Chapter 21: Surveillance for Adverse Events Following Immunization

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I. Public health importance

Immunizations have reduced the incidence of many vaccine-preventable diseases in the United States (and many other countries) by more than 95% compared with the prevaccine era (Table 1).[1, 2] For example, wild-type paralytic poliomyelitis has been eliminated from the Western Hemisphere[3] and endemic rubella virus transmission in the United States has ceased.[4] As the proportion of the vaccinated population increases, however, there is also an increase in the number of persons who experience an adverse event following vaccination—an event due either to reactions caused by the vaccination or to coincidental events not caused by the vaccination (e.g., an upper respiratory infection occurring after inactivated influenza vaccine). In recent years, the annual number of reports to the national Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system that monitors vaccine safety, has exceeded the total number of reports of routine childhood vaccine-preventable diseases (excluding varicella and pertussis). This historic decrease in disease rates is shown in Table 1. With the lower rates of disease, benefits of vaccination may be overshadowed by reports of vaccine adverse events, and media attention may result in loss of public confidence in the vaccine. This can result in resurgence of vaccine-preventable diseases, as experienced in several countries with pertussis[5–7] and in the United Kingdom with mumps.[8]

One of the best ways to enhance our understanding of vaccine safety is to improve surveillance for vaccine adverse events.

Vaccinations are usually administered to healthy persons and often are mandated; therefore, they are held to a higher standard of safety than other medications.[9] However, as with all medications, no vaccine is perfectly safe or effective. Vaccines can induce minor adverse events such as fever or local reactions at the injection site. Very rarely, they can induce serious adverse events such as seizures or severe allergic reactions. To reduce the occurrence of vaccine adverse events and maintain public confidence in vaccines, it is important to improve the understanding of vaccine safety, and, thereby, foster the development and use of safer vaccines.[10] One of the best ways to enhance our understanding of vaccine safety is to improve surveillance for vaccine adverse events.

Table 1. Decline in vaccine-preventable disease morbidity in the United States during the 20th century*

Disease	Baseline 20th century morbidity	2005 morbidity	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	25,616	>82
Tetanus	1,314	27	>97
Poliomyelitis	16,316	1	>99
Measles	503,282	66	>99
Mumps	152,209	314	>99
Rubella	47,745	11	>99
Congenital rubella	823	1	>99
Haemophilus influenzae disease (<5 years of age)	20,000 (estimated)	226 (serotype b or unknown serotype)	>98

**See references 1,2*

II. Background

Vaccines, like other pharmaceutical products, undergo extensive testing and review for safety, immunogenicity, and efficacy in trials with animals and humans before they are licensed. Because these trials usually include a placebo control or comparison group, it is possible to ascertain which local or systemic reactions were actually caused by the vaccine. However, prelicensure trials are relatively small—usually limited to a few thousand subjects—and usually last no longer than a few years. In addition, they may be conducted in populations less demographically, racially, and ethnically diverse than those in which the vaccine is ultimately used. During prelicensure testing, detection of uncommon adverse events with delayed onset is not highly sensitive. Postlicensure or postmarketing surveillance—the continuous monitoring of vaccine safety in the general population after licensure—is needed to identify and evaluate such adverse events.[9]

The history of postmarketing surveillance for vaccine adverse events in the United States has been reviewed elsewhere.[10] From 1978 through 1990, the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA) divided the responsibility for postmarketing surveillance of vaccines in the United States. Reports of adverse events following administration of vaccines purchased with public funds were submitted to CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI); the FDA received reports of adverse events after administration of vaccine purchased with private funds. Although collaboration was maintained between the two agencies, the use of different reporting forms and reporting requirements made combined analysis difficult.

