US Civilian Smallpox Preparedness and Response Program, 2003

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Variola virus, the cause of smallpox disease, has been deemed a possible bioterrorism agent. Since November 2001, federal, state, and local public health partners implemented activities to prepare for a possible smallpox outbreak. The Centers for Disease Control and Prevention (CDC) produced and delivered training and educational materials for smallpox preparedness in many formats, developed detailed smallpox vaccine information statements about vaccine contraindications and vaccination site care, and established mechanisms to monitor and respond to adverse events after smallpox vaccination. The last included enhancements to the Vaccine Adverse Event Reporting System, a pregnancy registry for inadvertently vaccinated pregnant women, and a Clinician Telephone Information Line to collect reports about adverse events. The civilian responder vaccination program was conducted with rigorous safety procedures, and few historically recognized adverse events were observed. However, myocarditis and/or pericarditis was newly recognized as an adverse event caused by the New York City Board of Health vaccinia vaccine strain. This smallpox preparedness program put into place a number of measures to advance the United States’ readiness for a smallpox outbreak that have assisted in preparedness for other threats.

Variola virus, the cause of smallpox, is a Centers for Disease Control and Prevention (CDC) category A bioterrorism agent [1]. It is an agent of great concern, for the following reasons: (1) uncertainty exists about whether all of the variola virus stocks of the former Union of Soviet Socialist Republics can be accounted for; (2) the virus can be highly infectious in susceptible populations (i.e., those unvaccinated or without history of smallpox disease), which now include most of the world; and (3) its ∼30% case fatality rate ranks it as one of the most deadly infectious agents [2].

In November 2001, the CDC developed a smallpox response plan that outlined the major requirements for a smallpox outbreak response [3]. In October 2002, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination of selected public health and hospital health care emergency response personnel [4]. The CDC also recommended that state and local areas receiving federal bioterrorism funds (i.e., the 62 Public Health Emergency Preparedness [PHEP] Cooperative Agreement grantees, including the 50 US states, Puerto Rico, the District of Columbia, New York City, Chicago, Los Angeles, and 7 US territories) take certain actions. These included preparing and training personnel to serve as responders in the event of a smallpox outbreak, improving detection and reporting (surveillance), and putting mechanisms in place to protect the public.

The most recently employed primary strategy to control smallpox was surveillance and containment, or ring vaccination, which has also been recommended by the CDC and ACIP [3, 4] as the initial response to any
smallpox outbreak. In addition, the CDC recommended that, in the event of an outbreak, state and local health departments develop plans to allow rapid expansion of vaccination efforts to achieve vaccination of their populations within 10 days, if needed, as an adjunct to ring vaccination. Ten days was the period chosen because the incubation period of smallpox was usually 12–14 days. Therefore, completing vaccination of the public within 10 days would permit vaccination of most persons within the incubation period of the first generation of cases, limit the second generation of cases, and prevent a third generation of cases.

In December 2002, President George W. Bush announced implementation of a smallpox vaccination program [5]. Two of the program’s components were vaccination of military personnel and voluntary vaccination of civilian public health and medical response teams. The military vaccination program has been described elsewhere [6]. The civilian program was authorized by the Secretary of the Department of Health and Human Services (DHHS) in a declaration on 23 January 2003, which has been annually renewed and is now authorized through 23 January 2008 [7]. The CDC was charged with implementing the civilian preparedness program. The program proposed to train and vaccinate ~500,000 hospital health care workers and first responders [8]. In the present article, we describe the implementation of that civilian smallpox responder vaccination program, also known as the DHHS Smallpox Preparedness and Response Program (DHHS SPRP), beginning in January 2003, and other aspects of smallpox preparedness, including training, surveillance, collaboration with partners, and program evaluation.

METHODS

The CDC smallpox response plan has been revised since 2001, with particular attention paid to disease surveillance. In addition, the CDC developed guidelines for large-scale vaccination, including supporting materials [9]. In 2002, the PHEP grantees developed their own postevent, or postoutbreak, response plans, as well as pre-event vaccination plans. Beginning in 2003, the CDC and its federal, state, and local partners, particularly state and local health departments, worked to further improve smallpox preparedness in a number of ways, described below.

