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Vaccine Safety Post-marketing Surveillance:
The Vaccine Adverse Event Reporting System

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I. Introduction

Vaccination is one of the ten great public health achievements of the 20th century.[1] Vaccination has directly resulted in smallpox eradication, elimination of wild poliovirus from the Western Hemisphere, cessation of indigenous measles virus transmission in the U.S., and the control of many infectious diseases that in the recent past caused significant morbidity, permanent disability, and death.[2] Morbidity for vaccine preventable diseases in the United States from the time prior to development of each vaccine to 1998 has decreased as follows: diphtheria 100%, pertussis 95.7%, tetanus 97.4%, non-vaccine associated poliomyelitis 100%, indigenous cases of measles 100%, mumps 99.6%, rubella 99.3%, congenital rubella syndrome 99.4%, Haemophilus influenzae type b (Hib) 99.7%.[2] In the ten years since introduction of an effective Hib vaccine for infants this serious cause of meningitis and bacteremia, which struck 1 in 200 children under the age of five in the prevaccine era, has become a clinical rarity.

The benefits of vaccination are measured by disease prevented. A common misconception is that since vaccine preventable diseases have been almost completely eradicated from this country, we do not need to immunize children anymore,[3] however, the benefits of vaccination are seen most with high levels of coverage. A case in point is the U.S. measles outbreak of 1989-1991, which resulted primarily from a failure to vaccinate preschool-aged children on time. Some areas that experienced measles outbreaks among preschool children had on-time vaccination rates as low as 50%. This epidemic resulted in an estimated 55,000 cases of measles, 11,000 hospitalizations, and 130 deaths.[4]

The risks of vaccination are the potential side effects they may cause. Most side effects of vaccination are mild and include local reactions at the injection site such as pain or swelling. However, in a small percentage of cases, side effects from vaccination can be serious. In an age when most people have never seen a clinical case of a vaccine preventable disease and in which there is low tolerance for risks, especially for healthy children, health care providers must be adept in communicating the benefits and risks of immunization to patients and parents and in responding to their concerns.

In the last decade, numerous changes in vaccine production and administration have reduced the number of adverse events associated with vaccination and resulted in safer vaccines. A more purified acellular pertussis (aP) vaccine has replaced the whole-cell pertussis vaccine used in DTP (diphtheria, tetanus, pertussis vaccine). Several studies have evaluated the safety and efficacy of DTaP as compared to DTP and have concluded that DTaP is effective in preventing disease and that mild side effects and serious adverse events occurred less frequently when the DTaP vaccine was given. Recent changes in the schedule of polio vaccines from the live attenuated oral vaccine to the inactivated vaccine have eliminated the rare cases of vaccine associated paralytic polio.

Many sources exist for the public to obtain information about vaccines. However, parents see primary health care providers as the most important information source on vaccinations.[5] Health care providers must listen with empathy, and address concerns of parents and patients with honest and direct information so that informed decision-making can occur.[6] Because unreliable immunization information sources exist, health care providers must address misinformation as well as valid concerns.

Each time a child is vaccinated, health care providers are required by law to provide a Vaccine Information Statement (VIS) to parents/legal guardian for the vaccines listed on the Vaccine Injury Table.[7] The VIS explains both benefits and risks of the vaccine. Copies of all current VIS can obtained from the following websites:

www.cdc.gov/nip/publications/VIS
www.immunize.org (see links to VIS)

II. Overview of Vaccine Safety Surveillance

Pre-licensure Evaluation of Vaccines

Licensure requires extensive clinical evaluation of the vaccine's safety and efficacy that is completed in stages over several years. First, laboratory and animal studies are performed. Then candidate vaccines are tested in small groups of adult volunteers to establish first the safety, and then, the efficacy of the vaccine. Finally larger scale clinical trials, usually randomized and placebo - controlled, measure the rates of the more common adverse events and the protective efficacy of the vaccine. The control groups in these clinical trials who do not receive the vaccine under study are critical to distinguishing between vaccine-related events and events unrelated to vaccine that occur spontaneously in the study population.

Rates of the most common vaccine reactions, such as injection site reactions and fever, can be estimated before licensure, but the comparatively small number of patients enrolled in these trials generally limits detection of rare events or events that occur a prolonged period of time after vaccine exposure. Even the largest pre-licensure trials (>10,000 persons) are inadequate to assess the vaccine's potential to induce rare but serious side effects. Food and Drug Administration (FDA) licensure occurs only after the vaccine has met rigorous standards of efficacy, safety, and purity and when its potential benefits in preventing disease clearly outweigh its risks. However, it is essential to continue to collect information on vaccine-associated adverse events after licensure that may only occur following wide-scale use of the vaccine in the general population.

Post-Marketing Surveillance

Post-marketing surveillance is a necessary component of vaccine safety monitoring. The manufacturers' label/product information approved at licensure can be continuously updated as significant adverse event information differing from that originally known at the time of approval is compiled. Due to the relatively small number of patients studied during pre-licensure, rarer side effects or events that may only occur in a sub-group of the population not significantly represented in pre-marketing studies (e.g., neonates and infants who receive hepatitis B vaccine, pregnant women, immunosuppressed patients), or side effects that occur only with chronic or repeated exposure to a vaccine antigen or vaccine component may not be revealed until the vaccine is licensed to the general public. Increasingly, vaccine manufacturers are being asked to conduct large-scale “Phase IV” postlicensure trials as a precondition for licensure.

