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The United States' long-standing vaccine safety program closely and constantly monitors the safety of vaccines. This chapter describes how vaccines licensed for use in the United States are monitored for safety and presents general information about the health care provider's role in immunization safety.

Adverse Events Following Immunization and Assessment of Causality

An adverse event following immunization refers to any medical event that occurs after vaccination. The adverse event may or may not be related to immunization. Further assessment is needed to determine if an adverse event is caused by a vaccine. A vaccine adverse reaction or side effect is an untoward effect caused by a vaccine.

Adverse events following immunization can be classified by frequency (common, rare), extent (local, systemic), severity (mild, moderate, severe), seriousness (life-threatening, requiring hospitalization, or causing disability or death), causality, and preventability (intrinsic to vaccine, production challenge, administration error). Adverse events following immunization may be coincidental, or the vaccine may have increased the risk of the adverse event. Many adverse events following vaccination are coincidental; they are temporally related to vaccination but occur by chance without a causal relationship.

To assess causality of an adverse event following immunization, a great deal of information is generally needed. An adverse health event can be causally attributed to a vaccine more readily if:

- The health problem occurs during a plausible time period following vaccination.
- The adverse event corresponds to adverse events previously associated with the vaccine.
- The event is consistent with a specific clinical syndrome where association with vaccination has strong biologic plausibility (e.g., anaphylaxis) or where the syndrome is known to occur following the natural disease.
- A laboratory result confirms the association (e.g., isolation of vaccine-strain varicella virus from skin lesions of a patient with rash).
- The event recurs with re-administration of the vaccine in the same patient.

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- A controlled clinical trial or epidemiologic study shows greater risk of a specific adverse event among vaccinated versus unvaccinated groups.
- A finding linking an adverse event to a vaccine has been confirmed by other studies.

Importance of Vaccine Safety Programs

Like any medical product, no vaccine is completely without risk. While most vaccine adverse reactions are minor and self-limited, some vaccines have been associated with extremely rare but serious health effects. The following key considerations underscore the need for an active and ongoing vaccine safety program.

Decreases in Disease Risks

Most vaccine-preventable diseases are at or near record lows. Many people no longer see reminders of the severity and potential life-threatening complications of these diseases. Parents and providers in the United States may be more likely to know someone who has experienced an adverse event (an event that may or may not be related to vaccination) following vaccination than they are to know someone who has experienced a vaccine-preventable disease. The success of vaccination has led to increased public attention on potential health risks associated with vaccines.

Public Confidence

Maintaining public confidence in vaccines is critical to prevent a decline in vaccination coverage that can result in outbreaks of disease. While most parents understand the benefits of vaccination and have their children vaccinated, some parents have concerns about the safety of vaccines. Despite high national vaccination coverage, there are local areas of low coverage that allow outbreaks of vaccine-preventable diseases to occur, often the result of parents refusing or delaying their children's vaccinations because of concerns about vaccine safety.

A higher standard of safety is generally expected of vaccines than of other medical interventions because, in contrast to most pharmaceutical products that are administered to ill persons for treatment purposes, vaccines are generally administered to healthy persons to prevent disease. Public tolerance for adverse reactions related to products given to healthy persons, especially healthy infants and children, is substantially less than for reactions to products administered to persons who are already sick. Less tolerance of risk associated with vaccines requires close monitoring and timely assessment of vaccine adverse events to help distinguish true vaccine adverse reactions from coincidental unrelated events and to help maintain public confidence in vaccination.

Balancing Immunization Recommendations with Risk of Disease

Public health recommendations for immunization programs and practices represent a dynamic balance of risks and benefits. Vaccine safety monitoring is necessary to accurately weigh this balance and adjust immunization policy. For example, monitoring of smallpox and oral polio vaccines being used in the United States as these diseases neared global eradication found complications associated with each vaccine that exceeded the risks of the diseases. This observation led to discontinuation of routine smallpox vaccination in the United States prior to global eradication and a shift from the oral poliovirus vaccine to a safer, inactivated poliovirus vaccine.