The passage of the National Childhood Vaccine Injury Act of 1986 (NCVIA) and its mandatory reporting requirement was an opportunity to correct these shortcomings. With enactment of the NCVIA, vaccine manufacturers licensed in the United States and healthcare providers who administer vaccines are required by law to report certain serious adverse events following specific vaccinations.[11] The NCVIA's purposes were to compensate persons who may have been injured by vaccines and to reduce threats to the stability of the immunization program (liability concerns, inadequate supply of vaccine, rising vaccine costs).[12] The NCVIA stipulates the vaccines, the adverse events, and the time of occurrence after vaccination for which reporting is required (Table 2). It also requires that any event listed in the manufacturer's package insert as a contraindication to subsequent doses of the vaccine be reported. In 1990, the Department of Health and Human Services (DHHS) directed that a single system be established for the collection and analysis of reports of adverse events following immunization.[13] This led to the establishment of the Vaccine Adverse Event Reporting System (VAERS), which is cosponsored by CDC and FDA. Programs such as VAERS exist in many countries; some monitor vaccines separately from other drug products, but many are joint programs. These programs form the cornerstone of drug safety monitoring efforts around the world.

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap	Anaphylaxis or anaphylactic shock	7 days
	Brachial neuritis	28 days
	Any acute complications or sequelae (including death) of above events	Not applicable
	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pertussis in any combination; DTaP, DTP, DTP-Hib, Tdap	Anaphylaxis or anaphylactic shock	7 days
	Encephalopathy (or encephalitis)	7 days
	Any acute complications or sequelae (including death) of above events	Not applicable
	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Measles, mumps and rubella in any combination; MMR, MR, M, MMRV, R	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	15 days
	C. Any acute complications or sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rubella in any combination; MMR, MMRV, MR, R	A. Chronic arthritis	42 days
	B. Any acute complications or sequelae (including death) of above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Measles in any combination; MMR, MMRV, MR, M	A. Thrombocytopenic purpura	7-30 days
	B. Vaccine-strain measles viral infection in an immunodeficient recipient	6 months
	C. Any acute complications or sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Oral Polio (OPV)	A. Paralytic polio	
	– in a non-immunodeficient recipient	30 days
	– in an immunodeficient recipient	6 months
	– in a vaccine-associated community case	Not applicable
	B. Vaccine-strain polio viral infection	
	– in a non-immunodeficient recipient	30 days
	– in an immunodeficient recipient	6 months
	– in a vaccine-associated community case	Not applicable
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Inactivated Polio (IPV)	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any acute complications or sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hemophilus influenzae type b (conjugate)	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Varicella	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Rotavirus	A. Intussusception	30 days
	B. Any acute complications or sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pneumococcal conjugate	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis A	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Influenza	Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

* ***Effective date: July 01, 2005.*** *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 caused 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.*

Reportable Events Table Definitions

Anaphylaxis and anaphylactic shock. Anaphylaxis and anaphylactic shock mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse.

Brachial neuritis is defined as dysfunction limited to the upper extremity nerve plexus (i.e., its trunks, division, or cords) without involvement of other peripheral (e.g., nerve roots or a single peripheral nerve) or central (e.g., spinal cord) nervous system structures. A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is followed in days or weeks by weakness and atrophy in upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature.

Encephalopathy. For purposes of the Reportable Events Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

1. An ***acute encephalopathy*** is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).
   a. For children less than 18 months of age who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "2" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.
   b. For adults and children 18 months of age or older, an acute encephalopathy is one that persists for at least 24 hours and is characterized by at least two of the following:
      i. A significant change in mental status that is not medication related: specifically a confusional state, or a delirium, or a psychosis;
      ii. A significantly decreased level of consciousness, which is independent of a seizure and cannot be attributed to the effects of medication; and
      iii. A seizure associated with loss of consciousness.

c. Increased intracranial pressure may be a clinical feature of acute encephalopathy in any age group.

2. A "significantly decreased level of consciousness" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:
   a. Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);
   b. Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
   c. Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.

3. ***Chronic Encephalopathy*** occurs when a change in mental or neurologic status, first manifested during the applicable time period, persists for a period of at least 6 months from the date of vaccination. Individuals who return to a normal neurologic state after the acute encephalopathy shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequelae of the acute encephalopathy. If a preponderance of the evidence indicates that a child's chronic encephalopathy is secondary to genetic, prenatal or perinatal factors, that chronic encephalopathy shall not be considered to be a condition set forth in the Table. An encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known).
4. ***Chronic Arthritis***. For purposes of the Reportable Events Table, chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:
   a. Medical documentation, recorded within 30 days after the onset, of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and
   b. Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination.
   c. Medical documentation of an antibody response to the rubella virus.