In contrast to pre-licensure studies, which are experimental in design, most post-licensure studies tend to be observational in nature. Thus, issues of confounding and bias, which were minimized by random allocation of vaccinated and unvaccinated persons in pre-licensure studies, must now be either rigorously controlled for in study design and analyses, or taken into account when interpreting surveillance data.

After licensure, vaccinated persons have diverse demographic characteristics (e.g. age, race, socioeconomic background), medical history (e.g. immunocompromised host), and/or multiple medical problems necessitating medication (potential drug interactions). These previously unstudied components of a patient's social or medical history may be risk factors that could contribute to the development of adverse events.

The objectives of post-marketing surveillance are to identify rare adverse reactions not detected during pre-licensure studies, monitor increases in known reactions, identify risk factors or pre-existing conditions that may promote reactions, identify particular vaccine lots with unusually high rates or types of events, and identify signals of possible adverse reactions which may warrant further study.

There are two types of post-marketing surveillance systems typically in use: active and passive surveillance. Active surveillance systems link the vaccination status of all persons in a defined population to their clinical outcomes, which minimizes under-reporting and allows rates of adverse events to be calculated. Such a system may provide comprehensive data, but may be very expensive and may lack the ability to detect very rare events or deaths because of the comparatively small number of participants involved in active systems.

Passive surveillance systems rely on health professionals, vaccinees, or others to voluntarily submit reports of illness following vaccination. Passive systems are simpler and less expensive. They do not limit the population from which reports are accepted, and because of the broad pool of reporters, these systems offer the potential for detecting rare events. However, limitations of passive surveillance systems include variability in reporting standards, reporter bias, and significant under-reporting of events. Both active and passive surveillance systems lack specificity, that is, reported post-vaccination events may be coincidental and not caused by the vaccine.

Determining causality of reported post-vaccination events associated with a specific vaccine is challenging and requires careful weighing of all the scientific evidence, evaluation of the quality and consistency of the data, and consideration of biologic plausibility of the association between vaccination and the event (Table 1). The stronger the vaccine-event relationship in each case, and the rarer the spontaneous incidence of the event in the general population (i.e., background rate in an unvaccinated population), the fewer cases are needed to establish a causal association. Biologic plausibility and strength of association aid in evaluating if an association is causal, as does a vaccination re-challenge ("positive rechallenge") which elicits an identical reaction each time the vaccine is administered. Surveillance data alone are usually insufficient to establish a causal relationship.

When faced with a suspicious event, it is important to try to determine the background incidence rate of the event before making a judgment as to causality. Defining the relationship between vaccine exposure and the occurrence of an event is not easy, and it is often impossible with the available data to reach a conclusion for an individual case. Since events may act through the same physiological and pathological pathways as normal disease, they are difficult to distinguish.

Table 1. Evaluating Side Effects After Vaccination: Temporal Versus Causal Associations

An adverse event can be causally attributed to vaccine more readily if:

1. The exact chronology of immunization and adverse event onset is known
2. The adverse event corresponds to those previously associated with a particular vaccine
3. The event conforms to a specific clinical syndrome whose association with vaccination has strong biologic plausibility (e.g., anaphylaxis)
4. A laboratory result confirms the association (e.g., isolation of vaccine strain varicella vaccine from skin lesions of a patient with rash)
5. The event recurs on re-administration of the vaccine ("positive rechallenge")
6. A controlled clinical trial or epidemiologic study shows greater risk of a specific adverse event among vaccinated vs. unvaccinated (control) groups

III. Overview of VAERS

Historical Background

Post-market surveillance for all drug products, including vaccines, became an organized activity after the thalidomide tragedy of the early 1960's. The National Childhood Vaccine Injury Act (NCVIA), passed in 1986, required health professionals and vaccine manufacturers to report to the Department of Health and Human Services specific adverse events following the administration of particular vaccines. In 1990, the Vaccine Adverse Event Reporting System (VAERS) was established under the joint administration of the Centers for Disease Control and Prevention (CDC) and the FDA to accept reports of suspected adverse events after administration of any U.S. licensed vaccine. The Reportable Events table (Table 2) lists post-vaccination events and the time frames in which they must occur to qualify as being reportable. It is updated periodically as the vaccination schedule changes and as new vaccines are introduced. However, reporting of all significant events is encouraged.

The National Vaccine Injury Compensation Program (VICP), also established by the NCVIA, is a no-fault system in which persons thought to have suffered an injury or death as a result of administration of childhood vaccines recommended by the CDC for routine use may seek compensation. Injuries following administration of vaccines not listed in the authorizing legislation are not eligible for compensation through the program. The VICP, which became operational on October 1, 1988, is intended to be an alternative to civil litigation. The program has achieved its policy goals of providing compensation to those injured by rare adverse events, liability protection for vaccine manufacturers and administrators, and vaccine market stabilization. **VICP is separate from the VAERS program. Reporting an event to VAERS does not file a claim for compensation to the VICP.** For more information about vaccine injury compensation call (800) 338-2382 or go to www.hrsa.gov/bhpr/vicp. Persons wishing to file a claim for vaccine injury should call or write: U.S. Court of Federal Claims, 717 Madison Place, N.W. Washington, D.C. 20005, Telephone: (202) 219-9657

How VAERS Works

VAERS accepts reports from health professionals, vaccine manufacturers, and the general public. Reports are submitted via mail and fax as well as emerging technologies such as reporting via the internet. See www.vaers.org for available reporting options. All reports, whether submitted directly to VAERS or via state or local public health authorities or manufacturers, are collected into the VAERS database.