Preparing Responders

Clinician education. Training and education materials for smallpox preparedness were produced and delivered in many formats. These materials covered smallpox disease history, differential diagnosis, vaccine storage and handling, vaccination, vaccine adverse events, and response plans to a smallpox outbreak. The formats included in-person courses held for federal, state, and local public health staff, satellite television broadcasts, CD-ROMs, videotapes, Web-based educational programs, and print materials.

Vaccination screening and vaccination. The CDC developed detailed information materials, including a smallpox vaccine information statement with a number of supplements about reactions after vaccination, vaccination site care, and contraindications to vaccination (including eczema, atopic dermatitis, immunosuppression, and pregnancy) [10]. These materials also included explanations of the role of vaccinia immune globulin (VIG) and cidofovir in treating adverse events after vaccination, as well as an information sheet for contacts of vaccinated persons [10]. A screening worksheet was also developed for potential vaccinees, enabling each to systematically review his or her own health status and that of his or her contacts to identify contraindications to vaccination. To ensure that potential vaccinees were well aware of requirements for vaccination and postvaccination care before vaccination, each completed a medical history and consent form, and, after vaccination, each received a postvaccination follow-up sheet. For health care workers, postvaccination site care included the use of gauze covered by a semipermeable dressing and a layer of clothing while engaged in patient care. In addition, daily vaccination site inspections, with dressing changes (as necessary), were recommended until the vaccination scab fell off [4]. Following reports of ischemic heart disease after smallpox vaccination, the CDC and ACIP revised their recommendations for vaccination to exclude persons with known heart disease and/or ≥3 risk factors for ischemic heart disease [11].

The vaccine used in the program was Dryvax (Wyeth), the vaccinia (smallpox) vaccine currently licensed in the United States. It is a lyophilized, live virus preparation of infectious vaccinia virus. It was prepared from calf lymph with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus and has a minimum concentration of 10⁸ pock-forming units/mL [12]. Two to 3 punctures are recommended for primary vaccination, and 15 punctures are recommended for revaccination. If no trace of blood is visible after vaccination, an additional 3 insertions are recommended, by use of the same bifurcated needle without reinserting the needle into the vaccine vial. If no evidence of vaccine take is apparent after 7 days, the person may be vaccinated again [4].

PHEP grantees identified public health and hospital health care response teams for smallpox vaccination. Public health teams included nursing, medical, epidemiologic, laboratory, and vaccinator personnel. Hospital health care teams included emergency department staff, intensive-care staff, general medical staff, primary-care house staff (i.e., medical, pediatric, and family physicians), medical subspecialists, infection control professionals, respiratory therapists, radiology technicians, security personnel, and housekeeping staff.
The CDC developed a vaccination administration reporting system for state and local health department use (known as the Pre-Event Vaccination System [PVS]), which permitted rapid reporting of vaccination data from states to the CDC. The PVS provided the country with the capability to not only report pre-event vaccination but also prepare for emergency vaccine administration in the event of a national response. The system included a secure Web-based reporting system. Because some states had their own established administration systems, a secure data-exchange system, including exchange specifications, was provided. By either Web-based reporting or data exchange, states were able to provide daily vaccination administration information to the CDC. The capability of the PVS has been refined, and it has become part of the CDC’s Countermeasure Response Administration (CRA) system. The CRA system expands significantly on the capacities of the PVS for national, state, and local use. The CRA system advances functionality that ensures that individuals receive recommended countermeasures and tracks and manages multiple vaccination types, pharmaceutical prophylaxis courses and treatments, isolation and quarantine, and other interventions [13]. The CRA system is one tool public health partners may choose to manage countermeasure and response administration activities within their jurisdictions.