Assessing and Monitoring Vaccine Safety

Prelicensure

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in sequentially phased human clinical trials prior to licensure. Phase I human clinical trials usually involve anywhere from 20 to 100 volunteers and focus on detecting serious adverse reactions. Phase II trials generally enroll hundreds of volunteers and determine the best dose and number of doses for effectiveness and safety. Phase I and II trials might take a few months or last up to three years. Phase III trials involve a few hundred to several thousand volunteers and may last several years. Some volunteers receive another vaccine that has already been licensed, allowing researchers to compare one vaccine with another for adverse health effects, anything from a sore arm to a serious reaction. If the vaccine is shown to be safe and effective in a Phase III trial, the manufacturer applies for a license from the Food and Drug Administration (FDA). During the application process, the FDA reviews the clinical trial results, product labeling, and manufacturing plant and protocols. If approved, the FDA licenses the vaccine itself (product license) and licenses the manufacturing plant where the vaccine will be produced (establishment license).

Postlicensure Vaccine Safety Monitoring

Monitoring for adverse reactions is essential even after vaccine licensure because rare reactions, delayed reactions, or reactions among subpopulations may not be detected before vaccines are licensed. While Phase III trials include enough persons to identify certain potential adverse reactions, such as injection-site reactions and fever, the comparatively small number of patients enrolled in these trials generally limits detection of rare adverse reactions, including those occurring many months after the vaccine is administered. For example, in the pentavalent

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rotavirus vaccine trials, 70,000 infants received either vaccine or placebo, permitting evaluation of safety with respect to intussusception, which occurs so rarely that large trials would be needed to detect even a single occurrence.

The objectives of postlicensure vaccine safety monitoring activities are to:

- Identify rare adverse reactions not detected during prelicensure studies.
- Monitor increases in known adverse reactions after vaccination.
- Identify risk factors or preexisting conditions that may be associated with a higher incidence of adverse reactions.
- Identify whether particular vaccine lots have unusually high rates or certain types of reactions.
- Identify possible adverse events that might warrant further study to establish the association of an adverse event with vaccination or affect current immunization recommendations.

To achieve these objectives, as part of the FDA approval process, some vaccines enter Phase IV clinical trials (postmarketing studies) to obtain information beyond what Phases I through III provided. Also, fundamental to preventing safety problems is the assurance that all vaccines are made using good manufacturing practices and undergo lot testing for purity and potency. Manufacturers must submit samples of each vaccine lot and results of their own tests for purity and potency to the FDA before releasing vaccine lots for public use. Several monitoring systems are used in the United States to detect and study adverse events following immunization. CDC and the FDA use four main systems to monitor the safety of vaccines in use: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Postlicensure Rapid Immunization Safety Monitoring System (PRISM), and the Clinical Immunization Safety Assessment (CISA) project.

Vaccine Adverse Event Reporting System (VAERS)

The National Childhood Vaccine Injury Act of 1986 mandates that vaccine providers and vaccine manufacturers report certain adverse events following vaccinations. This led to the creation of the Vaccine Adverse Event Reporting System (VAERS) in 1990. VAERS is a national, spontaneous surveillance system, jointly administered by CDC and the FDA. It receives about 30,000 reports per year, a seemingly large number, but relatively small considering that millions of doses of vaccines are administered yearly to adults and children in the United States.

Vaccine providers are required by law to report:

- Any adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine
- Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination (vaers.hhs.gov/resources/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf)

Vaccine providers are encouraged to report:

- Any adverse event that occurs after the administration of a U.S. licensed vaccine, whether it is or is not clear a vaccine caused the adverse event
- Vaccine administration errors

Vaccine manufacturers are required to report all adverse events that come to their attention.