Manufacturers notified of an adverse event must follow specific guidelines. Food and Drug Regulations (CFR 21, April 2000, section 600.80 c) currently require that the following adverse events be reported to VAERS by each manufacturer having a product license from FDA: all reports of adverse experiences occurring within the U.S., whether serious, non-serious, expected or unexpected; and all serious and unexpected adverse experiences occurring outside of the U.S. or reported in scientific/medical journals as case reports or as the result of formal clinical trials.

Data collected on the VAERS form includes information about the patient, the vaccination(s) given, the reported adverse event, and the person reporting the event. According to FDA regulations, serious reports include those involving hospitalization or prolongation of hospitalization, death, or reported life-threatening illness or permanent disability. All reports classified as serious according to this definition are followed up by a team of nurses to obtain additional information (such as medical records and autopsy reports) in order to provide as full a picture of the case as possible. The signs, symptoms, and diagnoses mentioned in the description of the adverse event are coded using FDA's Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). All information obtained from the original and follow-up

VAERS report is stored in a computerized database for subsequent analysis. Letters to obtain information about recovery status are mailed to the reporters at 60 days and 1 year after vaccination.

The patient's personal identifying information is kept confidential by law. Medical records submitted to VAERS spontaneously or as part of follow-up activities are also protected by confidentiality requirements. VAERS data stripped of personal identifiers are available for purchase through the National Technical Information Service and can also be reviewed on the world wide web at www.vaers.org.

Strengths and Limitations of VAERS

VAERS is a national public health surveillance system that represents the "front line" of vaccine safety activities. Post-marketing surveillance based on spontaneous reporting can generate signals of potential safety problems that can be tested through more rigorous epidemiologic methods such as case-control studies and use of large linked databases. Reporting of adverse events by clinicians has historically been the most reliable source of drug safety alerts.

Because of the diverse population it covers and the relatively large number of reports it receives, VAERS is useful for detecting new, unusual, or rare events and assessing newly licensed vaccines.[8,9,10] Careful review of reports during the initial months of licensed use can provide additional assurance about the safety of a new vaccine, uncover previously unexpected events which occur when a vaccine is used in a new sub-group, or rapidly identify problems not seen during pre-licensure evaluation.

VAERS is subject to the limitations inherent to any passive surveillance system. Underreporting of events is one of the main limitations, although more serious medical events are more likely to be reported than are minor ones.[11] This phenomenon is referred to as differential reporting. Other potential reporting biases include increased reporting in the first few years after licensure, preferential reporting of events occurring soon after vaccination, and increased reporting after publicity about a particular known or alleged type of adverse event, also known as stimulated reporting.

Overreporting also occurs, since VAERS accepts reports without prejudice with regards to their source, and some reported conditions do not meet standard diagnostic criteria. Many reported events, including serious ones, occur coincidentally after vaccination and are not causally related to vaccination. Individual reports may contain inaccurate or incomplete information, making their interpretation with respect to vaccine causality more difficult.

Significant methodologic limitations of VAERS include the fact that it does not collect information on incidence of adverse events in unvaccinated control groups, nor does it provide information on the total number of doses of vaccine or vaccine combinations actually given to patients. The number of vaccine doses of a particular type distributed can be used to calculate crude reporting rates, but these must be interpreted with caution because the crude rates do not represent the true incidence of adverse reactions.

Objectives of VAERS

Despite the above-described limitations, VAERS has been able to fulfill its primary purpose of identifying new and/or rare vaccine side effects, increases in rates of known side effects, and patient risk factors for particular types of adverse events. Examples include intussusception after Rotavirus vaccine[12,13,14] (see Case Studies) and anaphylactic reaction to MMR vaccine caused by gelatin allergy.[15] Additional studies are always required to confirm "signals" detected

by VAERS. For example, the Vaccine Safety Datalink (VSD) Project is a large-linked database (LLDB) that includes information on more than six million people. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations (those given during the same visit), vaccine manufacturer, lot number, and injection site. Medical records are then monitored for potential adverse events resulting from immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses. The database is also being used to test new vaccine safety hypotheses that arise from the medical literature, VAERS, changes in the immunization schedule, or from the introduction of new vaccines.

A secondary goal of VAERS is to identify vaccine lots with increased numbers of types of reported events. Advocacy groups, organized and led primarily by parents who believe their children have died or suffered serious injury as a result of vaccination, have questioned whether particular vaccine lots may be more likely to induce such injuries. These groups have reviewed the publicly available VAERS database, which includes the vaccine lot number for most reports, and have raised questions about the safety of particular lots that appear to be associated with a higher number of reports. Evaluating lot-specific reports is complicated by the variability in vaccine lot size (range: 3,000-700,000 doses), because more reports are usually received for a large lot than a small one. Additionally, lot identifier information may be absent or inaccurate in up to 20% of VAERS reports.

Vaccines are manufactured in large lots from which vials for individual administration are derived. Procedures for the manufacture and release of vaccine lots are strictly regulated; prior to public release, each vaccine lot must undergo stringent testing to assure both the potency of the vaccine and the absence of contamination. Because of these procedures, the likelihood that there could be something "wrong" with any bulk lot is extremely low--but not zero.

Since 1993, FDA medical officers have performed weekly reviews of lot-specific reporting. These reviews require much more information than simply the number of reports submitted for each vaccine lot; the numbers alone are inadequate to support any conclusions about safety, for several reasons.