The following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's syndrome, or blood disorders.

Arthralgia (joint pain) or stiffness without joint swelling shall not be viewed as chronic arthritis.

Sequela. The term "sequela" means a condition or event, which was actually caused by a condition listed in the Reportable Events Table.

III. Objectives of VAERS

- To detect previously unrecognized reactions from both existing and newly licensed vaccines
- To detect apparent increases or decreases in previously reported events
- To detect preexisting conditions that may promote reactions and may represent contraindications or precautions to additional doses
- To detect vaccine lots associated with unusual numbers and types of reported events
- To trigger further clinical, epidemiologic, or laboratory investigations regarding a possible causal relationship between a vaccine and adverse event
- To provide descriptive epidemiologic data on national numbers of reported adverse events following immunization (AEFI)
- To closely monitor the safety of newly licensed vaccines

Scope of reports sought

Table 2 lists the events mandated for reporting to VAERS. However, more importantly, reports should be submitted to VAERS for all serious and unusual events occurring after vaccination, in all age groups, even if the causal relationship to vaccination is uncertain. Such events include (but may not be limited to) all deaths, any life-threatening illness, an illness requiring an emergency department visit or hospitalization, prolongation of a hospital stay, or any illness resulting in a permanent disability, as well as less serious but previously unrecognized adverse events attributable to vaccination.

Reports should be submitted to VAERS for all serious and unusual events occurring after vaccination, in all age groups, even if the causal relationship to vaccination is uncertain.

The VAERS form allows description of the adverse event in narrative form by the reporter. Unlike other public health disease surveillance systems for which a distinct case definition exists, many adverse events reported to VAERS are clinical syndromes that may be poorly defined or understood or are diagnoses of exclusion. The Brighton Collaboration (http://brightoncollaboration.org) is an international voluntary collaboration whose primary aim is to develop globally accepted standardized case definitions of AEFI. These definitions are useful in defining the adverse events reported to VAERS. The term "adverse event" rather than "reaction" is used because attribution of causality to the vaccine usually is not possible. Some examples of case definitions developed by the Brighton Collaboration to date include seizure, intussusception, fever, persistent crying, nodule at injection site, and hypotonic–hyporesponsive episode. The VAERS form is designed to permit description of the adverse event, the type of vaccine(s) received, the timing of vaccination and the adverse event, demographic information about the recipient, concurrent medical illness or medications, and prior history of AEFI (see Appendix 22). Adverse events should be described as clearly as possible, with accurate timing with respect to vaccination. Additional medical records or discharge summaries are requested to be submitted if they assist in clarifying any aspects of the report

IV. Reporting to VAERS

Anyone can report any vaccine adverse event to VAERS. Healthcare providers and manufacturers are mandated by law to report certain adverse events after vaccination, and they are encouraged to report any serious or unusual event occurring after vaccination, even if they are not certain the event is causally related to a vaccine or vaccines. A table listing reportable events is available at http://www.vaers.hhs.gov/reportable.htm and is reprinted in this chapter (Table 2). Reports are also accepted from patients, parents and caregivers. Lay persons who report are encouraged to consult with a healthcare provider to ensure that information is complete and accurate and to ensure that their provider is aware of the adverse event. It is primarily by analyzing all reports in aggregate that possible causal relationships between vaccines and adverse events can be properly evaluated.

Reporting to VAERS can be done in one of three ways:

- Online through a secure website: https://secure.vaers.org/VaersDataEntryIntro.htm
- Fax a completed VAERS form to 877-721-0366

- Mail a completed VAERS form to

  VAERS
  P.O. Box 1100
  Rockville, MD 20849-1100

A VAERS reporting form, which can be copied for reporting purposes, is printed in Appendix 22. The form can also be downloaded from http://www.VAERS.hhs.gov/pdf/vaers_form.pdf or can be requested by telephone at 800-822-7967. The Vaccine Information Statements (VIS) developed by CDC for all U.S.-licensed vaccines also contain instructions on how to report adverse events to VAERS. Detailed instructions for completing the reporting form are provided below. Local health departments should follow the reporting instructions provided by their state immunization program.

