Adverse Events Associated With Smallpox Vaccination in the United States, January-October 2003

Christine G. Casey, MD
John K. Iskander, MD, MPH
Martha H. Roper, MD, MPH
Eric E. Mast, MD, MPH
Xiao-Jun Wen, MD
Thomas J. Töörö, MD, MPH
Louisa E. Chapman, MD, MSPH
David L. Swerdlow, MD
Juliette Morgan, MD
James D. Heffelfinger, MD, MPH
Claudia Vellozzi, MD, MPH
Susan E. Reef, MD
La Mar Hasbrouck, MD, MPH
Inger Damon, MD, PhD
Linda Neff, PhD
Claudia Vellozzi, MD, MPH
Mary McCauley, MTSC
Raymond A. Strikas, MD
Gina Mootrey, DO, MPH

Context On January 24, 2003, the US Department of Health and Human Services (DHHS) implemented a preparedness program in which smallpox (vaccinia) vaccine was administered to federal, state, and local volunteers who might be first responders during a bioterrorism event.

Objective To describe results from the comprehensive DHHS smallpox vaccine safety monitoring and response system.

Design, Setting, and Participants Descriptive study of adverse event reports from the DHHS smallpox vaccine safety monitoring and response system received between January 24 and October 31, 2003, through the Vaccine Adverse Event Reporting System (VAERS) and the Centers for Disease Control and Prevention. A total of 37 901 volunteers in 55 jurisdictions received at least 1 dose of smallpox vaccine.

Main Outcome Measures Number of vaccinations administered and description of adverse events and reporting rates.

Results A total of 38 885 smallpox vaccinations were administered, with a take rate of 92%. VAERS received 822 reports of adverse events following smallpox vaccination (overall reporting rate, 217 per 10 000 vaccinees). A total of 590 adverse events (72%) were reported within 14 days of vaccination. Nonserious adverse events (n=722) included multiple signs and symptoms of mild and self-limited local reactions. One hundred adverse events (12%) were designated as serious, resulting in 85 hospitalizations, 2 permanent disabilities, 10 life-threatening illnesses, and 3 deaths. Among the serious adverse events, 21 cases were classified as myocarditis and/or pericarditis and 10 as ischemic cardiac events that were not anticipated based on historical data. Two cases of generalized vaccinia and 1 case of postvaccinial encephalitis were detected. No preventable life-threatening adverse reactions, contact transmissions, or adverse reactions that required treatment with vaccinia immune globulin were identified. Serious adverse events were more common among older revaccinees than younger first-time vaccinees.

Conclusions Rigorous smallpox vaccine safety screening, educational programs, and older vaccinees may have contributed to low rates of preventable life-threatening adverse reactions. Other rare, clinically significant, or unexpected cardiac adverse events were detected by timely review of VAERS data and intensive clinical case investigation.

JAMA. 2005;294:2734-2743 www.jama.com

Author Affiliations: Smallpox Vaccine Adverse Event Monitoring and Response Activity, Epidemiology and Surveillance Division, National Immunization Program, CDC, Atlanta, Ga (Drs Casey, Iskander, Roper, Mast, Wen, Töörö, Chapman, Swerdlow, Morgan, Heffelfinger, Reef, Hasbrouck, Neff, Strikas, and Mootrey); Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases (Dr Damon); Office of Preparedness and Emergency Response (Drs Neff and Vellozzi), and Office of the Associate Director for Science (Ms McCauley), National Immunization Program, CDC, Atlanta, Ga, and Logistics Health Inc, La Crosse, Wis (Dr Vellozzi). Drs Casey, Iskander, Roper, Mast, Wen, Töörö, Swerdlow, Morgan, Heffelfinger, Reef, Hasbrouck, Neff, and Strikas are now affiliated with different divisions within the CDC.

Corresponding Author: Christine G. Casey, MD, Immunization Safety Office, Office of the Chief Science Officer, Office of the Director, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS E-61, Atlanta, GA 30333 (ccasey@cdc.gov).
tentional bioterrorism event requiring an immediate, coordinated response by public health, medical, and law enforcement personnel to control the outbreak and protect the public.4

In October 2002, the US Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices and Healthcare Infection Control Practices Advisory Committee recommended smallpox vaccine for eligible volunteers whom public health authorities might designate to investigate initial smallpox cases.3,6 In December 2002, the US Department of Defense (DoD) began mandatory smallpox vaccination for select service members and employees without contraindications to vaccination7 and in January 2003, the US Department of Health and Human Services (DHHS) implemented a voluntary civilian smallpox vaccination program.8,9 Both programs used a previously manufactured calf-lymph-derived New York City Board of Health (NYCBOH) vaccinia strain (Dryvax; Wyeth Laboratories Inc, Marietta, Pa), which received US Food and Drug Administration licensure for this exclusive purpose.