First, as noted earlier, there are errors in the database. Given that the vaccine lot number is a string of letters and numbers, it may easily be miscopied by the reporter onto the VAERS form. This results in numerous lots in the database with a single report or a very few reports, providing a misleading contrast with the numbers of reports for valid lots.

Second, lot sizes can vary greatly. Clearly, the number of reports generated from a vaccine lot containing half a million doses cannot be sensibly compared with the number of reports generated from a lot only one-tenth as large. Data on lot size, although available to the FDA for monitoring purposes, do not appear in the VAERS database because these data are legally considered proprietary to the manufacturer and their release by FDA is prohibited.

Third, there is a time factor. A vaccine lot on the market for only a few months will be associated with fewer reports than a lot that was released several years earlier.

Finally, there will always be chance variability in reporting rates. Even when the numbers of reports are standardized for lot size and length of time on the market (as they are for internal FDA review of the database), there will always be one lot associated with the highest rate of reports and one lot with the lowest. The more lots, the greater the difference between the highest and lowest rates will be; this difference may be quite large for "old" and widely used vaccines such as MMR even assuming all lots are equally safe.

When numbers of reports are compared between vaccines, there are further considerations. The database will contain more reports for a vaccine administered five times to each individual,

such as DTaP, than for a vaccine such as MMR that is administered only twice. There will be more reports for a vaccine that has been on the market for many years than for a vaccine that has been available for only a few years (such as Pneumococcal Conjugate vaccine). More death reports will be seen for vaccines given in infancy, when the background death rate is higher and SIDS is a factor, than for vaccines given later in childhood.

The FDA staff must take all of these factors into consideration when monitoring the database for unusual patterns of reporting from specific lots. Computerized methods are in place to identify lots with high reporting rates, accounting for lot size and time on the market. The threshold for identifying these lots is set deliberately low to ensure the earliest possible signal of a real problem.

Lots identified at this first screening stage are subject to additional scrutiny. The experience of related or "sister" lots (those made from the same large batch of product) is considered, since most problems should affect all lots from the same batch. The types of reports submitted are carefully reviewed; a series of similar events would be more suggestive than a scattering of events of different types with no unique syndrome evident. The results of the lot's initial safety testing are also reviewed. Additional information may be requested from the manufacturer, and in some cases the safety testing might be repeated.

No lot of any vaccine has been found to be unsafe to date, and there have been no safety related vaccine recalls since the early days of polio vaccine in the 1950's. Of the four FDA recalls of vaccines since 1987, 3 involved manufacturing problems and one involved decreased vaccine potency over time.[16,17] This result is not surprising given the stringency of the manufacturing and testing requirements to which vaccines are subject. Nevertheless, because of the possibility of a safety problem arising, regular attention to lot-specific reporting will remain an important aspect of FDA's program of vaccine safety monitoring.

Summary of VAERS Data

Since VAERS became operational in November 1990, more than 100,000 reports have been received. Though this seems like a very large number, it is relatively small compared with the approximately 100 million doses of childhood vaccines distributed during the past decade, as well as millions of additional doses given to adults. VAERS seeks to capture all clinically significant medical events occurring post-vaccination, even if the reporter is not certain that the incident is vaccine related. Reports are received primarily from manufacturers (42%) and health care providers (30%) with fewer reports filed by patients and their parents (7%) and state and local health departments (12%).

Forty nine percent of reports involve children age 5 and under and 41% concern adults age 18 and over. Thirty nine percent of reports list more than one vaccine as having been administered prior to the onset of the adverse event; for these cases determination of causality is more complex than if only a single vaccine was given. Only about 12% of reports received describe serious events, as previously defined. Most of the non-serious reports describe side effects such as fever and various types of injection site reactions.

Serious reports include reports of deaths occurring after vaccination. A clinical research team follows up all deaths reported to VAERS. Many of these deaths have been classified as Sudden Infant Death Syndrome (SIDS), a condition shown not to be caused by vaccines. No specific clinical syndrome has been observed. A syndrome would be expected if the deaths had the same cause (e.g. the existence of characteristic clinical syndromes permitted researchers in recent years to find the causes for Legionnaire's Disease, Toxic Shock Syndrome, and other "new" diseases).

Analysis of the age distribution and seasonality of infant deaths reported to VAERS show that they match the age distribution and seasonality of SIDS; both peaking about two months of age and during winter. Carefully controlled epidemiologic studies[18,19] have consistently failed to find any association between SIDS and vaccines. Recent evidence shows that the prone (on the stomach) sleeping position is associated with SIDS. Changing this practice alone has resulted in a major decline in the rate of SIDS.

Some deaths will occur following childhood immunization by chance alone. Because most infants are vaccinated during the first year of life, it is likely that a child experiencing medical problems (including those leading to death) will have been immunized. The mathematical chance of any adverse event, death or otherwise, occurring within 24 hours of vaccination by coincidence alone is 1/122 (365 days/3 vaccination visits in the first year of life). Since vaccination is such a memorable event, it is likely that parents will attribute the death to vaccination and file a report with VAERS.

The Institute of Medicine (IOM) reviewed 208 deaths reported to VAERS between 1990-1992. Only one death was believed to have resulted from a vaccine: a 28 year old woman who died from Guillain-Barre Syndrome (GBS) after tetanus vaccination. The IOM concluded that the "vast majority of deaths reported to VAERS are not causally related to vaccination" [20]. Every new death reported to VAERS is examined to ensure that it does not represent a new problem.