Section 304 of the Homeland Security Act, passed by Congress in November 2002, included provisions that offered liability protection to vaccinated response team personnel, vaccinators, and employers [14]. In April 2003, the Smallpox Emergency Personnel Protection Act was passed. It established the Smallpox Vaccine Injury Compensation Program, a no-fault program to provide benefits and/or compensation to certain individuals; these individuals include health care workers and emergency responders injured as the result of the administration of smallpox countermeasures, including the smallpox vaccine [7]. The Smallpox Emergency Personnel Protection Act also provides benefits and/or compensation to certain individuals who are injured as a result of accidental vaccinia inoculation through contact. The table of injuries included in its provisions was published on 27 August 2003. Additional information about the program and extension can be found at http://www.hrsa.gov/smallpoxinjury/ and http://www.hrsa.gov/smallpoxinjury/frn012907.htm.

Surveillance for adverse events after vaccination. The CDC established a number of mechanisms to both monitor and respond to adverse events after smallpox vaccination. Common reactions were assessed by a survey, performed by Northern California Kaiser Permanente, of 825 vaccinees from 7 states at 10 and 21 days after vaccination [15]. The Vaccine Adverse Event Reporting System (VAERS) was enhanced to allow for more-rapid (within several days of the report) summary reporting. Sixty percent of PHEP grantees (37 of 62) conducted active surveillance among vaccinees ~28 days after vaccination [16]. The active system was implemented on 24 January 2003. In addition, the CDC established the Hospital Smallpox Vaccination Monitoring System, a voluntary, Web-based application developed to assist hospitals or other facilities in real-time monitoring and tracking of health care workers who received smallpox vaccine [17]. This program enrolled 246 health care facilities in 38 states. A pregnancy registry was developed to monitor women who were inadvertently vaccinated while pregnant or who became pregnant shortly after vaccination [18]. The CDC developed a Clinician Information Telephone Line to rapidly respond to clinicians’ concerns about possible adverse events and to send out VIG and/or cidofovir promptly if indicated, with instructions for their use under an Investigational New Drug protocol. Finally, the CDC and the Department of Defense jointly created an independent smallpox vaccine safety working group from the ACIP and the Armed Forces Epidemiology Board (AFEB) membership and outside experts on vaccinia and smallpox. This working group was charged with oversight responsibility for the safety of both the civilian and military vaccination programs [19]. The goal of these measures was to limit adverse events to frequencies lower than those historically observed: (1) inadvertent inoculation (529.2 cases/million primary vaccinations), (2) generalized vaccinia (241.5 cases/million primary vaccinations), (3) eczema vaccinatum (38.5 cases/million primary vaccinations), (4) progressive vaccinia (1.5 cases/million primary vaccinations), and (5) postvaccinial encephalitis (12.3 cases/million primary vaccinations). Death also had occurred in ~1 per million primary vaccinations, usually as a result of progressive vaccinia, postvaccinial encephalitis, or severe eczema vaccinatum [20].

Detection and Reporting

The CDC developed a clinical rash illness algorithm that facilitates rapid assessment and reporting of any person presenting with a febrile rash illness for the likelihood of smallpox versus other similar rash illnesses, most commonly varicella [21]. In 1999, the CDC, in coordination with other partners, such as the Association of Public Health Laboratories and the Federal Bureau of Investigation, developed the Laboratory Response Network (LRN), a network of sentinel and reference hospital and state and local public health laboratories. The LRN included 120 reference laboratories as of December 2003 [22, 23]. Currently, there are >160 member laboratories, and the network continues to be an integral part of the public health system for assessing febrile rash illness. The purpose of the LRN now includes running a network of laboratories that can respond to biological and chemical terrorism and other public health emergencies. The LRN has also grown in the variety of
its member laboratories; it now includes state and local public health, veterinary, military, and international laboratories [23].

Protection of the Public from Smallpox
Since the fall of 2000, the federal government has worked to ensure an adequate smallpox vaccine supply for the entire population of the United States. This has been accomplished by evaluating the smallpox vaccine Dryvax at dilutions of 1:5 and 1:10, to assess how much the previous supply could be extended, and by contracting with Acambis for the development and production of a new tissue culture vaccine using the NYVAC vaccinia virus strain [24, 25]. In addition, following the CDC’s guidance, beginning in October 2002, PHEP grantees have developed contingency plans for rapid vaccination of their respective populations in the event of a smallpox outbreak [26].