The DHHS program presented unusual public health challenges because most practicing clinicians were unfamiliar with the safety profile of smallpox vaccine or how to administer it; therefore, vaccine safety education and monitoring were emphasized.10 Smallpox vaccine contains live vaccinia virus that replicates at the vaccination site, causing inflammatory changes during postvaccination days 6 to 8, referred to as a major reaction or take, which is an accepted correlate of smallpox immunity.11 In addition to expected self-limited local and systemic reactions, clinically significant adverse reactions have been reported in surveillance studies from the 1960s.12,15

An adverse reaction is an untoward effect that occurs after a vaccination and is extraneous to the vaccine’s primary purpose of producing immunity. Adverse reactions have been demonstrated to be caused by the vaccination. In contrast, adverse events are untoward effects observed or reported after vaccinations, but a causal relationship between the 2 have yet to be established. Adverse events include both adverse reactions and other events associated with vaccinations only by coincidence. Historically, vaccinia adverse reactions have included inadvertent inoculation, eczema vaccinatum, progressive vaccinia, fetal vaccinia, generalized vaccinia, erythema multiforme major, and postvaccinal encephalitis. Some reactions are termed preventable. Eczema vaccinatum and progressive vaccinia can be prevented by ensuring that at-risk persons or their close contacts are not vaccinated, fetal vaccinia can be prevented by ensuring that pregnant women and their household members do not receive smallpox vaccine, and inadvertent inoculation can be prevented by proper hand hygiene and vaccination site care.

Cardiac complications following vaccination with the NYCBOH vaccinia strain were not anticipated at the time of initial planning and implementation of the DoD and civilian smallpox preparedness programs. A number of reports and studies in Europe and Australia had documented an association between myopericarditis and vaccination with the more reactogenic vaccinia strains used in those regions.16-20 However, from 1955 to 1986, only 6 cases of myopericarditis were reported following vaccination of millions of individuals with the less reactogenic NYCBOH strain used in the United States.19,21-23 Following 7 cardiarelated adverse events, including 2 sudden deaths in civilian vaccinees, and 10 cases of myocarditis and/or pericarditis (myo/pericarditis) in DoD vaccinees,22 the CDC issued a Health Alert Notice on March 26, 2003,27 that described these events and provided provisional recommended deferral criteria for persons at risk for ischemic cardiac events; finalized criteria were published on April 4, 2003.28

We describe the vaccine safety profile among civilians who received smallpox vaccine between January 24 and October 31, 2003. Smallpox vaccine adverse events among DoD personnel or research participants in clinical trials are described elsewhere.7,20-32

METHODS

To minimize preventable adverse reactions and to detect expected, unexpected, and serious adverse events, the CDC, the Food and Drug Administration, DoD, and state or local public health officials, in consultation with medical subspecialists, established a comprehensive smallpox vaccine safety monitoring and response system. Access to vaccinia immune globulin for life-threatening adverse reactions was coordinated by the smallpox vaccine safety monitoring and response system. Data were collected, managed, analyzed, and interpreted under public health surveillance activities and therefore did not require human subject review or institutional review board approval.

Safety Oversight

The Institute of Medicine recommended rigorous prevaccination screening, postvaccination active surveillance for serious events, and establishment of a program to assist clinicians in the early recognition, evaluation, and treatment of adverse events.31 The Joint Smallpox Vaccine Safety Working Group of the Advisory Committee on Immunization Practices and the Armed Forces Epidemiological Board was responsible for safety oversight of both the DoD and DHHS smallpox vaccination preparedness programs. The Smallpox Vaccine Safety Working Group reviewed and revised the surveillance case definitions used to classify smallpox vaccination adverse event reports in collaboration with CDC and DoD personnel. They also conducted sentinel reviews of select cases to assess the degree of confidence the public could attribute to serious dermatological, cardiac, and neurological conditions to smallpox vaccination. The outcome of these reviews will be

©2005 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/5002/ on 06/16/2017
reported separately. The Institute of Medicine and the Smallpox Vaccine Safety Working Group also reviewed data to evaluate the effectiveness of the smallpox vaccine safety monitoring and response system. Summaries of these data were published periodically in CDC’s Morbidity and Mortality Weekly Report.34

Surveillance
Surveillance case definitions were based primarily on historical clinical descriptions of dermatological and neurological adverse reactions following smallpox vaccination (Box 1).35-38 The CDC encouraged reports of the adverse reactions included in Box 1, as well as the following: erythema multiforme major or Stevens-Johnson syndrome or other serious adverse event (ie, those resulting in hospitalization, permanent disability, life-threatening illness or death) or vaccination of persons with a contraindication to vaccination. Subsequently, surveillance case definitions also were established for myo/peri卡片itis39 and dilated cardiomyopathy.35 Investigated cases determined to have incidental findings or diagnoses clearly not attributable to smallpox vaccine were not included in our analysis. Additional data from other specialized safety surveillance systems will be reported elsewhere but it is not anticipated that their findings will differ significantly from the overall rates we present herein.34,40-43