VAERS Case Studies

Intussusception After Rotavirus Vaccine

Among participants of 27 pre-licensing trials of several candidate rotavirus vaccines, five cases of intussusception occurred among 10,054 (0.05%) vaccinees. One case of intussusception occurred among 4,633 (0.02%) infants who received a placebo vaccine. The difference between the groups was not statistically significant. The vaccine was licensed for use in the U.S. in August 1998 and recommendations for its use were published in March 1999. As a precaution, intussusception was listed in the package insert of the vaccine as a possible adverse reaction, and physicians were encouraged to report all adverse reactions to VAERS.

In July 1999, CDC recommended that health-care providers postpone use of the rhesus rotavirus vaccine-tetravalent (RRV-TV) at least until November 1999 pending results of a national case-control study. This action was based on reports to VAERS of intussusception among 15 infants who received rotavirus vaccine.[21] The manufacturer, in consultation with the Food and Drug Administration, voluntarily ceased further distribution of the vaccine in mid-July 1999.

On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP), after a review of scientific data from several sources, concluded that intussusception occurs with significantly increased frequency in the first 1-2 weeks after vaccination with RRV-TV, particularly following the first dose. ACIP withdrew its recommendation for vaccination of infants in the United States with RRV-TV.

Influenza Vaccine and Guillain-Barre Syndrome

The number of reports of influenza vaccine-associated Guillain-Barre syndrome to VAERS increased from 37 in 1992-1993 to 74 in 1993-1994, arousing concern about a possible increase in vaccine-associated risk. ACIP recommended that a special study be initiated to investigate the VAERS signal. Patients given a diagnosis of Guillain-Barre syndrome in the 1992-1993 and 1993-1994 influenza-vaccination seasons were identified in the

hospital-discharge databases of four states. Vaccination histories were obtained by telephone and were confirmed by the vaccine providers. Disease with an onset within six weeks after vaccination was defined as vaccine-associated. The vaccine providers confirmed influenza vaccination in the six weeks before Guillain-Barre syndrome onset for 19 patients. In 9 of the 19 vaccine-associated cases, the onset was in the second week after vaccination, all between day 9 and day 12. The relative risk of the Guillain-Barre syndrome associated with vaccination, adjusted for age, sex and vaccine season, was 1.7 (95 percent confidence interval, 1.0 to 2.8; p = 0.04). However there was no increase in the risk of vaccine-associated Guillain-Barre syndrome from 1992-1993 to 1993-1994. For the two seasons combined, the adjusted relative risk of 1.7 suggests slightly more than one additional case of Guillain-Barre per million persons vaccinated against influenza.[22] This is much less than the risk of severe influenza, which can be prevented by vaccination.

Adverse Events after Pertussis Containing Vaccines

Review of VAERS data from 1991-1993 provided a first perspective on the safety of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) vaccines in widespread use. Approximately 27 million doses of diphtheria and tetanus toxoids and pertussis vaccine (DTP) and 5 million doses of DTaP were distributed from 1991 to 1993 to children 15 months to 7 years of age. Rates of reported adverse events per 100,000 vaccinations were significantly lower after administration of DTaP vaccine than DTP vaccine for the following outcomes: all reports, 2.9 vs. 9.8; fever, 1.9 vs. 7.5; seizures, 0.5 vs. 1.7; and hospitalizations, 0.2 vs. 0.9. The overall reporting ratio for serious adverse events in children age 1-4 years declined to one third that of the whole-cell vaccine.[23]

FDA first approved acellular pertussis vaccine for infant administration in July 1996. A review of VAERS reports from 1995 (when whole cell vaccine was used exclusively) through mid-1998 (when acellular vaccine was used predominantly) found that both serious and non-serious reports for pertussis-containing vaccine had decreased significantly.[24]

These results confirm that minor adverse events are less frequent after administration of the acellular pertussis vaccine. In addition, these data suggest that serious events such as seizures and hospitalizations associated with pertussis vaccination occur less often after use of acellular pertussis vaccine.

IV. Conclusions and Discussion

The Critical Role of Health Professionals

The role of the health professional in supporting the national passive surveillance system is essential, as the first hint of a potential problem usually originates with the astute clinician who reports a case to the appropriate source. Health professionals have access to the most complete information related to adverse events experienced by their patients. Any index of suspicion that a serious event or death may be related to vaccination is reason for the health professional to submit a VAERS report. **Determination of whether an event was caused by the vaccine is not a prerequisite for filing a VAERS report.** VAERS solicits reports for all events temporally related to vaccination, some of which may be coincidental and some of which may merely indicate a change in the frequency of expected events, even minor ones. Post-marketing surveillance relies on health professionals to report suspicious events, thus improving the quality of reported data and contributing significantly to safeguarding public health.

Despite the limitations of spontaneous reports, VAERS provides vital information of clinical importance. The identification of signals in adverse event surveillance may initiate further

investigation of potential problems in vaccine safety or efficacy, and the subsequent dissemination of safety-related information to the scientific community and the public. This process begins with voluntary submission of reports of possible vaccine-associated events to VAERS by the informed and conscientious health professional.

Completion of VAERS Form and Submission of Reports

Report adverse events associated with vaccines on Form VAERS-1 (Figure 1). Do not use MEDWATCH forms to report vaccine-related events. MEDWATCH is a national passive surveillance system which monitors the safety of medical products and devices that are not vaccines. Events associated with tuberculosis screening tests (Tine, PPD, or Mantoux) or immune globulins should be reported to MEDWATCH at 1-800-FDA-1088.

