

Vaccine safety: current systems and recent findings

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Current Opinion in Pediatrics 2010, 22:88–93

Purpose of review

An understanding of vaccine safety is important for all immunization providers, who have responsibilities to identify, report, and prevent adverse events.

Recent findings

New analytic methods can provide more rapid information on adverse events compared with traditional observational studies. Some adverse events following vaccination are preventable. Syncope is increasingly recognized postvaccination and may be associated with severe injury or death. Both human and system factors should be addressed to prevent vaccine administration errors. Ongoing basic science and clinical research is critical to improved understanding of vaccine safety. A recent study suggests that many cases of encephalopathy following whole-cell pertussis vaccine were due to severe myoclonic epilepsy of infancy, a severe seizure disorder associated with mutations of the sodium channel gene *SCN1A*.

Summary

Vaccine safety requires prelicensure evaluation, postlicensure surveillance and investigation, addressing preventable adverse events, reconsideration of vaccine policy as understanding of risks and benefits changes, and ongoing research to better understand the response to vaccination and the pathogenesis of adverse events.

Keywords

immunization, pharmacoepidemiology, postlicensure surveillance, vaccine safety, vaccines

Curr Opin Pediatr 22:88–93
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1040-8703

Introduction

Vaccines are a major public health achievement and widespread use of vaccines has led to elimination or dramatic reductions in many diseases. The individual and societal benefits of immunization are great, in terms of prevention of morbidity and mortality, and high levels of vaccine coverage benefit the community, with decreased circulation of the disease-causing agents (herd or community immunity) and protection of those who cannot be vaccinated. Along with great benefits come great responsibilities to ensure that vaccines are as well tolerated as possible. Vaccines are routinely given to millions of healthy children, and it is critical that systems be in place to detect and respond to possible vaccine safety issues.

In 2010, vaccines that prevent 16 diseases are recommended for routine use in children and adolescents [1], and additional vaccines are recommended for adults [2]. Since 2005, new vaccines for prevention of pertussis in adolescents and adults have been licensed, along with new rotavirus vaccines, a meningococcal conjugate vaccine, vaccines for prevention of human papillomavirus-related disease, new combination vaccines, and a new vaccine to prevent zoster in persons 60 years of age

and older. Additionally, during that same period, there have been new recommendations to expand use of other vaccines, and in 2009, new recommendations were made for the use of new vaccines for prevention of pandemic H1N1 influenza. With new recommendations for use of so many new vaccines, as well as ongoing parental concerns about vaccines and developmental disorders, it is important that immunization providers understand the system that monitors and responds to vaccine safety, as well as the role they play in assuring the safety of vaccines and immunization practice.

Prelicensure assessment of vaccine safety

Before vaccines are licensed for use in the United States, they undergo extensive testing and careful review to evaluate both efficacy and safety. Clinical trials are of varying size, but are generally not large enough for assessment of the potential for the vaccine to be associated with rare adverse events [3,4]. Regulatory authorities also review manufacturing processes and inspect facilities to ensure compliance with current good manufacturing practices.

At the time of licensure, data are generally available on concomitant use of the vaccine with other vaccines

recommended for use at the same age. These studies are designed to detect immunological interference between the two vaccines and are of limited size, evaluating simultaneous administration of the new product with one specified set of other vaccines that are recommended for use at the same age.

Postlicensure monitoring of vaccine safety

Prior to licensure, vaccines are used in thousands of people in clinical trials; following licensure and once in routine use, vaccines are used in millions of people, and adverse events that occur too infrequently to detect in prelicensure studies may be identified. Additionally, clinical trials are generally performed in healthy populations and at protocol-specified ages and intervals; in actual use, vaccines are used in the general population, including those with underlying conditions and at ages and intervals that were not studied in the clinical trials. In order to assess the safety of the vaccine in the general population under conditions of routine use, postlicensure surveillance is needed.

In the United States, the Vaccine Adverse Event Reporting System (VAERS) is jointly managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS receives reports from physicians, manufacturers, patients or their families, or anyone else who chooses to report a case. Additionally, the National Childhood Vaccine Injury Act of 1986 requires reporting of certain adverse events by healthcare providers and manufacturers. Reporting is mandatory for any adverse event listed by the manufacturer as a contraindication to further doses of vaccine or any adverse event listed in the Vaccine Injury Table that occurs within the specified period after vaccination (www.hrsa.gov/vaccinecompensation/table.htm). Providers and others reporting to VAERS need not be certain that the adverse event is caused by the vaccine to report it; one of the primary objectives of VAERS is to detect new, unusual, or rare adverse events.