VAERS collects information about the patient, the vaccine(s) administered, the adverse event, and the person reporting the event. All reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms and entered into the VAERS database. Attempts are made to obtain additional medical information for all reports classified as a serious adverse event, including hospitalization or prolongation of hospitalization (if a vaccine was administered in the hospital), life-threatening illness, permanent disability, congenital deformity, or death. For these reports, letters to obtain information about recovery status are also sent to the persons reporting the events. All patient-identifying information submitted to VAERS, directly or as part of follow-up activities, is protected by strict confidentiality requirements.

VAERS has limitations inherent to spontaneous reporting systems. Also, VAERS is not designed to determine if a vaccine caused an adverse event, and additional studies are required to confirm possible safety signals detected by VAERS.

Despite these limitations, VAERS has been able to fulfill its primary purpose of detecting new or rare vaccine adverse events, increases in rates of known adverse reactions, and patient risk factors for types of adverse reactions. In addition, VAERS often provides early safety data after a vaccine is licensed or during a public health emergency. De-identified VAERS reports can be viewed on the VAERS web page.

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Vaccine Safety Datalink (VSD)

CDC established the VSD to address gaps in the scientific knowledge of rare and serious adverse events following vaccination. This project involves partnerships with large, integrated health plans to monitor vaccine safety. Each participating plan uses its electronic health records and immunization information systems to contribute to a large, linked database. These participating health plans serve more than 10 million people annually, representing nearly 3% of the U.S. population, and contain records for more than 180 million vaccinations, enabling the VSD to study possible rare adverse events. Available information includes vaccination data (vaccine type, vaccination date, concurrent vaccinations), health conditions, medical encounter types (outpatient, inpatient, urgent care), birth data, and census data.

The VSD allows for planned immunization safety studies, as well as timely investigations of hypotheses arising from review of medical literature, reports to VAERS, changes in immunization schedules, or the introduction of new vaccines. A rapid cycle analysis conducted by the VSD enables CDC and its co-investigators to monitor adverse events following vaccination for a specific disease in near real time, so the public can be informed quickly of possible risks.

Data files used in VSD studies remain at each participating site; specific data are pulled together for each analysis and do not contain personal identifiers.

Clinical Immunization Safety Assessment (CISA) Project

The CISA Project's mission is to improve the understanding of adverse events following immunization at the individual patient level. The CISA Project provides consultation to public health partners in the United States and conducts high-quality clinical research, including clinical trials across life stages, on the safety of influenza vaccines and the safety of vaccines in special populations. All clinical research studies conducted by the CISA Project are registered on clinicaltrials.gov.

The goals of the CISA Project are to:

- Serve as a vaccine safety resource for U.S. healthcare providers with complex vaccine safety questions about a specific patient to assist with immunization decision-making
- Assist CDC / Health and Human Services (HHS) and partners in evaluating emerging vaccine safety issues
- Conduct clinical research studies to better understand vaccine safety and identify preventive strategies for adverse events following immunization

Postlicensure Rapid Immunization Safety Monitoring System (PRISM)

FDA's PRISM uses a computer algorithm to conduct active vaccine safety surveillance. A cooperative effort between FDA's Center for Biologics Evaluation and Research and four health care and medical insurance organizations, PRISM analyzes health insurance claims data for potential vaccine safety signals. PRISM is also used to evaluate safety issues in targeted groups and to evaluate specific health conditions or outcomes.

PRISM is part of FDA's Sentinel Initiative, a national electronic system for medical product safety surveillance.

Vaccine Injury Compensation Program (VICP)

A main impact of the National Childhood Vaccine Injury Act (NCVIA) was the creation of the VICP. This program, administered by the Health Resources and Services Administration, provides financial compensation to persons who are found to have been injured by a vaccine covered by the program. VICP provides liability protection for vaccine manufacturers and administrators. Compensation is provided to persons who experience certain vaccine adverse reactions on a no-fault basis. No fault means persons filing claims are not required to prove negligence on the part of either the health care provider or manufacturer to receive compensation. The program covers most vaccines routinely given in the United States.