Copies of VAERS form can be obtained from:

VAERS
P.O. Box 1100
Rockville, Maryland 29849-1100

Copies of VAERS form and instructions may also be obtained by:

Mail: Call 800-822-7967 or FAX request to: 877-721-0366
If no access to 800 number: Call (301) 562-1086
Internet: Visit the VAERS Website at www.vaers.org

Instructions for completing the VAERS form are on the back of the form. As much of the requested information as possible should be obtained. Each report should be reviewed for completeness, accuracy and legibility with specific attention to the following:

1) Dates: All dates should make chronological sense. For example: the vaccine date cannot precede the birth date; the report date cannot precede the vaccine date, etc. Please provide the full month, date and year for all requested dates.

2) Patient name: Verify the patient's first and last names are correct. This assists in the identification of duplicate reports.

3) 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.

4) Critical boxes: Certain items are crucial to the analysis of VAERS data. 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: Determines whether a report is regarded as serious or non-serious, and identifies the most serious reports for 60-day and annual follow-up

VAERS forms may be submitted by mail or fax:

Mailing Address: VAERS
P.O. Box 1100
Rockville, Maryland 20849-1100
Fax: 877-721-0366 (toll free)

New Vaccine Safety Initiatives

In addition to VAERS and the VSD, the Centers for Disease Control and Prevention is undertaking several new collaborative projects with the goal of further increasing the safety of vaccines:

- The establishment of a national network of Clinical Immunization Safety Assessment (CISA) Centers to improve the scientific understanding of immunization safety issues at the individual patient level. Clinically significant adverse events are rarely seen in clinical trials and clinicians see them too infrequently to be able to manage them in a standardized fashion. The Centers will develop and disseminate standardized clinical evaluation protocols to clinicians; they will provide referral and consultation services to health care providers on how to evaluate patients who may have had an adverse reaction to vaccination, which will include how to manage the adverse reaction, as well as counsel on advisability of continued immunization; and they will undertake outreach and educational interventions in the area of immunization safety. The goals are to enhance understanding of known serious or unusual vaccine reactions, including the pathophysiology and risk factors (including genetics) for such reactions, as well as evaluate newly hypothesized syndromes or events identified from the assessment of VAERS case reports, in order to clarify any potential relationship with immunization.

- The Institute of Medicine (IOM) has established an independent expert committee to review hypotheses about existing and emerging immunization safety concerns at the request of the CDC and the National Institutes of Health (NIH). The Immunization Safety Review Committee is comprised of experts in public health, pediatrics, internal medicine, epidemiology and biostatistics, immunology, neurology, infectious disease, risk perception, decision analysis, nursing, genetics, ethics, and health communication. The committee will meet at least three times per year over the three-year study period (2001-2003) to address various vaccine safety concerns. A focused report will be published regarding each hypothesis addressed. The reports will summarize the current biologic and epidemiologic evidence of causality between an immunization and a hypothesized health effect, the biologic plausibility of the adverse event hypothesis, and the significance of the issue in a broader societal context. Based on its assessment of these factors, the committee will recommend the appropriate level of action or response (e.g., changes in surveillance, research, communication, and policy review). The Committee's first report, on the alleged association between MMR vaccine and autism, was released in April 2001. It concluded that "the evidence favors rejection of a causal relationship … between MMR and autistic spectrum disorders".[25]

- The Brighton Collaboration is an international voluntary collaboration whose primary aim is to develop globally accepted standardized case definitions of adverse events following immunization (AEFI). Some research groups, the pharmaceutical industry, public health, regulatory and reporting agencies have developed case definitions, but variations between them are often substantial. The known differences in immunization safety terminology used, as well as the different meaning attributed to the same terms can lead to misinterpretation of data shared between institutions and reporting systems. For example, the comparison of reactogenicity data between trials for the same or similar vaccines is difficult when the method of assessing an AEFI varies considerably, such as measurement of fever using monitoring for 3 versus 10 days post immunization, and temperature reported at different cut off points. The availability of globally accepted and implemented standardized case definitions of AEFIs will render important data comparable, which is a fundamental requirement for an international assessment of immunization safety.

Additional Information Sources on VAERS and Vaccine Safety

Websites:
www.vaers.org

www.cdc.gov/nip/home-hcp.htm

www.fda.gov/cber/vaers/vaers.htm

www.iom.edu/immsafety
(Institute of Medicine Immunization Safety Review Committee)

Telephone:
National Immunization Hotline
English: 1-800-232-2522
Spanish: 1-800-232-0233

Answers general inquiries from health care providers and the public about vaccines and vaccine safety, Monday through Friday, 8am to 11pm (EST).

VAERS
1-800-822-7967
Copies of forms for reporting to VAERS, the current vaccine schedule, the Reportable Events Table, and additional copies of this CME article.

