and/or validation with primary care providers for exposure ascertainment.[55] Interestingly, reliance on provider verification may lead to under-ascertainment of vaccination status, either because of poor record keeping[382] or concerns about liability in vaccine safety studies.[150]

Standards should be developed to further improve the accuracy and efficiency of transfer of vaccine identification information from the vaccine vial to either automated or paper immunization records, including: (i) abbreviations for new vaccine antigens and vaccine manufacturers, (ii) peel-off labels, (iii) bar codes, (iv) lot numbers, (v) immunization records, and (vi) presentation of key identifier information on vaccine packaging (as on the nutrition label). WHO has recently identified as a priority the development of a vaccine dictionary that will allow differentiation of vaccine formulations from various manufacturers.[387]

Outcomes

To ensure both high sensitivity and specificity for an AEFI, a multistep approach is usually required for case ascertainment.[167,168,170,365,388] In step one, the automated databases are screened to identify ICD-9 diagnostic codes for the condition of interest. The ICD-9 codes typically represent medical encounters in the inpatient, outpatient, and emergency department settings. Additional data sources, such as laboratory and pharmacy files, can also be used to identify potential cases. This initial screening definition tends to be highly sensitive but less specific. After the electronic cases have been identified, the medical records of the patients are often reviewed by a trained abstractor, blinded to vaccination status. On a standardized data collection form, the abstractor records detailed clinical information on presenting symptoms, sequelae, medications, underlying health conditions, diagnostic test results, and potential confounding variables. For outcomes with insidious onset such as multiple sclerosis, multiple dates (e.g., first symptom, first medical visit, first diagnosis) and sources of information (patient recall, medical chart) may also need to be collected.[161,389] In the last step of the case ascertainment process, clinical experts review the abstracted medical information to determine if patients meet the final study case definition. For difficult diagnoses such as GBS, a panel of specialists may also be asked to review the medical records after exposure status has been masked.[65]

This process minimizes the likelihood of a false negative conclusion (due to bias towards the null) by ensuring that only cases meeting the most specific case definition are included in the analysis. It is also possible, however, that using such a narrowly focused outcome definition may miss broader syndromes or groups of symptoms related to the outcome. Follow-up analyses of rhesus rotavirus vaccine reports to VAERS suggest that intussusception[213] may have been just the tip of the "iceberg" of a broader syndrome that also included bloody stool, vomiting, diarrhea, and abdominal pain.[306] Adverse neurologic outcomes other than GBS were reported among the 1976–1977 and 2009 H1N1 influenza vaccinees.[390,391] Unfortunately, whether these associations are causal remains unknown and controversial, as formal studies have not been done.

Should the concern be a new, previously undescribed syndrome, analyses of existing databases may be inadequate. A study of "Gulf War

syndrome" and vaccinations relied on a thorough interview of patients meeting a *de novo* complex case definition before linkage with vaccination history.[392]

In the context of real-time surveillance, influenza vaccine safety monitoring is hindered by the rate at which large, linked databases capture medical encounter data. In the VSD, for example, some of the MCO sites contract with independent hospitals to provide inpatient care. Therefore, there is often a considerable lag between the inpatient encounter and the date at which the encounter (outcome) is captured in the databases. At some sites, the average lag can be as long as 4 months.[393] For influenza vaccine safety monitoring, the influenza season may be over by the time the outcome data are fully captured, thereby rendering the real-time analysis moot.