Upon receipt by VAERS, reports are entered into a database, verified, and coded using a standard set of coding terms. The person reporting is sent a letter from VAERS verifying receipt of the form and is requested to supply any critical information that is missing. The FDA reviews reports of deaths and other serious events and conducts analyses of reports by vaccine lots. CDC routinely reviews selected serious outcomes (e.g., anaphylaxis, Guillain-Barré syndrome) and conducts additional analyses as needed to address specific concerns and to evaluate trends in reporting.

Completion of VAERS form and submission of reports

Instructions for completing the VAERS form are on the back of the form.

Note: *Report adverse events associated with vaccines on the VAERS form. Do not use MEDWATCH or the old MSAEFI forms to report vaccine adverse events.*

Do not report events associated with tuberculosis screening tests (Tine, PPD, or Mantoux), immune globulins, or other nonvaccine injectable medical products to VAERS. These events should be reported to the FDA's MEDWATCH program at 800-FDA-1088 (800-332-1088) or at http://www.fda.gov/medwatch/

Reporting responsibilities

Local health departments may request reporting forms from their state immunization program or obtain them from www.vaers.hhs.gov. Clinic staff at the local level are responsible for completing a VAERS report when an adverse event is suspected or occurs following immunization. As much of the requested information as possible should be obtained. Although reporting priority may be given to serious or unexpected events or unusual patterns of expected nonserious events, all clinically significant adverse events should be reported. Each report should be reviewed for completeness, accuracy, and legibility before it is sent to VAERS or to the State Health Coordinator (SHC) or VAERS Coordinator, with specific attention to the following:

- *Dates*—All dates should make chronological sense. For example, the vaccine date cannot precede the birth date, or the report date cannot precede the vaccine date. All date fields require entry of the full month, date, and year.
- *Patient name*—Verify that the patient's first and last names are correct. This check assists in identification of duplicate reports.
- *Reporter information (upper right corner of form)*—The reporter name and complete mailing address are required. Verification letters and requests for missing or follow-up information are sent to this address. Some SHCs prefer to receive and submit verification letters, requests for missing information, and related correspondence; they may delete the original reporter's name and address and insert the SHC name and address. If you do not receive a verification letter within a reasonable amount of time (e.g., 1 month), check with your SHC.

- *Critical boxes*—Certain items are crucial to the analysis of VAERS data and have been designated as critical boxes. Persons reporting will be asked to supply this information later if it is missing. Critical boxes are differentiated by a square around their respective item numbers on the form as follows:
  - Box 3: Date of birth
  - Box 4: Age of patient at the time of vaccination
  - Box 7: Narrative description of adverse events, symptoms, etc.
  - Box 8: Indicates whether a report is regarded as serious or nonserious, and identifies the most serious reports for 60-day and annual follow-up
    - Serious
      - Patient died and date of death
      - Life-threatening illness
      - Resulted in permanent disability
      - Required hospitalization and number of days hospitalized
      - Resulted in prolongation of hospitalization
    - Nonserious
      - Required emergency department or doctor visit
      - None of the above
  - Box 10: Date of vaccination (and time, if known)
  - Box 11: Date of onset of adverse event (and time, if known)
  - Box 13: All vaccines given on the date listed in Box 10, including name of vaccine, vaccine manufacturer, vaccine lot number, route and site of administration and number of previous doses given. Accurate lot information is needed to examine events occurring within specific vaccine lots.
- *Timely reporting*—All reports from the public health domain are to be sent to VAERS as they occur, especially reports of any serious event. Programs are discouraged from sending batches of reports. VAERS data are downloaded on a daily basis by the FDA and CDC. Timely reporting is essential to timely follow-up investigation.

State health coordinator responsibilities

The SHC receives VAERS reports from local health departments or immunization projects and is responsible for the following activities:

- Reviews each report for completeness (especially the critical boxes), obtains any other necessary information, and clarifies any questions about the report.
- Assigns an identifying immunization project number using the 2-letter state postal abbreviation, 2- or 4-digit representation for year, and the state numbering sequence. For example, the 57th report received in Arizona in 2006 begins with AZ, followed by 06, followed by 057, and should look like this: AZ06057. This number is entered into box 24 of the VAERS report.
- Sends the original report with the identifying number to VAERS and keeps a copy. As with local reporting, the cases should be forwarded rapidly to VAERS and not sent in a batch.