Collaboration with Partners
From the outset of expanded smallpox preparedness activities in November 2000, the CDC has worked with a variety of partners. Within the federal government, these included the US Food and Drug Administration and the National Institutes of Health on vaccine development, licensure, and production issues; the Health Resources Services Administration on hospital preparedness; and the Departments of Defense and Veterans Affairs on vaccination programs. At the state and local level, these included health departments and their representative organizations, notably the Association of State and Territorial Health Officials, the National Association of County and City Health Officials, the Council of State and Territorial Epidemiologists, and the Association of Public Health Laboratories.

Program Evaluation
The Institute of Medicine (IOM), following a request from the CDC, convened the Committee on Smallpox Vaccine Program Implementation. The IOM committee met 5 times in open session between December 2002 and March 2004 and issued 6 letter reports, as well as a final summary report [27]. The CDC has conducted a number of evaluations of the smallpox preparedness program. These included evaluation of individuals’ and hospitals’ reasons for participation or non-participation [28–30], individual states’ rates of vaccine take, utility of the information systems used, and long-term follow-up of selected individuals with adverse events after vaccination, with particular emphasis on myocarditis, pericarditis, and other possibly related syndromes [31]. Beginning in 2004, the CDC also submitted target capabilities and measures to the PHEP grantees to guide their assessment of state and local programs in enhancing their overall preparedness to manage responses to all hazards, including smallpox [32]. In the fall of 2005, PHEP grantees were required to assess their capacity to implement mass prophylaxis, including mass vaccination. PHEP grantees were expected to meet the critical task of ensuring that smallpox or other vaccines can be administered appropriately [33]. In the case of smallpox, this assessment included vaccine administered to all known or suspected contacts of cases within 3 days and, if indicated, to the entire jurisdiction within 10 days.

RESULTS
Preparing Responders
Clinician education. In 2003, in-person training courses were attended by 3676 persons. Three special training sessions on smallpox vaccination methods were attended by 318 persons, who, in turn, reported having trained an additional 15,349 persons by December 2003. In 2003, 7 comprehensive satellite television courses were broadcast. Online registration data for these courses indicate that there were at least 69,830 live viewers. Smallpox preparedness was also included in general CDC immunization updates televised in 2004 and 2005. It is estimated that 9248 persons viewed these latter 2 programs. Videotape and CD-ROM versions of the satellite broadcasts were distributed to an additional 172,085 individuals and organizations. Web-based educational programs and materials have been accessed by >1.7 million persons. Beginning in February 2003, the CDC and its state health department partners mailed an information packet on smallpox disease and differential diagnosis to all physicians in the United States. The CDC also published guidance for clinicians, regarding the evaluation and treatment of patients with complications from smallpox vaccination [34], and guidance providing uniform criteria used for surveillance case definition and classification for these previously recognized adverse reactions during the DHHS SPRP [35].

Vaccination screening and vaccination. Through 31 December 2003, 38,783 civilian personnel from all 50 states received licensed smallpox vaccine as part of state and local smallpox preparedness programs (table 1). Of those vaccinated for whom complete data were available (38,518), 16,608 were hospital health care staff, 12,722 were public health response team personnel, and 9188 were defined as other personnel (most of whose occupations were listed as “other health care”). At least 2992 of these other personnel were first responders, such as law enforcement personnel, fire fighters, and emergency medical technicians. The median age of vaccinees was 48 years, with 80% ≥ 40 years of age. Sixty-three percent of vaccinees were women. Too few vaccinees reported racial and ethnic categories to allow meaningful analysis. The number vaccinated per state ranged from 19 in Nevada to 4599 in Texas. The vaccination take rates were 93% in primary vaccinees and 93.5% in revaccinees. At least 1 employee was vaccinated in each of 1854 acute care hospitals (37% of all US acute care hospitals identified by PHEP grantees). Subsequent to 2003, vaccination of response
of illness or pain ascribed to the vaccination [15]. In addition, 53 (8.8%) reported having missed work because their symptoms interfered with performing usual activities, occurred in 6.2% at 10 days and in 4.0% at 21 days. Of the 601 vaccinees surveyed at 21 days after vaccination, 73 (12.5%) reported having missed work for any reason, and 53 (8.8%) reported having missed work because of illness or pain ascribed to the vaccination [15].