Claims may be based on a *Vaccine Injury Table*, which lists conditions associated with each vaccine and provides a rebuttable presumption of causation, or by proving by preponderant evidence that the vaccine caused an injury not listed in the table. The *Vaccine Injury Table* was developed initially by Congress to provide swift compensation to persons possibly injured by vaccines. The table continues to be amended by the Secretary of the Department of Health and Human Services (DHHS) to better reflect current science as more information becomes available from research on vaccine adverse reactions.

During the 2009 H1N1 influenza pandemic, the federal government implemented another compensation program, the Countermeasures Injury Compensation Program (CICP). This program provides compensation for certain persons who are seriously injured by countermeasures as specified in a declaration by the Secretary of DHHS. Both bioterrorism and pandemic countermeasures are covered. Covered countermeasures within the CICP are not limited to vaccines and may include certain medications or devices used to diagnose, prevent, or treat the covered condition. People have one year from receipt of the countermeasure to file a claim with the CICP.

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The Vaccination Provider's Role in Vaccine Safety

Even though the testing phases to approve a vaccine can take years before the vaccine can be licensed and vaccines are monitored continually for safety and effectiveness, vaccination providers also play a key role in helping to ensure the safety and efficacy of vaccines. Vaccine providers are responsible for proper vaccine storage, handling, and administration; timing and spacing of vaccine doses; observation of contraindications and precautions; and reporting of adverse events following vaccination to VAERS. Providers are also responsible for communicating with patients and parents about vaccine benefits and risks and for managing of vaccine adverse reactions.

Benefit and Risk Communication

Patients and parents should be informed of the benefits and risks of vaccines in understandable language. An opportunity for questions should be provided before each vaccination. Discussion of the benefits and risks of vaccination is sound medical practice and is required by law.

The NCVIA legally requires vaccine information statements (VISs) be provided to the patient, parent, guardian, or legal representative by vaccine providers before each dose of vaccine. Documentation that the VIS was provided is also required. Copies of VISs are available from state and local immunization programs or can be downloaded from https://www.cdc.gov/vaccines/hcp/vis/index.html. Translations of VISs into languages other than English are available from some immunization programs and the Immunization Action Coalition and are available at https://immunize.org/vis/.

Vaccine providers should anticipate questions parents or patients may have regarding the need for or safety of vaccination. Some people may refuse certain vaccines or even reject all vaccinations. Some people might have religious or personal objections to vaccination. It is essential that health care providers have a basic understanding of how patients view vaccine risk and develop effective approaches to deal with vaccine safety concerns when they arise. When a parent or patient initiates discussion of a vaccine concern, the provider should discuss the specific concern and use appropriate language to provide facts. Effective, empathic vaccine risk communication is essential in responding to misinformation and concerns. It is important to remind parents that state laws for school or childcare entry might require

unvaccinated children to stay home from school during outbreaks. For patients who question or refuse vaccination, identifying common ground and discussing measures for deferring vaccination are more effective public health strategies than excluding these patients from a practice.

VISs provide an outline for discussing vaccine benefits and risks. While documentation of VIS distribution is required, additional information about discussions should be documented in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal). Such documentation might reduce any potential liability if a vaccine-preventable disease occurs in the unvaccinated patient.

Managing Adverse Reactions after Vaccination

Health care providers should be familiar with identifying immediate-type allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration. While severe allergic reactions to vaccines are rare, occurring at an approximate rate of one to two for every 1 million doses of vaccine administered, all vaccine providers should have emergency procedures in place and be prepared to provide emergency care for a person who experiences an anaphylactic reaction. This includes the ability to administer epinephrine and certification in cardiopulmonary resuscitation (CPR). Equipment for maintaining an airway should be available for immediate use. All health care personnel should be familiar with their office emergency plan.

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