Study design and analytic methods

Different analytical strategies are needed depending on how a vaccine is used in the population. For vaccines used infrequently and typically in vaccinees who are generally no different than non-vaccinees (e.g., travel vaccines), comparison between two groups with adequate matching or adjustment is relatively straightforward. For example, in a cohort study, groups of vaccinated and unvaccinated individuals may be matched on several factors such as sex, MCO, age, high-risk condition, and calendar time. The cohort of vaccinated and unvaccinated individuals is then followed forward in time, and the incidence of events in the two groups is compared within predefined exposure windows following vaccination. These exposure windows are defined *a priori* based on current understanding of the most plausible biologic mechanism, should such an association actually exist. For most acute events, exposure windows of 0–2, 1–14, 1–30, and 1–42 days are often used.[157,166,168,170] This study design provides a direct estimate of effect (the incidence rate ratio, IRR), is well-suited for rare exposures (but not rare outcomes), and can be used to analyze multiple outcomes.[394,395] Matching on age and calendar time helps to adjust for time-varying variables that can confound the results when the vaccine and outcome are either seasonal or highly dependent on age. When the outcome is rare, however, the cohort design can be costly to implement, and, for childhood vaccines that are universally recommended, there may be too few unvaccinated children for the comparison group. The design is also susceptible to selection bias that can be introduced by comparing vaccinated and unvaccinated populations, as these groups may differ by factors frequently missing from large, linked databases such as ethnicity, socioeconomic status, and underlying health state.[121]

In contrast to the cohort design, case–control studies are conducted by first identifying individuals who experienced a particular event over a predefined time period. This group of cases is then compared to a control group of outcome-free individuals from the same time period. Cases are often matched to controls by variables such as sex, age, MCO site, and calendar time.[66,160,396] This design tends to be more economical than the cohort design, and it is well-suited for rare illnesses. As with the cohort method, however, the case–control design is limited when vaccine coverage rates are high and few unvaccinated cases and controls are available for analysis. In contrast to the cohort design, matching on confounding variables in a case–control study will bias the results to the null hypothesis (i.e., toward no effect) if not explicitly adjusted for in the analysis.[394]

To address some of these limitations, alternative methods known as the risk-interval (or vaccinated cohort) and self-controlled case series (SCCS) study designs have been developed for vaccine safety epidemiology.[66,106,166,170,173,174,397–401] These designs differ from more traditional epidemiologic methods in that time intervals both before and after vaccination *within the same individual* are used to classify a person as exposed or unexposed. In the risk-interval design, incidence rates for risk and non-risk time periods are compared, but only vaccinated individuals are included in the analysis. A time period immediately following vaccination is defined as the risk interval, and events that occur during this period are classified as exposed cases. Time periods outside of the risk interval—before and after the vaccination—are considered the non-risk (or control) periods, in which occurrences of events

are classified as unexposed cases. Because only vaccinated individuals are included in the study, the design eliminates biases associated with fixed factors that remain constant over time in the same individual but differ between vaccinated and unvaccinated populations. In addition, because control time periods both before vaccination and after the risk period are included in the analysis, the design is used to examine the risk of acute, self-limiting events following vaccination.

The SCCS method is a similar design in which incidence rates for risk and non-risk time periods are compared, but only cases with an event are included in the analysis.[173,358,397,398,402] The study population comprises cases that occur over a predefined observation period, and each case acts as its own control, thereby controlling for both measured and unmeasured confounding variables that do not vary over time (i.e., fixed confounding). With the SCCS method, multiple occurrences of independent events within an individual can be analyzed. Since only cases are required for the analysis, the SCCS study population is considerably smaller than that of the cohort, case–control, and risk-interval designs. As discussed below, the SCCS has nearly as much statistical power as the cohort approach when a high proportion of the population is vaccinated.

Possible limitations of the risk-interval and SCCS methods stem from their inability to implicitly control for time-varying confounders, such as seasonality or age. In contrast to the matched cohort analysis, these time-varying variables must be explicitly defined as either continuous functions or categorical variables and added to parametric Poisson regression models.[397,400] Mis-specifying such variables can lead to biased results—particularly when the event is rare.[402] Alternatively, it has also been shown that semiparametric Poisson regression models can be used to analyze SCCS data in which the time-varying effects of age do not have to be explicitly defined before analysis.[398]

An additional important limitation of the SCCS is that bias can be introduced if the occurrence of an event influences the probability of receiving vaccination. For example, individuals with a history of contraindicating or precautionary conditions to vaccination—such as GBS, idiopathic thrombocytopenia, anaphylaxis, and HIV—may have their immunizations either delayed or withheld indefinitely. In such a situation, the SCCS design would be limited since only cases (i.e., those with an event) are followed forward in time, and time periods before vaccination could not be included in the analysis. This assumption of event-independent exposure (vaccination) is not required for the more traditional epidemiologic methods because vaccination status is ascertained retrospectively from the date of diagnosis in a case–control study, and the onset of an event is ascertained prospectively from the date of vaccination in a cohort study. A recent analytic method has been developed to account for the postevent dependence in an SCCS analyses when the postvaccination risk period is short and when the event is both rare and non-recurrent.[399] Simulation analyses demonstrated that the estimation method helped to correct for bias associated with event-dependent exposures, but it also produced IRR estimates that were attenuated to the null hypothesis (i.e., they underestimated the true effect). Future research is needed to develop this analytic technique further.