Reports may be submitted by mail, telephone, fax, or online (vaers.hhs.gov/esub/index). Once received, the report is reviewed and the adverse event is classified using the Medical Dictionary for Regulatory Activities (MedDRAs) codes. VAERS staff request medical records on adverse events that result in hospitalization, disability, or death. Both FDA and CDC staff review VAERS reports, looking for unexpected patterns and specific adverse events of concern. Data-mining methods are used to identify patterns of disproportional reporting for further investigation [5].

Although VAERS provides important information, it is important to note that usually it cannot be determined

from either individual or groups of VAERS reports whether or not a specific adverse event is caused by a vaccine. There are a few exceptions; local reactions at the site of vaccine administration or acute responses associated with vaccination (e.g., anaphylaxis or syncope) are considered vaccine-associated. If an individual develops a specific adverse event multiple times following vaccination ('challenge-rechallenge'), causation is inferred. Additionally, adverse events associated with live vaccines are often associated with replication of vaccine strains, and isolation of the vaccine strain can provide supportive evidence of a causal role for the vaccine (see below).

Analysis and interpretation of VAERS reports is complex [6]. Reports may not contain sufficient information, and especially for complex clinical syndromes, coding may be inconsistent. VAERS only provides information on vaccinated persons who developed the adverse event, thus limiting the ability to identify whether or not there is an association. VAERS is a passive surveillance system, and reporting is incomplete [7]. Some adverse events are more likely to be reported than others – those that are severe and are temporarily closely linked to vaccination are more likely to be reported than other events. Reporting is also influenced by publicity and public awareness of specific vaccines and adverse events.

In spite of these limitations, VAERS data do serve to identify adverse events that warrant additional investigation. Most diagnoses of concern are not uniquely associated with vaccination and occur at some rate in the population, apart from any additional cases that may be associated with vaccination. If the rate of a condition in the population (unrelated to vaccine use) is known (the background rate) and the number of doses of vaccine administered can be estimated, then the number of cases of the condition that are expected to occur among recently vaccinated persons due to chance alone can be calculated; these are cases that are not caused by vaccination but occur in recently vaccinated persons assuming that vaccine neither causes nor prevents the diagnosis. Although the number of doses of vaccine administered may not be known, it can be estimated with the number of doses of vaccine distributed as an upper limit. The degree of underreporting to VAERS is also unknown for specific diagnoses, and there may be uncertainty as well about true background rates in different population groups. However, this approach can still be useful to help identify potential vaccine safety issues that require additional investigation. This approach was used in 1999 when intussusception cases were reported to VAERS among recipients of a then recently licensed rotavirus vaccine [8] and more recently in evaluation of cases of Guillain-Barré syndrome reported among recipients of meningococcal conjugate vaccine [9]. The concept is particularly important for the current H1N1

influenza vaccine effort, to facilitate interpretation and communication regarding adverse events that occur after vaccination but may or may not be caused by vaccination [10*].

Evaluation of potential vaccine safety concerns

In order to determine whether or not a specific adverse event is causally associated with vaccination, almost always additional information beyond what is reported to VAERS is required. For some adverse events – those associated with replication of vaccine strain viruses – identification of the vaccine strain in association with a specific clinical outcome can provide strong evidence of causality. Molecular sequencing methods are now routinely employed to identify strains as vaccine-derived or wild-type, allowing cases of paralytic poliomyelitis to be characterized as caused by wild-type or vaccine-derived virus [11]. These molecular methods were recently used to document transmission of vaccine-derived poliovirus in an undervaccinated community in the United States [12]. Similarly, cases of zoster caused by varicella vaccine strain virus have been documented [13], as have cases of meningitis associated with mumps vaccine virus [14]. In contrast, cases of subacute sclerosing panencephalitis following measles vaccination have been associated with wild-type virus rather than vaccine strain [15].

Other approaches are needed to assess the relationship between vaccination and adverse events. Prelicensure, clinical trials are performed, with random allocation of participants to the vaccine group and the comparison group; if there are other important factors that influence the outcome, random assignment usually results in balanced allocation between the groups. Postlicensure, adverse events are usually evaluated in observational studies in which the differences in vaccine exposure among persons in the study results from variations in clinical practice or choice, and these study approaches – although extremely valuable – are more subject to being influenced by differences between study groups that may influence the outcome. Although there are limitations in observational studies, they can provide powerful evidence regarding the relationship between vaccine exposure and adverse events.

