

Chapter 21: Surveillance for Adverse Events Following Immunization Using the Vaccine Adverse Event Reporting System (VAERS)

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I. Public health importance

Vaccination is one of the ten great public health achievements of the 20th century.¹ Vaccines have reduced the incidence of many vaccine-preventable diseases in the United States by more than 98% compared with the prevaccine era.^{2,3} This historic decrease in disease rates is shown in Table 1.

Vaccinations are usually administered to healthy persons and often are mandated; therefore, they are held to a higher standard of safety than other medical products.⁴ However, as with all medical products, no vaccine is perfectly safe or effective. Vaccines can cause minor adverse effects such as fever or local reactions at the injection site. Rarely, they can cause serious adverse effects such as febrile seizures or severe allergic reactions. Adverse events (AE) can also occur coincidentally after vaccines (i.e. they would have occurred in the absence of vaccination). To reduce the occurrence of vaccine AE and maintain public confidence in vaccines, it is important to improve the understanding of vaccine safety. Robust vaccine safety monitoring may foster the discovery of adverse events associated with vaccination, and thus the development and use of safer vaccines and recommendations to minimize the risk of AE after vaccination (e.g., define new recommendations, contraindications and precautions).⁵ One way to enhance our understanding of vaccine safety is to improve surveillance for vaccine AE.

Table 1. Decline in vaccine-preventable disease morbidity in the United States during the 20th century^{2,3}

Disease	Baseline 20th century total cases	2009 total cases	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	16,858	>88
Tetanus	1,314	18	>98
Poliomyelitis (paralytic)	16,316	1	>99
Measles	503,282	71	>99
Mumps	152,209	1991	>98
Rubella	47,745	3	>99
Congenital rubella	823 (estimated)	2	>99
<i>Haemophilus influenzae</i> disease (<5 years of age)	20,000 (estimated)	213 (serotype b or unknown serotype)	>98

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 in the United States. 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, precensure 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. Persons with certain health conditions, such as pregnancy, may be excluded

from the trials. Prelicensure trials usually do not have the ability to detect rare AE or AE with delayed onset. Postlicensure or postmarketing surveillance—the continuous monitoring of vaccine safety in the general population after licensure—is needed to identify and evaluate risk for such AE after vaccination.⁴

With the passage of the National Childhood Vaccine Injury Act of 1986 (NCVIA) healthcare providers who administer vaccines are required by law to report certain AE following specific vaccinations.⁶ 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 (e.g., liability concerns, inadequate supply of vaccine, rising vaccine costs).⁷ The NCVIA stipulates the vaccines, the AE, and the time of occurrence after vaccination for which reporting by healthcare providers 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 by healthcare providers. 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 AE following immunization.⁸ This led to the establishment of the Vaccine Adverse Event Reporting System (VAERS), which is cosponsored by CDC and FDA. Spontaneous reporting systems for AE 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 and vaccine safety monitoring efforts around the world.

Table 2. VAERS Table of Reportable Events Following Vaccination*~

Vaccine/Toxoid	Event and interval from vaccination
Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Brachial neuritis (28 days) C. Any acute complications or sequelae (including death) of above events (interval— not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)
Pertussis in any combination; DTaP, DTP, DTP-Hib, Tdap, P, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Encephalopathy or encephalitis (7 days) C. Any acute complications or sequelae (including death) of above events (interval— not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)
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 (interval— not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— 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 (interval— not applicable) C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— 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 (interval— not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)