The characteristics of cohort, case–control, risk interval, and SCCS designs have been compared empirically with simulation studies.[174,397] In a study using VSD data and simulated cases of a rare, acute illness (immune thrombocytopenic purpura or ITP) after MMR vaccination, the risk-interval, SCCS, and case–control study designs produced valid IRR estimates that were within 3% of a cohort gold standard. The case–control design, however, produced estimates that were less powerful, less precise, and biased by unmeasured fixed confounding when compared to the other study designs. The SCCS and risk-interval, in contrast, were as powerful as the cohort design and produced unbiased estimates in the presence unmeasured fixed confounding. Of note, the SCCS design displayed similar characteristics to those of the risk-interval and cohort, but required only a fraction (0.01%) of the study population for analysis. On average, the size of the simulated cohort, risk-interval, and SCCS study populations were 2.7 million, 1.4 million, and 200 individuals, respectively.

Using similar simulation analyses, the characteristics of these four designs were evaluated in the context of real-time, active surveillance of AEFI.[280] When the exposure and outcome were acute, the cohort proved to be the best study design for active surveillance, in terms of bias, statistical power, and signal detection time. When selection bias was a concern, the risk-interval design was shown to be a valid alternative. Of all the designs, the case–control design had the longest signal detection time and most biased relative-risk estimates. Although the SCCS lagged behind the cohort and risk-interval designs in signal detection time, it was acceptably accurate and powerful and required only a minimum of data. Thus, the results from these simulation studies demonstrate that the SCCS design is a valid, powerful, and economic epidemiologic tool for studying vaccine safety.

Clearly, the current methods for studying vaccine safety have contrasting strengths and limitations. In some instances, researchers employ multiple methods to address the various factors that can bias the results.[106,170,393,400] Studying the safety of the influenza vaccine, as an example, poses multiple methodologic challenges that cannot be addressed with one particular design. In a typical influenza season, more than 85% of the vaccines are administered in October and November.[393,403] It is also likely that certain conditions of interest—such as febrile seizures, gastrointestinal disorders, or rash—have a seasonal distribution across the influenza season from October through April, with the incidence peaking in winter months. Such distributions would make season a strong confounder, as it would be highly associated with both vaccination and the outcome of interest. The correlation may, in fact, be so high that one could not disentangle the individual effects of vaccination and season in the analysis. Although little can be done to rectify this potential dilemma with any design, the SCCS and risk-interval designs are particularly susceptible to this type of seasonal bias.

In addition to seasonality, studying the safety of influenza vaccination is challenged by the potential for selection bias, since it can be assumed that individuals who receive influenza vaccination are different from those who do not. For example, for those vaccinated early, a large percentage of the vaccinated may have co-morbidities, placing them at high risk for infection resulting in them being targeted for vaccination; for those vaccinated later, after universal recommendations, the inherent differences between the vaccinated and unvaccinated populations may change. Moreover, in large, linked MCO databases, it is possible that a certain proportion of the population received an influenza vaccination outside of the MCO, which may not be captured in the automated databases.[393] As described earlier, these potentials for selection bias and exposure misclassification are problematic for the cohort and case–control designs.

The future

Although considerable progress has been made in the development of vaccine safety analytic methods, several challenges remain. Areas of particular importance include the following: (i) minimizing seasonal time-varying bias, (ii) identifying optimal risk windows, (iii) detecting a lifetime dose response from multiple influenza and tetanus-containing vaccinations, (iv) evaluating the safety of simultaneous vaccination, and (v) data mining for unknown AEFIs in real-time active surveillance.