Regardless of the specific study design, vaccine safety studies require consistent criteria for defining the adverse event as well as accurate information on vaccine history. Field investigations may be undertaken by public health authorities in response to specific events of high concern, such as clusters of death postvaccination [16] or when there is great urgency to address a potential vaccine safety problem [17] or when other approaches are not feasible. In 1955, cases of paralytic poliomyelitis among children

who had been vaccinated with inactivated polio vaccine were identified soon after vaccine licensure. A rapid field investigation was undertaken by CDC, and within days it was learned that the cases of paralytic disease were occurring among recipients of vaccines from a single manufacturer, allowing vaccination with vaccines from other manufacturers to be resumed [18].

Comprehensive health record databases, including claims data and those from managed care organizations, are now widely utilized for vaccine safety studies. Databases that allow systematic identification of cases of specified outcomes and provide comprehensive immunization histories of defined groups of individuals are most useful. The approach using administrative data is especially useful for events with discrete onset for which healthcare is likely to be sought (e.g., seizures). Although these approaches are very powerful, there are limitations to use of administrative data, including misclassification (miscoding, diagnoses that were considered but eliminated as the evaluation proceeded, and diagnoses that were made in the past being carried forward in the patient's record). Because of these limitations, the availability of chart review to confirm potential cases identified in administrative data can greatly strengthen studies done using large linked databases [19]. In the United States, CDC works with the Vaccine Safety Datalink, a consortium of eight large managed care organizations. The participating managed care organizations are geographically diverse, with a combined population of over 9.2 million persons and a birth cohort of approximately 95 000. Healthcare utilization and diagnostic codes are available from outpatient, emergency department, and inpatient settings [20]. Similar approaches are used in other countries. Globally, these systems are an important component of current plans to monitor the safety of new H1N1 influenza vaccines [21*].

Completing an observational study, even using a system like the Vaccine Safety Datalink, can take several years. In order to identify and confirm potential vaccine safety issues in a more timely way, new approaches using sequential analytic methods have been developed. In this approach – called rapid cycle analysis by its developers – specific diagnoses of interest are looked for in specific intervals of time following vaccination in datasets that are regularly updated as additional persons are vaccinated and outcomes of interest are accrued [22]. This approach is now used routinely for safety monitoring in the United States. Its utility has been demonstrated with early recognition of an increase in risk of febrile seizures following receipt of the combination measles, mumps, rubella (MMR), and varicella vaccine [23]. Similar results were obtained from a traditional cohort study in a different managed care population [24]. It has also been applied to evaluate the safety of the adolescent and adult

formulation of tetanus and diphtheria toxoids and acellular pertussis vaccine [25].

Vaccine safety and vaccine policy

Decisions about use of vaccines are based on an assessment of the risks associated with vaccine use and the benefits to be derived from vaccination. Changes in either the understanding of risks or in the expected benefits of vaccination can lead to a reassessment of immunization policy. Decreasing risk of exposure to smallpox led the United States to discontinue routine smallpox vaccination of children in 1972, prior to global eradication of naturally occurring disease. Similarly, progress in the global polio program and decreasing risk of importation of disease was one factor that led the United States to discontinue use of oral polio vaccine in 2000. In 1999, the first licensed vaccine for prevention of rotavirus gastroenteritis was found to be associated with intussusception, a type of bowel obstruction in infants, leading to withdrawal of the recommendation for use of that vaccine [26]. (Since then, two different rotavirus vaccines have been developed and licensed in the United States; prelicensure [27,28] and postlicensure [29] studies have supported that neither vaccine is associated with a risk of intussusception comparable to the earlier vaccine.) A combined measles–mumps–rubella–varicella vaccine was found to have an increased risk of febrile seizures, compared with the use of separate MMR and varicella vaccines. The Advisory Committee on Immunization Practices (ACIP) had previously indicated that the combined vaccine was preferred over administration of MMR and varicella vaccines separately. Given the evidence for an increase in risk of febrile seizures associated with use of the combination vaccine, in 2008 the preference for the combination product was withdrawn [23].

Prevention of adverse events following vaccination

Although most persons who are vaccinated experience no or only mild adverse events following vaccination, serious illness or even deaths caused by vaccination do occur. These events are rare, but to the extent that adverse events are preventable, immunization providers should make every effort to prevent them.