Any further correspondence about a report must include the 6-digit VAERS ID number, which is assigned by the VAERS system. Reports are entered into the VAERS database under this number. It is also helpful to have the patient's name and date of birth, if available, to help identify the specific report. VAERS maintains the confidentiality of patients' personal identifying information, consistent with the requirements of the NCVIA.

- Completes the quarterly update report that is sent by VAERS to each SHC. (Although these follow-up requests are sent quarterly, the case reports are scanned upon receipt at VAERS and available to CDC and FDA for evaluation in near real time upon request.). This report contains a list of all initial reports received during the quarter, by VAERS ID number and SHC project number, and serves as an acknowledgment of those reports. Specific missing or incomplete information for these reports is noted and completed in the appropriate boxes.

The quarterly update report also lists reports for which VAERS requests recovery status at 60 days postvaccination and at 1 year postvaccination. The SHC submits to VAERS any requested missing information, as well as follow-up recovery status information for each listed report at 60 days and 1 year postvaccination. The SHC may update any other pertinent information about these individuals, such as vaccination information or date of birth. In the case of a patient death, include date of death and supporting documentation (copies of hospital records, autopsy report, and death certificate) as available.

Quarterly reports are submitted to VAERS by mail, fax, or email.

Mail: VAERS
P.O. Box 1100
Rockville, MD 20849-1100
Fax: 877-721-0366
E-mail: info@vaers.org

- Updates VAERS with any personnel, fax, phone, or address changes. This is done by means of a quarterly e-mail request from VAERS to the state health department.

V. Evaluation of VAERS

Approximately 20,000 reports of AEFI are now received by VAERS each year. All reports are accepted and entered without case-by-case determination of whether the adverse event could have been caused by the vaccine in question. To put the number of reports of adverse events in perspective, it should be noted that each year over 200 million doses of vaccine are distributed in the United States. Additionally, the type and severity of events reported vary from minor local reactions or fever to death. Of the reports received between 1991 and 2001, 1.7% reported death as the outcome; 12.6% reported a serious nonfatal adverse event, and 85.8 % reported less serious events.[14]

From 1991 through 2001, vaccine manufacturers submitted 36.2% of the VAERS reports; 20% were from private healthcare providers. State and local health departments accounted for 27.6% of the reports, patients or parents submitted 4.2% of the reports, and 7.3% came from other sources.[14]

Direct reporting to VAERS or to the SHC by healthcare providers is encouraged, as these reports arrive on a more timely basis than those submitted to manufacturers. Manufacturers are not required to provide these reports to VAERS immediately upon receipt unless serious or unexpected events have occurred. As a result, evaluation of less serious vaccine-associated events may be delayed.

Usefulness

The data from VAERS have been used by FDA, CDC, and the Division of Vaccine Injury Compensation at the Health Resources and Services Administration (HRSA). The FDA investigates all deaths, reports classified as serious according to the Code of Federal Regulations, and certain nonserious events that have unusual characteristics. Assessments of lot-specific reporting rates are conducted weekly, using manufacturer-supplied data on lot size. The FDA has regulatory authority to withdraw a vaccine lot if it is determined that the rate of reported vaccine-associated adverse events is unusually high.

CDC has used VAERS data in analyses of the safety of acellular versus whole-cell pertussis vaccine; the rates of allergic reactions after first and second doses of measles-containing vaccines; intussuception occurring after the earlier rotavirus vaccine Rotashield®, which is no longer licensed; the safety of newly licensed vaccines such as meningococcal conjugate, the tetanus-diphtheria-acellular pertussus combined vaccine, and the human papillomavirus vaccine; the association between influenza vaccinations and Guillain-Barré syndrome; the suspected potential association between meningococcal conjugate vaccine and Guillain-Barré syndrome; evaluation of reporting efficiency; and use of safety profiles as tools for assessing

vaccine safety. VAERS data, without identifying information, are available to the public through the VAERS website (http://vaers.hhs.gov/) and are updated monthly.