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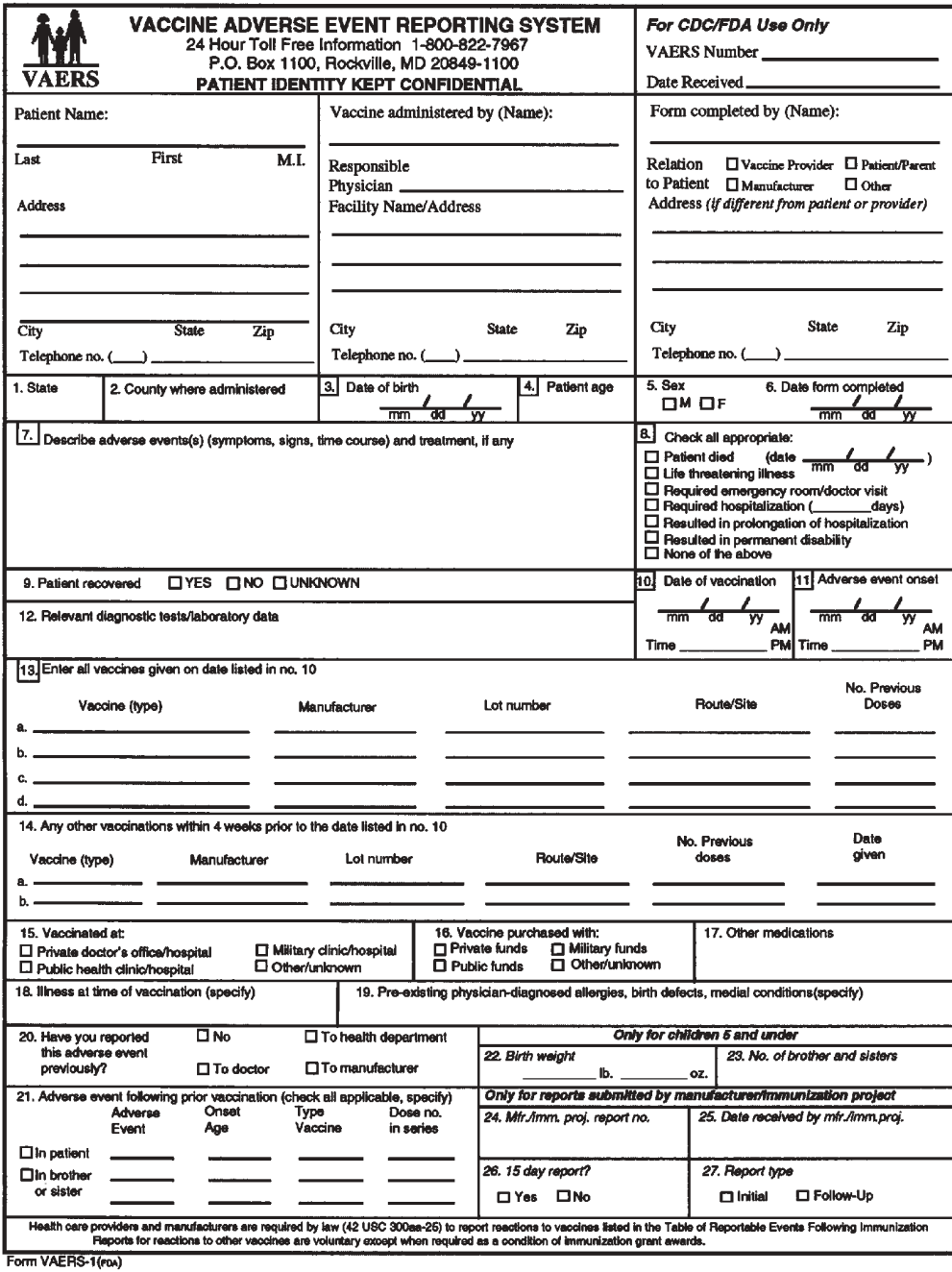
Table 2. VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-HiB, DT, Td, TT	A. Anaphylaxis or anaphylactic shock B. Brachial neuritis C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 28 days No limit See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, P	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 7 days No limit See package insert
Measles, mumps and rubella in any combination; MMR, MR, M, R	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 15 days No limit See package insert
Rubella in any combination; MMR, MR, R.	A. Chronic arthritis B. Any sequela (including death) of above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	42 days No limit See package insert
Inactivated Polio (IPV)	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days No limit See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days No limit See package insert
Haemophilus influenzae type b (polysaccharide)	A. Early-onset Hib disease B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days No limit See package insert
Haemophilus influenzae type b (conjugate)	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Varicella	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rotavirus	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pneumococcal conjugate	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

*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 manufacturer's 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. Effective December 18, 1999

Figure 1



VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (___) _____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (___) _____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (___) _____

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex ☐M ☐F | 6. Date form completed mm dd yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy Time _____ AM PM

11. Adverse event onset mm dd yy Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medial conditions(specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brother and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization
Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1(FDA)

Continuing Education Activity Sponsored by CDC

Vaccine Safety Post-Marketing Surveillance:
The Vaccine Adverse Event Reporting System
Activity Number SS3092
Expiration - September 19, 2004

You must complete this continuing education activity using the CDC Training and Continuing Education Online system by September 19, 2004 to receive continuing education credit. If you answer all the questions, you will receive an award certificate for 1.25 hours of Continuing Medical Education (CME) credit, 1.3 hours Continuing Nursing Education (CNE) credit, or 0.1 hour Continuing Education Units (CEUs). No fees are charged for participating in this continuing education activity.

Instructions

1. Read this document, which contains the correct answers to the questions beginning on the next page.
2. Go to the CDC Training and Continuing Education online system internet site at http://www.phppo.cdc.gov/phtnonline
3. Follow the instructions to register as a new participant. If you have previously registered as a participant, log in using your log-in name and password.
4. Search to locate the course description and register for the activity.
5. Complete the entire evaluation and exam. You must answer all the questions in order to receive continuing education credit.
6. Submit your answers no later than September 19, 2004.
7. Immediately print your award certificate for your records.

Accreditation

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.25 hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Nursing Education (CNE). This activity for 1.3 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center Commission on Accreditation.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association of Continuing Education and Training and awards 0.1 hour CEU.