The rates of these adverse events were similar to, or lower than, those historically reported [20] (table 2). Of the 8163 women of childbearing age vaccinated during the civilian program in 2003, 10 (0.12%) were discovered, after vaccination, to have become pregnant shortly before or after vaccination, and they were enrolled in the National Smallpox Vaccine in Pregnancy Registry ([18] and CDC, unpublished data). One additional woman vaccinated in the DHHS SPRP was enrolled after 2003. As of September 2006, pregnancy outcome data were available for 376 women vaccinated in both civilian and military programs. Most (77%) were vaccinated near the time of conception, before results of a standard pregnancy test would have been positive. To date, outcome evaluations have not revealed higher-than-expected rates of pregnancy loss (11.9%), preterm birth (10.7%), or birth defects (2.8%), compared with those in healthy referent populations [38–42]. No cases of fetal vaccinia have been identified. Of the 11 women enrolled from the DHHS SPRP, 7 delivered at term, 3 had pregnancy loss, and 1 was lost to follow-up and was not reported in the overall registry results. The Smallpox Vaccine in Pregnancy Registry continues to actively enroll women and to follow infant and early childhood health outcomes [18].

Surveillance for adverse events after vaccination. Active surveillance data for 17,316 vaccinees collected 28 days after vaccination indicated that 81 vaccinees (0.47%) acknowledged having contraindications that were not discovered before vaccination [16]. Common adverse events were reported from the Northern California Kaiser Permanente 10- and 21-day survey [15]. Severe symptoms, such that vaccinees were unable to perform usual activities, occurred in 6.2% at 10 days and in 4.0% at 21 days. Of the 601 vaccinees surveyed at 21 days after vaccination, 73 (12.5%) reported having missed work for any reason, and 53 (8.8%) reported having missed work because of illness or pain ascribed to the vaccination [15].

The CDC continues to provide licensed smallpox vaccine, available on request, to state public health authorities for vaccination of designated smallpox response teams, as outlined in the supplemental recommendations of the ACIP and the Healthcare Infection Control Practices Advisory Committee for using smallpox vaccine in a pre-event vaccination program [4]. This is in coordination with the state smallpox response plans. In addition, the Biologics License Application for intravenous VIG produced by the Cangene Corporation was approved by the US Food and Drug Administration on 2 May 2005. VIG is the recommended agent of choice for treating certain adverse events after smallpox vaccination, including eczema vaccinatum and progressive vaccinia [12]. Physicians seeking consultation on an adverse event were, and are, advised to first notify their state health department. If further consultation is required, VIG is recommended, the physician or state health department should contact the CDC Director’s Emergency Operation Center at 770-488-7100. A CDC smallpox vaccine subject matter expert will provide in-depth consultation and facilitate VIG release as appropriate. As with other vaccine adverse events, smallpox vaccine adverse events should also be formally reported through VAERS.

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Table 1. Demographic characteristics of US civilian smallpox vaccinees, 24 January–31 December 2003.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>47 (9.48)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>48 (17–95)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24,721 (63.7)</td>
</tr>
<tr>
<td>Male</td>
<td>14,062 (36.3)</td>
</tr>
<tr>
<td>Vaccination status, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Primary vaccineee</td>
<td>8914 (23.0)</td>
</tr>
<tr>
<td>Revaccinee</td>
<td>29,315 (75.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>554 (1.4)</td>
</tr>
</tbody>
</table>

NOTE. N = 38,783 for whom complete data are available.
with cardiac risk factors or known heart disease were deferred from vaccination; since that time, no ischemic cardiac events have been reported [36]. The ACIP-AFEB Smallpox Vaccine Safety Working Group concluded that insufficient evidence was available to reject or accept a causal relationship between smallpox vaccination and ischemic heart disease events [19].