Training, Screening, Education, and Technical Support
Training, screening, and education programs were provided to state and local health officials to limit preventable adverse events.10,44-47 All volunteer vaccinates received an educational packet that contained a confidential self-administered screening questionnaire and vaccine information sheet, which included adverse event reporting guidelines and vaccination site care instructions. The questionnaire was designed to identify and exclude at-risk persons or their close contacts in accordance with Advisory Committee on Immunization Practices recommendations.5,6,48-52 All vaccinates were required to sign an informed consent form and were instructed to keep the site loosely covered with a gauze bandage and first aid adhesive tape until the scab fell off. Supplemental screening and educational materials detailing cardiac deferral criteria were distributed to state and local health officials on March 31, 2003, and published on April 4, 2003 (Box 2).38

Vaccine Adverse Events Monitoring
State and local jurisdictions collected and stored data on every smallpox vaccinates, including demographic characteristics, history of previous smallpox vaccination, vaccine vial lot number, diluent information, and vaccine take status in the Pre-Event Vaccination System database, a secure Web-based tracking system.34 Smallpox vaccine adverse events were identified by reports submitted directly to the CDC, the Vaccine Adverse Event Reporting System (VAERS), and the CDC Clinician Information Line, a 24-hours, 7-days-a-week telephone information system for clinicians.53 VAERS is a national passive surveillance system that receives reports of possible adverse events following receipt of any US-licensed vaccine. Because there is no automated linkage between the Pre-Event Vaccination System (denominator) and VAERS, at least 40 years of age is used within VAERS system as a surrogate for vaccination status (first time vs revaccinates). Routine childhood smallpox vaccination was terminated in 1971 and therefore will likely result in a low estimate of the proportion of revaccinates.

Medical reviewers at the CDC or Food and Drug Administration monitored all VAERS reports for symptom keywords or coding terms that might represent dermatological and neurological conditions or contact and maternal-fetal transmission as described in previous surveillance reports.34 After April 4, 2003,28 reviewers included keywords consistent with ischemic and inflammatory heart disease and new onset heart failure (Box 2). Reported adverse events with keywords consistent with cardiac disease are herein referred to as cardiac events; although, for many cases, a cardiac etiology could not be confirmed or an alternative etiology was identified. Acute cardiac events occurring 6 weeks or more after vaccination were excluded from the analysis of reported cardiac events. Because dilated cardiomyopathy often has an insidious onset, no exclusionary time frame was applied to those cases.

Trained medical officers and nurses conducted intensive clinical investigation of identified potential adverse events. Clinical and demographic data were collected using a standard form, and available medical records were reviewed in collaboration with adverse event coordinators from the state health departments and the treating clinicians. When indicated, specimens were obtained from affected vaccinates and tested at the Laboratory Response Network for evidence of vaccinia virus. Confirmatory testing was performed at the CDC.

Length and Type of Follow-up
Only VAERS reports designated serious by internationally accepted regulatory criteria are routinely followed up. Serious criteria include hospitalization or prolongation of hospitalization, permanent disability, and life-threatening illness or death.35 Letters to obtain information on recovery status are mailed to the reporters (individuals who report to VAERS) at 60 days and 1 year after vaccination. We did not follow up vaccinates routinely after surveillance classification was determined or reexamine noncardiac serious cases in long-term follow-up. State and local jurisdictions followed up vaccinates at 21 to 28 days postvaccination to ensure that serious adverse events and unrecognized contraindications in vaccinates and their close contacts were identified.34 Other stand-alone active surveillance and cardiac follow-up activities are reported elsewhere (M. M. Snidadack, MSN, unpublished data, 2005).40,52,53
Between January 24 and October 31, 2003, 37,901 volunteers in 55 jurisdictions received 38,885 smallpox vaccinations through the DHHS program with a take rate of 92%. Most vaccinees were women (64%), aged 40 to 64 years (78%), and had been previously vaccinated (76%). Vaccinees reported the following occupational categories: hospital health care staff (65%), public health team response personnel