Goals and Objectives

This document provides information about the Vaccine Adverse Event Reporting System (VAERS) and provides guidance on reporting adverse events following vaccination. The goal of this document is to improve reporting of adverse events following vaccination. Upon completion of this educational activity the reader should be able to a) describe the primary purposes of VAERS, b) identify the strengths and limitations of VAERS, and c) describe events following vaccination that should be reported to VAERS.

For assistance or additional information about this continuing education activity contact the CDC Continuing Education Unit by telephone at (800) 41-TRAIN, or by email at ce@cdc.gov. To receive continuing education credit you must answer all of the following questions.

1. What type of certificate of continuing education do you wish to receive?
   - A. CME for physicians
   - B. CME attendance for non-physicians
   - C. CNE (Continuing Nursing Education)
   - D. CEU (Continuing Education Unit)
   - E. Not participating in this activity for credit
   - F. None of the above

2. Are you a...
   - A. Nurse
   - B. Physician
   - C. Veterinarian
   - D. None of the above

3. What is your highest level of education?
   - A. High School
   - B. Associate
   - C. Bachelors
   - D. Masters
   - E. Doctorate
   - F. Other

4. Do you administer vaccines to children and/or adults?
   - A. Yes, children only
   - B. Yes, adults only
   - C. Yes, both children and adults
   - D. No, I don't administer vaccines

5. Which of the following best describes your current occupation?
   - A. Epidemiologist
   - B. Health Educator
   - C. Laboratorian
   - D. Pharmacist
   - E. Physician Assistant
   - F. Administrator
   - G. Nurse Practitioner
   - H. Infection control practitioner
   - I. Other office or clinic patient care provider
   - J. Student
   - K. None of the above

6. Which of the following best describes your current work setting?
   - A. Academic (public and private)
   - B. Private health care organization
   - C. Public health organization
   - D. Environmental health organization
   - E. Non-profit organization
   - F. Other work setting

7. Which of the following best describes the type of organization in which you work?
   - A. Federal government
   - B. State government
   - C. County government
   - D. Local government
   - E. Non-governmental agency
   - F. Other type of organization

8. How did you first learn about this activity?
   - A. State publication (or other state-sponsored communication)
   - B. From a colleague
   - C. CDC Internet site or homepage
   - D. PHTN source (PHTN website, email announcement)
   - E. Other

9. What was the most important factor in your decision to do this activity?
    A. Content
    B. Continuing education credit
    C. Supervisor recommended
    D. Previous participation in CDC self-study material
    E. Convenience of self-study format
    F. Other

10. How much time did you spend reading this document and completing the evaluation and exam?
    A. Less than 1 hour
    B. 1 to 2 hours
    C. More than 2 hours but less than 3 hours
    D. More than 3 hours

11. Please rate your level of knowledge prior to completing this activity.
    A. Great deal of knowledge about the content
    B. Fair amount of knowledge about the content
    C. Limited knowledge about the content
    D. No prior knowledge about the content
    E. No opinion

12. Please estimate your knowledge gain due to completing this activity.
    A. Gained a great deal of knowledge about the content
    B. Gained a fair amount of knowledge about the content
    C. Gained a limited amount of knowledge about the content
    D. Did not gain any knowledge about the content
    E. No opinion

13. The objectives stated are relevant to the goal.
    A. Agree C. Disagree
    B. No opinion D. Not applicable

14. The content in this activity was appropriate for my training needs.
    A. Agree C. Disagree
    B. No opinion D. Not applicable

15. Participation in this activity enhanced my professional effectiveness.
    A. Agree C. Disagree
    B. No opinion D. Not applicable

16. I will recommend this activity to my colleagues.
    A. Agree C. Disagree
    B. No opinion D. Not applicable1

17. Overall, reading this document enhanced my ability to understand the reporting system for adverse events in the United States.
    A. Agree C. Disagree
    B. No opinion D. Not applicable

18. I am confident I can describe the primary purposes of VAERS.
    A. Agree C. Disagree
    B. No opinion D. Not applicable

19. I am confident I can identify the strengths and limitations VAERS.
    A. Agree
    B. No opinion
    C. Disagree
    D. Not applicable

20. I am confident I can describe events following vaccination that should be reported to VAERS.
    A. Agree
    B. No opinion
    C. Disagree
    D. Not applicable

Posttest

21. Which of the following is NOT a primary purpose of VAERS?
    A. Identify new vaccine side effects
    B. Identify increases in of known side effects
    C. Identify patient risk factors for adverse events
    D. Generate incidence rates of vaccine adverse events
    E. All the above are primary purposes of VAERS

22. What source accounts for the largest proportion of VAERS reports?
    A. Manufacturers
    B. Health care providers
    C. Vaccine recipients
    D. Parents of vaccine recipients
    E. State and local health departments

23. Which of the following is a limitation of VAERS?
    A. Underreporting of adverse events
    B. Increased reporting of events occurring soon after vaccination
    C. Increased reporting after publicity about a particular known or alleged adverse event
    D. Lack of information on the incidence of adverse events in control groups
    E. All the above are limitations of VAERS

24. It is necessary for the provider to determine that an event was caused by a vaccine before filing a VAERS report.
    A. True
    B. False

25. What type of clinically significant events following vaccination should be reported to VAERS?
    A. All events temporally related to vaccination
    B. Only events that persist more than 6 weeks after vaccination
    C. Only events that result in hospitalization
    D. Only events that result in death of the vaccinated person
    E. Only events that occur within 1 hour of vaccination

Correct answers for questions 21-25:
21. D; 22. A; 23. E; 24. B; 25. A