As described, accounting for seasonal time-varying bias is particularly challenging in safety studies of influenza vaccination. Because a large majority of influenza vaccinations are administered in October and November, there may not be enough variability in the temporal distribution of vaccination to control for seasonal fluctuations in the outcome of interest. A potential strategy is the case-centered approach.[403] This strategy has been used to assess influenza vaccine effectiveness in the elderly. In cases occurring during an influenza season, the method uses data from the entire cohort (cases and non-cases) to calculate the probability of exposure (vaccination) for the day of the event. The logit of this probability is then placed into logistic regression model as an offset term. In essence, this method provides a seasonal adjustment for exposure by conditioning on the odds of vaccination over the course of an influenza season.

Future work needs to focus on how to apply this method in studies of vaccine safety, where the study population is young and healthy, and both the exposure and outcome are acute and transient. Moreover, the method could be developed for use in real-time active surveillance of newly licensed vaccines.

Although risk window lengths are often based on prior biologic knowledge, they are also somewhat arbitrarily defined (e.g., 0–2, 1–14, 1–42 days after vaccination). Inaccurate specification of the risk window can result in either including the true control period in the risk window or including a segment of the risk window in the control period, both of which would introduce bias. After an elevated risk has been identified in a prespecified risk window, a two-step data-driven approach to identify the period of greatest risk has been proposed. Step 1 begins by specifying a minimum risk window length, for which a risk estimate is calculated using an appropriate regression model. The risk window is incrementally lengthened and risk estimates are generated for each subsequent window. The risk estimates are plotted versus the variable risk window lengths, and the researcher notes where risk is maximized. If the specified risk window is longer than the true risk window, an analytic approach is possible in step 2. Preliminary simulation and theoretical work has shown that there is a linear relationship between the calculated risk and risk window length.[404] The analytic approach calculates an optimal risk window length based on maximum likelihood methods and the study design of interest. Thus far, this approach has been applied to the SCCS design with conditional Poisson regression. Future work should focus on applying the approach to other study designs and regression models.

Unlike all other vaccines, influenza vaccine is administered on an annual basis indefinitely. It is currently not known if the risk of certain adverse events increases with each subsequent dose. For children in particular, studying this relationship is problematic since dose number is likely to be strongly correlated with age. In other words, since both age at vaccination and dose increase over time, it would be difficult to explain how much of the risk associated with a particular dose can be explained by age. To study adequately the relationship between dose number and the risk of adverse events, new methods for disentangling the correlation between dose and age are needed.

An increasing number of parents are choosing to either decline or delay immunizations for their children.[405,406] This implies that there may be a certain amount of variability in the timing at which routine childhood vaccines are administered in the first 5 years of life. This variability may in turn present a natural experiment where the risk of adverse events in an otherwise healthy population of children on alternative schedules can be compared to a cohort of healthy children on the recommended schedule. It is also possible, however, that children on alternative schedules have different health-care utilization patterns than children who are up-to-date, thereby creating a selection bias.[407] Large, linked databases represent an ideal resource to explore this potential natural experiment.

Lastly, data mining methods have been developed to identify signals for unexpected AEFI. These methods for vaccine safety have been applied to passive surveillance systems and *ad hoc* epidemiologic studies.[168,408] In these respective settings, however, data mining analyses have been limited by reporting bias, lack of denominator data, and low statistical power for rare events. Conducting data mining analyses in large, linked databases with real-time active surveillance will address some of these limitations. Such methods would be a natural complement to targeted active surveillance, in which adverse events are specified *a priori*. For targeted active surveillance (see Chapter 46), sequential testing methods have been developed to protect against false-positive signals (Type I error rates) when data are analyzed on a weekly or monthly basis. The potential for Type I error, however, will increase significantly when multiple unspecified outcomes are analyzed at the same time. New analytic tools for using large, linked databases to identify unsuspected adverse events in real time are needed. These methods should be sensitive enough to detect potentially serious adverse events but also conservative enough to protect against too many false signals. Such methods

also need to account for seasonality, selection biases, and other factors that can distort the findings. Perhaps most importantly, a process for signal validation (e.g., controlled epidemiologic studies with medical chart review) and a plan for risk communication must to be in place should a signal arise.[409]

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