Table 2. VAERS Table of Reportable Events Following Vaccination*~

Vaccine/Toxoid	Event and interval from vaccination
Oral Polio (OPV)	<p>A. Paralytic polio</p> <ul style="list-style-type: none"> • in a non-immunodeficient recipient (30 days) • in an immunodeficient recipient (6 months) • in a vaccine-associated community case (interval— not applicable) <p>B. Vaccine-strain polio viral infection</p> <ul style="list-style-type: none"> • in a non-immunodeficient recipient (30 days) • in an immunodeficient recipient (6 months) • in a vaccine-associated community case (interval— not applicable) <p>C. Any acute complication or sequelae (including death) of above events (interval— not applicable)</p> <p>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)</p>
Inactivated Polio -IPV, DTaP-IPV, DTaP-IPV/HIB, DTaP-HepB-IPV	<p>A. Anaphylaxis or anaphylactic shock (7 days)</p> <p>B. Any acute complication or sequelae (including death) of the above event (interval— not applicable)</p> <p>C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)</p>
Hepatitis B in any combination- HepB, HepA-HepB, DTaP-HepB-IPV, Hib-HepB	<p>A. Anaphylaxis or anaphylactic shock (7 days)</p> <p>B. Any acute complications or sequelae (including death) of the above event (interval— not applicable)</p> <p>C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)</p>
<i>Hemophilus influenzae</i> type b in any combination (conjugate)- Hib, Hib-HepB, DTP-Hib, DTaP-IPV/Hib	Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)
Varicella in any combination- VAR, MMRV	Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)
Rotavirus (monovalent or pentavalent) RV1, RV5	Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— 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 (interval— 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 (interval— 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 (interval— see package insert)
Meningococcal - MCV4, MPSV4	Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)
Human Papillomavirus (Quadrivalent or Bivalent)- HPV4, HPV2	Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval— see package insert)

* **Effective date: 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, healthcare professionals are encouraged to report any clinically significant or unexpected events (even if 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.

~ See the end of this chapter for the Reportable Events Table definitions

For a list of vaccine abbreviations, see <http://www.cdc.gov/vaccines/recs/acip/vac-abbrev.htm>

For a link to the Reportable Events Table online, see <http://www.vaers.hhs.gov/reportable.htm>

III. Objectives of VAERS

The objectives of VAERS are to:

1. Detect new, unusual, or rare vaccine AE
2. Assess the safety of newly licensed vaccines
3. Identify vaccine lots with increased numbers or types of reported AE
4. Identify potential risk factors in vaccinees for particular types of AE
5. Monitor trends in known AE, particularly increases
6. Rapidly respond to vaccine safety concerns or public health emergencies

Scope of reports sought

The Reportable Events Table (Table 2) lists the events mandated for healthcare providers to report to VAERS. In addition, healthcare providers should submit reports to VAERS for all clinically significant AE 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 a hospitalization, prolongation of a hospital stay, or any illness resulting in a permanent disability, and congenital anomalies, as well as less serious AE of concern to the reporter. The VAERS form requests information about the adverse event(s), the type of vaccine(s) received, the timing of vaccination before the AE, demographic information about the recipient, concurrent medical illness or medications, and prior medical history and history of prior AE (see Appendix 22). The VAERS form allows description of the AE in a narrative format by the reporter. AE 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 by the VAERS staff during follow-up for reports of serious AE.

IV. Reporting to VAERS

Anyone can report any vaccine AE to VAERS. As described above, healthcare providers are mandated by law to report certain AE after vaccination, and they are encouraged to report any clinically significant event occurring after vaccination, even if they are not certain the event is causally related to a vaccine(s). As previously stated, a table listing required vaccine 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 vaccine manufacturers, public health providers, patients, parents and caregivers. Persons who are not healthcare providers 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 AE. Manufacturers are required to report to VAERS all adverse events made known to them for any US licensed vaccine.

Reporting to VAERS can be done in one of three ways, but online reporting (i.e., web-based reporting) is strongly preferred since it allows for quicker receipt and processing of the information:

- Online through a secure website: <https://vaers.hhs.gov/esub/step1> (exit site)
Or
- Fax, a completed VAERS form to 877-721-0366
Or
- 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://vaers.hhs.gov/resources/vaers_form.pdf or can be requested by telephone at 800-822-7967. The Vaccine Information Statements (VIS) (available at <http://www.cdc.gov/vaccines/pubs/vis/default.htm>) developed by CDC for all U.S.-licensed vaccines and given to patients at the time of vaccination also contain instructions

on how to report AE 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.

Completion of VAERS form and submission of reports

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

Note: Report AE associated with vaccines on the VAERS form. Do not use MEDWATCH forms to report vaccine AE.