<table>
<thead>
<tr>
<th>Box 1. General Clinical Description of Surveillance Case Definitions Used to Classify Smallpox Vaccine Adverse Reactions Detected in the DHHS Smallpox Preparedness Program*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated Cardiomyopathy</td>
</tr>
<tr>
<td>Dilated cardiomyopathy is defined by the World Health Organization as a disease of the heart muscle characterized by “... dilatation and impaired contraction of the left ventricle or both ventricles. It may be idiopathic, familial/genetic, viral, and/or immune, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. Histology is nonspecific. Presentation is usually with heart failure, which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and may occur at any stage.”†</td>
</tr>
<tr>
<td>Eczema Vaccinatum</td>
</tr>
<tr>
<td>Localized or generalized papular, vesicular, pustular, or erosive rash syndrome approximately 5 to 19 days after exposure through vaccination or close contact with smallpox vaccinee, with a high mortality rate. Lesions can occur anywhere on the body but have a predilection for areas currently or previously affected by atopic dermatitis lesions. Persons with history of atopic dermatitis (or eczema) are at highest risk and often require vaccinia immune globulin treatment. Most severe among first-time vaccinees, young children, and unvaccinated close contacts of vaccinees.</td>
</tr>
<tr>
<td>Fetal Vaccinia</td>
</tr>
<tr>
<td>Rare but often fatal condition characterized by multiple skin lesions, including macules, papules, vesicles, pustules, scars, ulcers or areas of maceration, and epidermolysis (blisters or bullae) in fetus.</td>
</tr>
<tr>
<td>Generalized Vaccinia</td>
</tr>
<tr>
<td>Disseminated maculopapular-vesicular rash containing vaccinia virus that is thought to be due to hematogenous spread and occurs 4 to 19 days following vaccination. More likely to occur in first-time vaccinees. Immunocompetent hosts usually experience a benign self-limited clinical course. Can be life-threatening condition in immunocompromised persons and often requires vaccinia immune globulin treatment.</td>
</tr>
<tr>
<td>Inadvertent Inoculation</td>
</tr>
<tr>
<td>Inadvertent Autoinoculation: Unintentional virus transfer from the vaccination site to elsewhere on the vaccinee’s body. Ocular Vaccinia: Unintentional virus transfer to the eye and surrounding ocular adnexa. Contact Transmission: Unintentional virus transfer to a close contact of a smallpox vaccinee.</td>
</tr>
<tr>
<td>Myocarditis and/or Pericarditis</td>
</tr>
<tr>
<td>A spectrum of disease caused by inflammation of the myocardium and/or pericardium. Patients might have symptoms and signs consistent with myocarditis, pericarditis, or both. For the purpose of surveillance reporting, patients with myocarditis or pericarditis will be reported as having myocarditis and/or pericarditis.</td>
</tr>
<tr>
<td>Postvaccinial Encephalitis or Encephalomyelitis</td>
</tr>
<tr>
<td>Inflammation of central nervous system parenchyma following smallpox vaccination that cannot be attributed to other etiologies.</td>
</tr>
<tr>
<td>Progressive Vaccinia</td>
</tr>
<tr>
<td>Progressive viral replication and infection of skin surrounding the vaccination site or inadvertent inoculation site in persons with underlying immune deficit (humoral or cellular). Development of secondary metastatic lesions can occur. The condition is rare, severe, and often lethal despite aggressive treatment with vaccinia immune globulin.</td>
</tr>
<tr>
<td>Superinfection of the Vaccination Site or Regional Lymph Nodes</td>
</tr>
<tr>
<td>Local reaction that meets temporal and clinical or diagnostic criteria for infection caused by vaccinia. Often confused with major reaction with peak symptoms of redness, pain, swelling, and warmth on postvaccination days 6 to 12.</td>
</tr>
</tbody>
</table>

*DHHS indicates Department of Health and Human Services. For full details of clinical and epidemiology criteria, see Centers for Disease Control and Prevention.†Richardson et al.35
cardiac events to VAERS had already begun to increase, with almost half of the reports describing onset of symptoms before March 26, 2003. A total of 544 VAERS reports (66%) were submitted electronically via a secure Web-based mechanism.26 The comparison of general characteristics of cardiac and noncardiac VAERS reports through October 31, 2003, are shown in the Table.

Overall, vaccinees with adverse events reported to VAERS were similar to the entire pool of vaccinees in terms of age, sex, and vaccination status. Although 64% of all vaccinees were women, 75% of vaccinees reporting adverse events were women. Sixty-six percent of VAERS reports involved persons 40 years or older. When compared with the number of all revaccinees (76%), the percentage of revaccinees involved in reports of adverse events (66%) does not appear to differ, taking into account likely misclassification of vaccinee status due to the use of the age surrogate. In 279 VAERS reports involving persons younger than 40 years (presumed first-time vaccinees), fever, rash, pain, pruritus, and headache were the most common symptoms. Among presumed revaccinees (≥40 years), chest pain, fever, pain, headache, and fatigue were most commonly described (n=541 reports). Chest pain in this context refers to both potential cardiac etiologies and chest pain as a mild systemic symptom.

For the 737 VAERS reports, which included dates for onset of symptoms (87 missing onset interval [11%]), a total of 371 VAERS reports (50%) described onset of symptoms within 7 days (range, 0-181 days) following vaccination, 590 (72%) within 14 days, and only 52 (7%) occurred more than 30 days following vaccination. Symptoms reported on the day of vaccination included local reactions, rashes, dizziness, flushing, headache, and flu-like symptoms. A single VAERS report noted the appearance of a transient and self-limited raised bump at the vaccination site on post-vaccination day 181.

Table. General Characteristics of VAERS Reports Captured by the US DHHS Smallpox Vaccine Safety Monitoring and Response System, January-October 2003

<table>
<thead>
<tr>
<th>VAERS Reports (n = 822)*</th>
<th>Cardiac Event Reports (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All DHHS Vaccinees (N = 37 901)</strong></td>
<td><strong>Myocarditis and/or Pericarditis (n = 21)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Noncardiac Events (n = 613)</strong></td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>48 (18-82)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>24 257 (64)</td>
</tr>
<tr>
<td>Revaccinee, No. (%)</td>
<td>28 805 (76)</td>
</tr>
<tr>
<td>Symptom onset interval, median (range), d</td>
<td>NA</td>
</tr>
<tr>
<td>Met cardiac deferral criteria, No. (%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: DHHS, Department of Health and Human Services; NA, not applicable; VAERS, Vaccine Adverse Event Reporting System.