VAERS data have also been used by the Institute of Medicine (IOM) Vaccine Safety Committee (http://www.iom.edu/?id=4705&redirect=0) in an extensive assessment of the causal relations between common childhood vaccines and adverse events. IOM established an independent expert committee that reviewed hypotheses about existing and emerging immunization safety concerns during 2001–2004. A focused report has been published regarding each hypothesis addressed. These IOM reports summarize the current epidemiologic evidence (including information obtained from VAERS) for causality between an immunization and a hypothesized health effect, the biologic mechanisms relevant to the adverse event hypothesis, and the significance of the issue in a broader societal context. Hypotheses reviewed and published include the following: Measles-Mumps-Rubella Vaccine and Autism,[15] Thimerosal-Containing Vaccines and Neurodevelopmental Disorders,[16] Multiple Immunizations and Immune Dysfunction,[17] Hepatitis B Vaccine and Demyelinating Neurological Disorders,[18] SV40 Contamination of Polio Vaccine and Cancer,[19] Vaccinations and Sudden Unexpected Death in Infancy,[20] Influenza Vaccines and Neurological Complications,[21] and Vaccines and Autism.[22] Executive summaries for each of these reports are available free of charge at the IOM Vaccine Safety Committee website listed above. These references may be useful to providers or public health officials who are called on to answer the public's questions on vaccine safety and the occurrence of adverse events.

Reporting sensitivity

The completeness of reporting of adverse events associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.

Like all passive surveillance systems, VAERS is subject to varying degrees of underreporting. The sensitivity of VAERS is affected by the likelihood that parents and/or vaccinees detect an adverse event, parents and/or vaccinees bring the event to the attention of their health-care provider(s), parents and/or healthcare providers suspect an event is related to prior vaccination, parents and/or healthcare providers are aware of VAERS, and that parents and/or health-care providers report the event. The completeness of reporting of adverse events associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.[23, 24]

Table 3 shows the reporting efficiency to VAERS for various adverse events. For example, the reporting efficiency for paralytic poliomyelitis following oral polio vaccine (severe event, very specific vaccine association, and very rare) was 68%, yet the reporting efficiency for rash following MMR is <1% (mild event, many causes).

Table 3 Reporting efficiency To VAERS for various adverse events

Event *	Reporting efficiency %
OPV and vaccine-associated paralytic polio	68%
Rotavirus vaccine and intussusception	47%
MMR + MR and seizures	37%
DTP and seizures	24%
MMR and thrombocytopenia	4%
DTP and hypotonic hyporesponsive episodes	3%
MMR and rash	<1%

**See References 23,24*

Limitations of VAERS

The limitations of VAERS, which are common to many passive reporting systems, should be considered in interpreting VAERS data.

Dose distribution data. An important limitation is that vaccine dose distribution data used to calculate reporting rates are not age or state specific. Dose distribution information, derived from Biologics Surveillance data provided by vaccine manufacturers, also does not track the amount of vaccine actually administered.

Quality of information. Since there are no strict guidelines for reporting, and because anyone may submit reports to VAERS, the accuracy and amount of information vary significantly between reports.

Underreporting. Underreporting may occur for several reasons. These include limitations in detection of an event, lack of recognition of association between vaccine and event, or failure to submit a report. Underreporting can affect the ability of VAERS to detect very rare events, although clinically serious events are more likely to be reported than non-serious events.[23]

Biased and stimulated reporting. Reports to VAERS may not be representative of all adverse events that occur. Events that occur within a few days to weeks of vaccine administration are more likely to be submitted to VAERS than events with a longer onset interval. Media attention to particular types of medical outcomes can stimulate reporting, as occurred after the initial 1999 *Morbidity and Mortality Weekly Report (MMWR)* publication describing reports of intussusception associated with rotavirus vaccine.

Confounding by drug and disease. Many reports to VAERS describe events that may have been caused by medications or underlying disease processes. Many adverse event reports encompass clinical syndromes that are poorly defined, not clearly understood, or represent diagnoses of exclusion (e.g., sudden infant death syndrome). Often multiple vaccines are administered at the same visit, making attribution of causation to a single vaccine or antigen difficult.