Do not report events associated with tuberculosis screening tests (Tine, PPD, or Mantoux), immune globulins, or other nonvaccine 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 report AEs online at www.vaers.hhs.gov. Clinic staff at the local level are responsible for completing a VAERS report when an AE 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 non serious events, all clinically significant AE 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, day, 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. Any person reporting other than manufacturer or state immunization program staff is sent a mailed letter from VAERS verifying receipt of the form and is requested to supply any critical information that was missing from the VAERS report. State Immunization program staff are sent quarterly reports via Epi-X (<http://www.cdc.gov/epix/>) which acknowledge report receipt and request missing information. In order to receive reports via Epi-X, SHC must first contact Epi-X at epiXhelp@cdc.gov to obtain a digital certificate to gain access to the secure system.
- 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. As stated previously, reports submitted by States receive verification letters and requests for missing information via Epi X quarterly reports
- *Critical boxes*— Certain items on the VAERS form are crucial to the analysis of VAERS data and have been designated as critical boxes (data fields). 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 AE, symptoms, etc.
 - Box 8: Indicates whether a report is regarded as serious or non serious, and identifies the most serious reports for 60-day and annual follow-up
 - Serious (serious status is based on the Code of Federal regulations (see <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=600.80>))

- Patient died and date of death
- Life-threatening illness (based on the judgment of the reporter)
- 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 AE (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 assessment of vaccine safety concerns and follow-up investigation.

State Health Coordinator (SHC) or VAERS Coordinator responsibilities

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

- Registers with Epi-X at epiXhelp@cdc.gov so that they can receive quarterly report summaries of the VAERS reports that they submitted.
- 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 2011 begins with AZ, followed by 11, followed by 057, and should look like this: AZ11057. 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 via Epi-X 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. Responses to quarterly report questions can be submitted to VAERS by mail, fax, or email.
- Update 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

VAERS reports are received and processed by staff at the VAERS contract site. Upon receipt by VAERS, reports are entered into a database, and trained staff use a standard set of coding terms from the Medical Dictionary for Regulatory Affairs (MedDRA) (<http://www.meddrasso.com/>) to code the adverse event(s); a report may include more than one AE. FDA and CDC medical officers and vaccine safety experts review reports of deaths and other serious events and conduct other analyses to address specific safety concerns and to evaluate trends in reporting. FDA also conducts analysis of reports by vaccine lots. Although all serious reports are reviewed, it is primarily by analyzing all reports in aggregate that possible causal relationships between vaccines and AE can be properly detected and assessed. When vaccine safety concerns are detected in VAERS they almost always require further assessment in other systems such as the Vaccine Safety Datalink (VSD) (see below).

Approximately 28,000 US reports of AE following immunization (AEFI) are now received by VAERS each year (CDC, unpublished data). All reports are accepted and entered without case-by-case determination of whether the AE could have been caused by the vaccine in question. To put the number of reports of AE in perspective, it should be noted that each year over 220 million doses of vaccine are distributed in the United States (CDC unpublished data). Additionally, the type and severity of events reported vary from minor local reactions or fever to death. Of the US primary reports received between 2006 and 2010, 0.6% reported death as the outcome; 7.7% reported a serious nonfatal adverse event (as defined above), and 91.7% reported non-serious events (CDC unpublished data).

From 2006 through 2010, vaccine providers submitted 37% of US VAERS reports, vaccine manufacturers submitted 27%; patients or parents submitted 10%, and 26% came from other or unknown sources (CDC unpublished data).

Direct reporting to VAERS or to the SHC by healthcare providers is strongly encouraged, as these reports usually arrive on a more timely basis than those submitted first 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 non-serious vaccine-associated events may be delayed.

Usefulness

1. Detect new, unusual, or rare vaccine AE
2. Assess the safety of newly licensed vaccines
3. Identify potential risk factors in vaccinees for particular types of AE
4. Rapidly respond to vaccine safety concerns or public health emergencies
5. Identify vaccine lots with increased numbers or types of reported AE
6. Monitor trends in known AE, particularly increases

The data from VAERS have been used by FDA, CDC, and the National Vaccine Injury Compensation Program at the Health Resources and Services Administration (HRSA), vaccine policy bodies, including the Advisory Committee on Immunization Practices (ACIP) (<http://www.cdc.gov/vaccines/recs/acip/default.htm>), and other stakeholders. Below are some recent examples of how VAERS data has contributed to public health, listed by some of the major objectives of VAERS:

1. To detect new, unusual, or rare AE: The classic example is that VAERS detected an unexpected number of intussusception reports after an earlier rotavirus vaccine Rotashield®.⁹ Further investigation in other systems verified this association and the Rotashield® vaccine is no longer licensed.¹⁰⁻¹²
2. Assess the safety of newly licensed vaccines: VAERS has been used to assess the safety profile of the human papillomavirus vaccine; these findings have supported the indications and recommendations.¹³

3. Identify potential risk factors in vaccinees for particular types of AE: VAERS contributed data to support severe combined immunodeficiency syndrome (SCID) as a new contraindication for rotavirus vaccine.^{14, 15}
4. Rapidly respond to vaccine safety concerns or public health emergencies: VAERS provided first national data during 2009-10 H1N1 response. The first 2 months of data was published 3 months after the start of the program.¹⁶

VAERS data have also been used by the Institute of Medicine (IOM) Vaccine Safety Committee (<http://www.iom.edu/Activities/PublicHealth/ImmunizationSafety.aspx>) in an extensive assessment of the causal relations between common childhood vaccines and AE. 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,¹⁷ Thimerosal-Containing Vaccines and Neurodevelopmental Disorders,¹⁸ Multiple Immunizations and Immune Dysfunction,¹⁹ Hepatitis B Vaccine and Demyelinating Neurological Disorders,²⁰ SV40 Contamination of Polio Vaccine and Cancer,²¹ Vaccinations and Sudden Unexpected Death in Infancy,²² Influenza Vaccines and Neurological Complications,²³ and Vaccines and Autism.²⁴ 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 AE. Another IOM report is expected to be released in late 2011 and will review adverse health effects associated with eight vaccines.

Reporting sensitivity

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 AE, 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 AE associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.^{25,26} Stimulated reporting also occurs due to media attention on specific AE.

Table 3 shows the reporting efficiency to VAERS for various AE from two studies published in 1995 and 2001. The reporting efficiency is the proportion of occurrences of an event after administration of a particular vaccine that are reported to VAERS.²⁷ For example, the reporting efficiency for paralytic poliomyelitis following oral polio vaccine (severe event, very specific vaccine association, and very rare) was 68%; the reporting efficiency for rash following MMR vaccine was <1% (mild event, many causes).

Table 3 Reporting efficiency To VAERS for various adverse events^{25,26}

Event *	Reporting efficiency %
OPV and vaccine-associated paralytic polio	68%
Rotashield® 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%

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. This biologics surveillance data is proprietary and is not available to the public. The only exception is for annual influenza vaccine. Data on the number of doses of influenza vaccine administered is calculated by CDC and made available to the public, but is not product specific by brand or manufacturer.

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.²⁵

Biased and stimulated reporting. Reports to VAERS may not be representative of all AE 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 a previously licensed rotavirus vaccine, Rotashield®.⁹

Confounding by drug and disease. Many reports to VAERS describe events that may have been caused by medications or underlying disease processes. Many AE reports encompass clinical syndromes that are poorly defined, not clearly understood, or represent diagnoses of exclusion (e.g., sudden infant death syndrome).

Inability to determine causation. VAERS reports are usually not helpful in assessing whether a vaccine actually caused the reported AE because they lack either unique laboratory findings or clinical syndromes necessary to draw such conclusions.⁴ Often multiple vaccines are administered at the same visit, making attribution of causation to a single vaccine or antigen difficult. Additionally, there is lack of an unvaccinated group for comparison. Therefore, reports to VAERS are useful for generating hypotheses, but controlled studies are necessary to confirm any hypotheses generated by VAERS observations.⁵

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 (including the electronic submission form) should be reviewed for completeness and accuracy. The reporter should be contacted if any information is missing. For death and serious outcomes after vaccination, the VAERS staff will attempt to obtain additional documentation (e.g., hospital discharge summaries, laboratory reports, death certificates, autopsy reports). The VAERS staff contacts reporters, health care providers and parents or vaccine recipients routinely to obtain missing information or to correct inaccurate information for all reports of deaths, serious AE, and other selected clinically significant events.