*Noncardiac and cardiac events do not sum to total number of VAERS reports received because of data exclusion criteria applied to cardiac event reports and 1 report was classified as both generalized vaccinia and nonspecific chest pain.
†Included nonspecific chest pain, arrhythmias, palpitations, dyspnea, and hypertension.
§Insidious onset (2-3 months after vaccination).
§Defined by the Centers for Disease Control and Prevention.29

Box 2. Supplemental Cardiac Deferral Criteria and Select Keywords for VAERS Cardiac Case Ascertainment*

**Cardiac Deferral Criteria**

History of underlying cardiac disease, or at least 3 of 5 major risk factors for atherosclerotic heart disease: hypertension, diabetes mellitus, hypercholesterolemia, smoking, or a history of heart disease in first-degree relative before age 50 years.

**Examples of VAERS Cardiac Case Ascertainment Keywords**

Chest pain, dyspnea, palpitations, hypertension, myocardial infarction, myocardial ischemia, angina pectoris, myocarditis, pericarditis, arrhythmia, atrial fibrillation, ventricular fibrillation, extrasystoles, ventricular tachycardia, heart failure, and cardiomyopathy.

*VAERS indicates Vaccine Adverse Event Reporting System.*
## Serious and Nonserious Reports

One hundred VAERS reports (12%) met internationally accepted regulatory criteria for serious reports, which included hospitalization or prolongation of hospitalization (n=85, 85%), permanent disability (n=2, 2%), life-threatening illness (n=10, 10%), or death (n=3, 3%)\(^{35}\), yielding a rate of 26.4 per 10 000 vaccinees. Three reported deaths included 2 women, aged 55 and 57 years who had myocardial infarctions 1 and 4 days after vaccination, and 1 man, aged 45 years who had a myocardial infarction 69 days after vaccination. Smallpox vaccinees involved in serious adverse events reports did not differ from vaccinees overall in terms of age or sex. Eighty-three percent of persons who experienced serious adverse events were revaccinees, in comparison with 76% of all vaccinees. Inpatient evaluations of potential cardiac-related symptoms yielding negative findings accounted for 33% of all serious adverse events. We categorized the serious reports based on the overriding symptom reported: 33% cardiac, 25% non-specific chest pain, 21% neurological, 14% infection, 3% malignancy, 3% pulmonary (noninfectious), and 1% normal vaccination response.

Seven hundred twenty-two nonserious reports to VAERS included multiple signs and symptoms of mild systemic and self-limited local reactions. Fever (n=137, 18.9%), rash (n=133, 18.4%), pain (n=116, 16.0%), and headache (n=110, 15.2%) were most commonly described. Fatigue (n=98, 13.5%) and pruritus (n=97, 13.4%) were also frequently noted. A total of 443 (61%) of all nonserious reports noted 1 or more of these 6 most frequent symptoms, all of which are consistent with mild expected reactions following receipt of smallpox vaccine.\(^{37,38}\)

In comparing persons involved in serious vs nonserious reports, we found that they differed in age (≧40 years, 81 [81%] vs 458 [64%], respectively). The number of serious and nonserious reports involving women was 68 (68%) and 545 (76%), respectively. For nonserious adverse events, interval to symptom onset was consistent with minor events attributable to viral replication (mean, 13.8 days; median, 7.0 days); however, for serious adverse events, the symptom onset was longer (mean, 17.6 days; median, 9.0 days). Reports without specified date of symptom onset or with onset of more than 120 days post-vaccination were excluded from aggregate data analysis (n=6). All reports were included in case-level analysis.

## Historically Recognized Dermatological and Neurological Adverse Events

No cases of preventable life-threatening adverse reactions, such as eczema vaccinatum, progressive vaccinia, and fetal vaccinia, were reported.\(^{38,43}\) Unintentional transmission of the vaccine virus from the vaccination site accounted for 7 cases of nonocular inadvertent autoinoculation (reporting rate, 1.8 per 10 000 vaccinees) and 3 cases of ocular inadvertent autoinoculation (reporting rate, 0.8 per 10 000 vaccinees). There were no cases of vaccinia contact transmission. Although practicing health care workers were vaccinated, no nosocomial transmissions were reported. Detected nonpreventable adverse reactions included 2 cases of generalized vaccinia, 1 probable and 1 confirmed (reporting rate, 0.5 per 10 000 vaccinees); 1 suspected case of postvaccinal encephalitis with atypical clinical presentation (reporting rate, 0.26 per 10 000 vaccinees); and 2 suspected cases of superinfection of the vaccination site or regional lymph nodes (reporting rate, 0.5 per 10 000 vaccinees).\(^{37,38}\) Reported neurological events were generally mild and self-limited; in a previously published analysis, 17.2% of reports received by VAERS involved headache.\(^{43}\) No cases of erythema multiforme major (Stevens-Johnson syndrome) have been reported among civilian smallpox vaccinees. No vaccinee or contact of our program received vaccinia immune globulin. However, CDC supplied vaccinia immune globulin for the successful treatment of a civilian contact of a DoD vaccinee.