Serious allergic reactions to vaccines or vaccine components are rare; a large study in the Vaccine Safety Datalink reported a risk of less than two cases per million doses of vaccine [30]. Yellow fever vaccine and currently available influenza vaccines are produced in eggs and contain residual egg protein, which can result in hypersensitivity reactions in persons who are allergic to eggs. The components of MMR are not produced in eggs and persons who are allergic to eggs can safely receive MMR;

MMR (and several other vaccines) do contain gelatin as a stabilizer, which may produce hypersensitivity reactions in persons with gelatin allergies. A complete listing of US licensed vaccines, and product inserts containing all vaccine ingredients, is available on the FDA Web site (www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm). Clinical guidance for evaluation and subsequent vaccination of persons with hypersensitivity reactions has been published [31].

Because of the risk of adverse events, live attenuated vaccines are generally contraindicated in severely immunocompromised persons. Contraindications vary based on the nature and severity of the immunodeficiency. General guidance is published [32], but consultation with an infectious disease or immunology specialist may be required.

As more vaccines are recommended for use among adolescents and young adults, reports of syncope following vaccination have markedly increased [33]. Syncope following vaccination can be associated with serious injury or death [34,35,36]. The ACIP recommends that vaccine providers strongly consider observing patients for 15 min after they are vaccinated. If syncope develops, patients should be observed until symptoms resolve [32]. Personnel should be aware of the signs and symptoms of presyncope and take appropriate measures to prevent injury if weakness, dizziness, or loss of consciousness occurs [37].

Another category of adverse events that should be preventable are those due to vaccine administration errors. Although vaccine administration errors rarely result in serious adverse events, administration of a contraindicated live vaccine to a severely immunocompromised person can result in serious injury or death. A review of medical errors reported to VAERS during the period January 2006 to September 2007 found that the wrong product was given in 24% of the reports [38]. For example, inadvertent administration of vaccines instead of tuberculin purified protein derivative (PPD) for tuberculosis skin testing as well as administration of PPD instead of various vaccines have been reported to VAERS and the FDA's Adverse Event Reporting System [39,40], and other errors, including unintentional administration of varicella vaccine instead of varicella zoster immune globulin [41], have been reported to other systems. To prevent such errors, both human and system factors should be addressed. Immunization providers should always carefully read labels and record the product name and lot number before each tuberculosis skin test or vaccination. ACIP discourages prefilling of syringes because of the risk of vaccine administration errors [32]. Improved storage practices, improved packaging and labeling, and bar code scanning can also help reduce such errors.

Genetic factors likely contribute to risk of adverse events associated with vaccines, and future research will undoubtedly lead to better understanding of the relationship among genomics, the immune response, and adverse events following vaccination [42–45]. Even if screening is not feasible, improved understanding of the pathogenesis of adverse events may lead to the development of safer vaccines.

Ongoing basic science and clinical research is critical to better understanding of vaccine safety. Soon after the whole-cell pertussis vaccine (combined with diphtheria and tetanus toxoids, DTP) began being used in the United States, there were reports of serious neurological events occurring following immunization, some of which were associated with long-term sequelae. Subsequent studies supported that DTP might rarely produce acute encephalopathy, but a causal relationship between DTP and permanent brain damage was not demonstrated. Nonetheless, concerns about the reactogenicity of whole-cell pertussis vaccines led to the development of less reactogenic acellular pertussis vaccines, which have replaced the whole-cell vaccine in the United States. In 2006, researchers in Australia and New Zealand reported that eight of 14 patients diagnosed with vaccine encephalopathy following receipt of DTP vaccine met clinical criteria for severe myoclonic epilepsy of infancy (SMEI), and an additional four patients were classified as borderline SMEI. Of these 12 patients, 11 were found to have mutations of the sodium channel gene *SCN1A*, an established finding in SMEI that typically arises as a de-novo mutation [46].

New technologies including systems biology approaches are now being applied to the study of vaccines [47,48,49]. These and other new methods will no doubt lead to better understanding of the response to vaccination and the myriad of factors – including vaccines – that result in human disease.

Conclusion

With newly recommended vaccines come responsibilities to assess the safety of these new products and to respond in a timely way to any vaccine safety issues that are identified. Newer methods, including data-mining approaches and sequential analytic methods, are now being used to monitor the safety of new vaccines, allowing more rapid understanding of their safety. Ongoing clinical and basic science research is critical for continued progress in development of safer vaccines.

Acknowledgements

I appreciate the helpful comments from Frank DeStefano and Michael McNeil in the preparation of this manuscript. The findings and conclusions in this article are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 126).

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