Evaluation of system attributes

An unpublished survey was conducted to assess the knowledge, attitudes, and practices of both private and military healthcare providers about reporting to VAERS. Data from 2005 indicated that 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 CDC is supporting efforts to further evaluate providers perceptions and behaviors about VAERS and about reporting AE after vaccination.

Promoting awareness

Current outreach and education efforts to promote VAERS include general information brochures in English and Spanish (<http://vaers.hhs.gov/resources/vaersmaterialspublications>) and an online public use data set (<http://vaers.hhs.gov/data/index>) and search engine (<http://wonder.cdc.gov/vaers.html>). 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>. A bibliography of VAERS and vaccine safety publications is available at (<http://vaers.hhs.gov/resources/biblio>).

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.

VAERS data, without identifying information, are available to the public through the VAERS website (<http://vaers.hhs.gov/>) for downloading raw data files or via search engine on the CDC WONDER site (<http://wonder.cdc.gov/vaers.html>) and are updated monthly.

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. As previously stated, the sentinel role of VAERS is particularly significant for newly licensed vaccines, as evidenced in 1999 by the detection of intussusception following a previously licensed rhesus–human rotavirus reassortant tetravalent vaccine, Rotashield®.⁹ Although manufacturers are now routinely asked to conduct or sponsor 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 may not be large enough to detect novel very rare AE, or may take several years to accumulate enough data to assess a rare occurrence. The major strengths of VAERS are: 1) it is national in scope and therefore can be used during public health emergencies (as was done during the H1N1 influenza vaccine program), 2) it is timely, 3) it can detect new AE in addition to monitoring prespecified AE found in the pre licensure trials, and 4) it is a national system and anyone can report.

VII. The National Vaccine Injury Compensation Program

The National Childhood Vaccine Injury Act of 1986 (NCVIA) established the National Vaccine Injury Compensation Program (VICP) to provide compensation for certain AE following immunization. VICP is a “no-fault” system to compensate individuals whose injuries may have been caused by any routinely recommended childhood vaccines. **VICP is separate from VAERS. Reporting an event to VAERS does not result in the filing of a claim to 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.^{6, 29}

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.

VIII. Other Vaccine Safety Monitoring Activities

In addition to VAERS, several other systems exist to monitor the safety of vaccines. Some of these systems are listed below.

The Vaccine Safety Datalink (VSD) project (<http://www.cdc.gov/vaccinesafety/activities/vsd.html>) is a collaborative effort between CDC's Immunization Safety Office and 10 managed care organizations (MCOs) to monitor immunization safety and address the gaps in scientific knowledge about AE following immunization.³⁰ The VSD links computerized vaccination and medical records for approximately 9.2 million persons (3% of the total U.S. population). Because these programs have enrollees numbering from thousands to millions, large cohorts may be assembled to examine less frequent AE. Denominator data and control groups are also readily available. Hence the VSD provides a way of testing hypotheses related to vaccine safety. VSD also has implemented a system to conduct near real-time monitoring for specific AE after vaccines in the VSD population.

The Clinical Immunization Safety Assessment (CISA) Network, consisting of six academic centers with vaccine safety expertise working in partnership with CDC (<http://www.cdc.gov/vaccinesafety/Activities/CISA.html>) is designed to improve scientific understanding of vaccine safety issues at the individual patient level. The CISA network's goal are to study mechanisms of vaccine AE, study individual risk factors for AE, serve as a resource to provide consultation for difficult vaccine safety issues, and to assist in developing vaccine safety guidance.

The Vaccine Analytic Unit (VAU) (<http://www.cdc.gov/vaccinesafety/Activities/brighton.html>) complements the other CDC vaccine safety surveillance systems (VAERS, VSD, and CISA). VAU works in collaboration with the U.S. Department of Defense (DoD) and with input from the FDA to evaluate longer term safety of vaccines administered to young adults of military age. The VAU uses data from the Defense Medical Surveillance System (DMSS) for its investigations. The DMSS is a unique source of active surveillance data, and contains medical, vaccination and deployment information for US military personnel (active component is approximately 1.4 million individuals).

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Appendix: 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.

1. **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).
2. **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 (<http://vaers.hhs.gov/resources/vaersmaterialspublications>)