## Cardiac Events

After application of exclusion criteria, 203 possible cardiac events were reported during the study period. These events were characterized by symptoms suggestive of cardiac disease, including chest pain, palpitations, dyspnea, and/or hypertensive episodes, for a rate of 1 possible cardiac event for every 187 civilian smallpox vaccinees (54 per 10 000 vaccinees). Nineteen cardiac events (9%) were first reported to the Clinician Information Line; 184 (91%) were reported to VAERS only. The interval between vaccination and onset of possible cardiac symptoms was 1 to 2 weeks (median, 8 days; range, 0-42 days). Seventy percent of reports were received within 1 month of symptom onset (median interval, 18 days; range, 0-210 days). Ninety-six reported possible cardiac events (47%) occurred before March 26, 2003, the date of the first cardiac Health Alert Notice, although only 20 cardiac events (10%) had been reported by that time. At the time the final cardiac screening criteria were published on April 4, 2003, 138 reported cardiac events (78%) had occurred, 66 (32%) of which had been reported.

Smallpox vaccinees reporting cardiac events were similar to those reporting noncardiac events with regard to age (median [range], 47 [20-70] years vs 43 [17-77] years), percentage of women (75% vs 75%), and onset interval (8 [0-42] days vs 8 [0-181] days). Smallpox vaccinees reporting cardiac events were also similar to civilian vaccinees overall (age, 48 [18-82] years; women, 64%) (Table). One notable exception was the group reporting ischemic cardiac events who tended to be older, more likely to be men, and more likely to meet the recommended criteria for deferral from smallpox vaccination based on risk for atherosclerotic heart disease. Although 27% of the vaccinees reporting cardiac events met the cardiac deferral criteria, all but 1 was vaccinated before April 4, 2003, when the final deferral criteria went into effect. All reported ischemic events occurred in persons vaccinated before the March 26, 2003, Health Alert Notice.
Ten of the reported cases with cardiac symptoms were classified as ischemic cardiac events (5% of total cases or 2.6 per 10,000 vaccinees): 6 myocardial infarctions (2 fatal) and 4 cases of new or accelerated angina. Twenty-one reported cases met the surveillance case definition for myo/pericarditis (5 probable and 16 suspected). The incidence of myo/pericarditis in the civilian smallpox vaccinee population was 1.3 per 10,000 vaccinees, if only probable cases are considered, and 5.5 per 10,000 vaccinees, if suspected cases are included. Two cases of dilated cardiomyopathy with insidious onset 2 to 3 months following vaccination also were detected. There were no cases that had a history of heart failure before vaccination and no cases that had symptoms consistent with acute myo/pericarditis after vaccination but before development of symptoms of dilated cardiomyopathy. A third case of dilated cardiomyopathy with onset in April 2003 was not reported until January 2004, and thus is not included in our analysis. Details about cases of myo/pericarditis, ischemic cardiac events, and dilated cardiomyopathy will be discussed elsewhere.

The remaining 170 cardiac cases, some with more than 1 symptom or condition, included 107 episodes of nonspecific or atypical chest pain, 47 episodes of palpitations without documented arrhythmias, 16 episodes of dyspnea of unclear etiology, 6 documented arrhythmias, and 27 hypertensive episodes (18 isolated episodes of new-onset or accelerated hypertension and 9 episodes that occurred in conjunction with other symptoms). For many, the underlying etiology of the events remains unclear.

**COMMENT**

The comprehensive smallpox vaccine safety monitoring and response system achieved its goal of safe administration of smallpox vaccine among a limited number of DHHS volunteers through successful exclusion of at-risk individuals and rapid detection of unexpected adverse events. Previously known life-threatening adverse reactions, such as eczema vaccinatum and progressive vaccinia historically associated with smallpox vaccination, were not detected. Although direct comparison between historical and present day vaccinated populations is not possible, observed occurrence of other non–life-threatening adverse reactions is similar to descriptions in previous surveillance summaries. Furthermore, myo/pericarditis was successfully recognized and characterized as an adverse reaction associated with the receipt of the NYCOBOH vaccinia strain. Rates of expected, preventable, and noncardiac smallpox adverse events detected in the DHHS smallpox preparedness program were comparable with rates detected in the larger-scale DoD smallpox program. The absence of preventable serious adverse reactions provides indirect evidence of effective vaccination screening and education, as well as attentive vaccination site care and monitoring. Adverse events surveillance through VAERS and the CDC Clinician Information Line also resulted in the early recognition of a number of cases of myo/pericarditis occurring in DoD and civilian smallpox vaccinees. A statistically significantly increased risk of myocardiits among DoD personnel recently vaccinated with the NYCOBOH vaccinia strain compared with unvaccinated military personnel has been demonstrated. The overall rates of probable or confirmed myo/pericarditis in the 2 programs were similar (1.3 per 10,000 vaccinees in the DHHS program and 1.2 per 10,000 vaccinees in the DoD program).