Inability to determine causation. VAERS reports are usually not helpful in assessing whether a vaccine actually caused the reported adverse events because they lack either unique laboratory findings or clinical syndromes necessary to draw such conclusions.[9] Reports to VAERS are useful for generating hypotheses, but controlled studies are necessary to confirm any hypotheses generated by VAERS observations.[9, 25–27]

VI. Enhancing surveillance

Several activities can be undertaken to improve the quality of VAERS as a surveillance system.

Improving quality of information reported

At the state and local levels, VAERS forms should be reviewed for completeness and accuracy. The reporter should be contacted if any information is missing. For death and serious outcomes after vaccination, efforts should be made to obtain additional documentation (e.g., hospital discharge summaries, laboratory reports, death certificates, autopsy reports). The VAERS staff contacts reporters and parents or vaccine recipients routinely to obtain missing information or to correct inaccurate information for all reports of deaths, serious adverse events, and selected clinically significant events.

Evaluation of system attributes

Surveys have been conducted to assess the knowledge, attitudes, and beliefs of both private and military healthcare providers about reporting to VAERS. Although 90% of pediatricians had knowledge of VAERS, only 55% of internal medicine physicians were familiar with it. Approximately 40% of healthcare providers had identified at least one adverse event after immunization, but only 19% stated that they had ever reported to VAERS. Vaccine Information statements (VIS) were the most common source used to learn about VAERS.[28]

Promoting awareness

Current outreach and education efforts to promote VAERS include general information brochures in English and Spanish and an online public use data set (http://www.vaers.hhs.gov/info.htm). Continuing Education articles for healthcare professionals are periodically published or posted on the VAERS website. A Surveillance Summary for VAERS data covering 1991–2001 was published in 2003 and is available at http://www.cdc.gov/MMWR/preview/MMWRhtml/ss5201a1.htm.

The VAERS contact information is provided on all VISs that are to be handed out at each vaccination visit to persons receiving a vaccine that is covered by the Vaccine Injury Compensation Program (i.e., is listed on the Vaccine Injury Table). VIS use is strongly encouraged for all vaccines, including those not covered by the Vaccine Injury Compensation Program.

Despite its limitations, VAERS is useful in that it generates signals that trigger further investigations.

To complement VAERS' role in hypothesis generation, CDC created the Vaccine Safety Datalink (VSD) project in 1990 to test and validate hypothesized vaccine adverse events.[29] The VSD links computerized vaccination and medical records for approximately 5.5 million persons (2% of the total U.S. population) at eight geographically diverse health maintenance organizations (HMOs). Because the databases are usually generated during routine administration of the HMO, the problems of underreporting or recall bias are minimized. Because these programs have enrollees numbering from thousands to millions, large cohorts may be assembled to examine less frequent adverse events. Denominator data and control groups are also readily available. Hence the VSD provides an economical and rapid means of generating and testing hypotheses related to vaccine safety.

Despite its limitations, VAERS is useful in that it generates signals that trigger further investigations. VAERS can detect unusual increases in previously reported events, and it indicates the number of suspected adverse reactions reported nationwide. The sentinel role of VAERS is particularly significant for newly licensed vaccines, as evidenced by the detection of intussusception following introduction of rhesus–human rotavirus reassortant tetravalent vaccine in 1999. Although manufacturers are now routinely asked to conduct postlicensure studies designed to collect additional safety data for large numbers of vaccine recipients, the need for a national postlicensure surveillance system remains. Like pre-licensure studies, postlicensure studies are generally not large enough to detect rare adverse events.

VII. The National Vaccine Injury Compensation Program

The NCVIA established the National Vaccine Injury Compensation Program to provide compensation for certain AEFI. VICP is not related to VAERS and is a separate government "no-fault" system to compensate individuals whose injuries may have been caused by any routinely recommended childhood vaccines. Reporting an event to VAERS does not automatically result in the filing of a claim with the VICP. A claim for compensation must be filed directly with VICP. The Vaccine Injury Compensation Program website (http://www.hrsa.gov/vaccinecompensation/table.htm) lists specific injuries or conditions and time frames following vaccination that may be compensated under the VICP.[11, 30]

The toll-free number for the Vaccine Injury Compensation Program is 800-338-2382. Further information can be obtained by visiting their website at http://www.hrsa.gov/vaccinecompensation/ or by writing to National Vaccine Injury Compensation Program, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, MD 20857.

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