Dilated cardiomyopathy is a recognized rare, serious complication of myocardiits and may result from multiple etiologies. None of the 3 civilian vaccinees with dilated cardiomyopathy (2 in this analysis and 1 reported later) met clinical indications for endomyocardial biopsy and therefore alternative etiologies of dilated cardiomyopathy could not be excluded. Furthermore, reliable data on expected dilated cardiomyopathy rates in comparable populations are not available. Further research on the possible association between smallpox vaccination and myo/pericarditis and dilated cardiomyopathy, the identification of risk factors predisposing to these events, and elucidation of potential biological mechanisms may help to determine additional contraindications to smallpox vaccination.

Limitations of our analysis include those inherent to passive surveillance (underreporting, reporting of temporal associations or unconfirmed diagnoses, and lack of unbiased comparison groups). Some degree of misclassification is inherent with the regulatory distinction between serious and nonserious reports. Designation of an adverse event report as serious does not imply causal association with vaccination. In fact, approximately 90% of all serious reports meeting regulatory criteria described
events not causally attributed to smallpox vaccine during the current or historical vaccination programs (eg, cholecystectomy). 70 Because persons involved in reports of serious adverse events were more likely to be older than those involved in nonserious reports, this may reflect a greater burden of underlying chronic disease associated with aging. Because of the association between increasing age and likelihood of being a revaccinee, it is not surprising that revaccinees were slightly overrepresented among serious adverse events. Determining causal associations between vaccines and adverse event from VAERS reports alone is usually not possible; further study is required. 71 Because of the program’s limited size and lack of complete and specific information on vaccination status and occupational data, full subanalyses of adverse events by these variables could not be performed. Delayed or other adverse events reported after October 31, 2003 (total time, 280 days), will not be captured by this analysis.

In this DHHS program, the Health Alert Notice stimulated reporting to VAERS; the rate of reporting increased and reporting delays decreased following the notice. Stimulation of VAERS reports following timely communication of safety findings is not unexpected. 72 An increase in reports of cardiac-related adverse events was detected by VAERS within 4 days of the Health Alert Notice about possible adverse cardiac consequences. However, data do not support the conclusion that cardiac symptoms were evoked from vaccinates because of the Health Alert Notice, since symptom onset dates preceded the Health Alert Notice. The time course of reporting of smallpox vaccine adverse events to VAERS was not dependent on whether the event reported was cardiac in nature or not; reporting of both cardiac and noncardiac adverse events increased in an accelerated manner for a 2- to 3-week period following the notice, and then decreased in a similar manner.

There are many differences between these adult smallpox vaccinates in the current program compared with the US smallpox vaccine program in the 1960s, which included a predominantly pediatric cohort, many of whom were first-time vaccinates. In some studies, the historical postvaccinal encephalitis frequencies for individuals older than 1 year were so low that temporally associated encephalitis with other etiologies might explain its occurrence. 11-14 Therefore, the single adult postvaccinal encephalitis case should be cautiously interpreted especially in a context of an atypical clinical presentation and small denominator. Another important difference is that the majority of vaccinations in the 2003 DHHS program were administered to health care workers (n = 36 813) with considerable medical knowledge, which may have resulted in more accurate and higher rates of self-deferral for immunological, dermatological, and cardiac exclusion criteria and better vaccination site care. The absence of eczema vaccinatum, postvaccinal encephalitis, and contact transmission supports the success of screening and education efforts, which were similar to the DoD program. 59 The lack of contact transmission may also reflect the population of adult health care worker vaccinates and greater attention to vaccination site care, which minimized opportunities for transfer of the virus from a vaccination site. Notably, in the past, secondary vaccinia transmission typically occurred between young vaccinated and unvaccinated siblings who had close contact. 73 Overall, the 2003 program was conducted with more stringent contraindications, safety surveillance, and educational programs. 12-13

This comprehensive smallpox vaccine safety monitoring and response system can serve as an effective model for vaccine campaigns that may occur in response to public health emergencies. Unique aspects included rapid detection, investigation, and response to rare and potentially serious adverse events. Our report highlights the success of education, screening, and clinical investigations and reviews in augmenting a robust safety monitoring system to minimize preventable adverse events. Additional reduction of overall vaccinia adverse events might be achievable through study of cardiac and dermatological risk factors, a better understanding of vaccinia host-pathogen interaction, and development of a less reactogenic vaccinia vaccine.

Author Contributions: Drs Casey, Iskander, and Mootrey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Casey, Iskander, Roper, Mast, Torök, Chapman, Swerdlow, Morgan, Vitek, Neff, Strikas, Mootrey. Acquisition of data: Casey, Iskander, Roper, Mast, Wen, Torök, Chapman, Swerdlow, Morgan, Heffelfinger, Vitek, Reef, Hashbrouck, Damon, Vellozzi. Analysis and interpretation of data: Casey, Iskander, Roper, Wen, Torök, Chapman, Morgan, Reef, Hashbrouck, Neff, McCauley, Mootrey. Drafting of the manuscript: Casey, Iskander, Roper, Heffelfinger, Mootrey. Critical revision of the manuscript for important intellectual content: Casey, Iskander, Roper, Mast, Wen, Torök, Chapman, Swerdlow, Morgan, Heffelfinger, Vitek, Reef, Hashbrouck, Damon, Neff, Vellozzi, McCauley, Strikas, Mootrey. Statistical analysis: Roper, Torök. Administrative, technical, or material support: Casey, Iskander, Roper, Mast, Chapman, Heffelfinger, Vitek, Reef, Hashbrouck, Damon, Vellozzi, McCauley, Strikas, Mootrey. Study supervision: Casey, Mast, Torök, Swerdlow, Morgan, Heffelfinger, Vitek, Strikas, Mootrey. Financial Disclosures: None reported.

Smallpox Vaccine Adverse Events Monitoring and Response Activity (SVAEMRA) Surveillance Team: Sara Critchley, Hayley Hughes, John K. Iskander, Joyce Coff, Madeline Sutton, Phuc Nguyen-Dinh, Roumiana S. Boneva, Roseanne English, and John Copeland. SVAEMRA Executive Team: Gina Mootrey, Eric E. Mast, Herschel Lawson, and Mary McCauley. SVAEMRA Cardiac Team: Christine Robinette Curtis, Patricia Galloway, Beth Hibbs, Paige Hightower, Nidhi Jain, Nancy H. Levine, Mona Marin, Jacqueline Miller, Juliette Morgan, Pedro L. Maceo, Martha H. Roper, Richard A. Schieber, Margaretta M. Sniadack, and David Swerdlow. SVAEMRA Clinical Team: Francisco M. Averhoff, Christine G. Casey, Louisa E. Chapman, Rosaline Dhara, Kristina L. Ernst, Kirsten Ernst, Kathleen Fullerton, Michael Deming, Daniel Fishbein, Lamar Hashbrouck, James Heffelfinger, Barbara L. Herwaldt, Andrew Kroger, Anne C. Moore, Juliette Morgan, Monica Parise, Meredith Reynolds, Scott Santibanez, James Sejvar, Bruce Tierney, Thomas Torök, Claudia Vellozzi, Charles Vitek, and Xiaojuan Wen. SVAEMRA State Team: Susan Reef, Eduard Eduardo, Masa Tanaka, John H. McCowan, Danice K. Eaton, Carol Knowles, Kathleen McDuffie, Jennifer L. Cleve- land, Jamie L. Fraze, Elizabeth Bolyard, Lynne M. Shulster, Philip M. J. Baptiste III, Cell Threat, Fred Ingram, and Tracy Thomas. Funding/Support: All financial and material support for the surveillance efforts was conducted as part of the Centers for Disease Control and Prevention (CDC) and state health department public health response. No additional funding was sought to support these activities.

Role of the Sponsor: The CDC is responsible for the surveillance activities; data collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript.
SMALLPOX VACCINE SAFETY

Disclaimer: The findings and conclusions in this article do not necessarily represent the views of the funding agency.

Acknowledgment: We gratefully thank the case patients, health care practitioners, state and local health department directors, vaccine adverse event reporting system reporters, State Adverse Event Coordinators, and the CDC SVAERMA team for their assistance in adverse event identification, evaluation, report, and management follow-up.

For assistance in the development of the surveillance case definitions, we thank the Joint Advisory Committee on Immunization Practices—Armed Forces Epidemiologic Board Smallpox Vaccine Safety Working Group, Katrin S. Kohl (CDC), and J. M. Lane (former director of CDC Smallpox Eradication Unit, who was contracted for expertise). We appreciate the surveillance efforts of the Pre-Event Vaccination System staff, David Walker, and Kimm Walton. For coordination of military and civilian data, we thank John Grabenstein and Penina Haber. We appreciate the dermatologic expertise and assistance of Scott A. Norton, Toby Mau- ter, and Art Papier. We thank our CDC colleagues for their expertise and support: Robert T. Chen, Kris Shandy, Lisa Rotz, Connae Cono, Rus Regnery, John Becher, Christopher Allen, Cindy Dougherty, Joe Mu- linare, Karen Broder, Kristin Kenyan, Bruce Weniger, Frank DeStefano, Scott Campbell, Allison Kennedy, Susanne Pickering, Sean Shadomy, Elaine R. Miller, William Flewellyn, and members of the Clinician Information Line and Strategic Pharmaceutical Stockpile. We thank Ann McMahan, Jacquelyn Polder, Marthe G. Bryant Genevier, and Frederick E. Varricchio, our colleagues at the Food and Drug Administration, Center for Bio- logics Evaluation and Research, for their contribution. We thank the CDC staff April Vance, Candice Jackson, Angus Key, Maureen Hernandez, Jans Janson- s, Jamila Rentz, and Tamera Murphy for manage- ment and administrative support.

REFERENCES


©2005 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/5002/ on 06/16/2017