Between its inception on 28 January 2003 and 31 December 2003, the CDC’s Clinician Information Line received 3569 smallpox vaccine-related calls, of which 263 (7.4%) were referred to CDC staff. None of the patients discussed in these calls required VIG or cidofovir to treat an adverse reaction to smallpox vaccine. Only 1 civilian received VIG during this period. She developed ocular vaccinia after contact with a military vaccinee [45]. No cidofovir was released under an Investigational New Drug Protocol.

It is important to compare these results from the DHHS SPRP with those from the Department of Defense. As of 17 May 2007, the Department of Defense has reported vaccinating >1.2 million operational forces and health care workers [46]. Most adverse events reported occurred at rates below historical rates. One hundred forty cases of myo/peri carditis developed after smallpox vaccination. Another 16 cases of ischemic heart disease (such as heart attacks, atherosclerosis, or angina) occurred within 6 weeks after smallpox vaccination. This number of ischemic heart disease cases is reported as similar to what normally occurs among unvaccinated military personnel of similar age. Among 27,700 smallpox-vaccinated health care workers, there were no cases of transmission of vaccinia from worker to patient. However, 61 cases (36 laboratory confirmed) of contact transfer of vaccinia virus have occurred after vaccination of military personnel, principally to spouses and adult intimate contacts. One case of eczema vaccinatum occurred, but no cases of progressive vaccinia occurred [47]. The total number of treatments with VIG given to military personnel or their contacts has been 6: 1 patient with burns, 1 patient with eczema vaccinatum, 1 contact transmission, 2 patients with ocular vaccinia, and 1 unconfirmed contact transmission. Forty-three patients with possible generalized vaccinia were reported, all of whom were treated primarily as outpatients. Eight deaths due to disease after vaccination have been reviewed; 1 after an acute lupus-like illness may have been caused by vaccinia.

### Table 2. Selected adverse events associated with smallpox vaccination in the civilian Smallpox Preparedness and Response Program, by type—United States, 24 January–31 December 2003.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Suspected</th>
<th>Probable</th>
<th>Confirmed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema vaccinatum</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fetal vaccinia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Generalized vaccinia</td>
<td>2 (51.6)</td>
<td>0 (0)</td>
<td>1 (25.8)</td>
<td>3 (77.3)</td>
</tr>
<tr>
<td>Inadvertent inoculation, nonocular</td>
<td>11 (283.6)</td>
<td>0 (0)</td>
<td>9 (232.1)</td>
<td>20 (515.7)</td>
</tr>
<tr>
<td>Ocular vaccinia</td>
<td>1 (25.8)</td>
<td>0 (0)</td>
<td>2 (51.6)</td>
<td>3 (77.3)</td>
</tr>
<tr>
<td>Progressive vaccinia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Erythema multiforme major (Stevens-Johnson syndrome)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocarditis and/or peri carditis</td>
<td>16 (412.6)</td>
<td>5 (128.9)</td>
<td>0 (0)</td>
<td>21 (541.5)</td>
</tr>
<tr>
<td>Postvaccinal encephalitis or encephalomyelitis</td>
<td>1 (25.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (25.8)</td>
</tr>
<tr>
<td>Pyogenic infection of vaccination site</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of cases (rate per million vaccinated persons) and include those under investigation or completed as of 31 December 2003; nos. and classifications of adverse events are updated regularly in *Morbidity and Mortality Weekly Report* as more information becomes available.

- **Suspected** if they have clinical features compatible with the diagnosis but either further investigation is required or additional investigation of the case did not provide supporting evidence for the diagnosis and did not identify an alternative diagnosis.
- **Probable** if possible alternative etiologies are investigated and supportive information is found.
- **Confirmed** if virologic test results are positive. The last 4 events are classified as “confirmed” on the basis of diagnostic testing (e.g., histopathological testing); confirmation of events thought to be immunologically mediated (i.e., erythema multiforme, myocarditis and/or peri carditis, postvaccinal encephalitis, or encephalomyelitis) does not establish causality.

### Table 3. Number of cases of other adverse events reported after smallpox vaccination among civilians, by severity—United States, 24 January–31 December 2003.

<table>
<thead>
<tr>
<th>Other adverse events</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriousb</td>
<td>97</td>
</tr>
<tr>
<td>Nonseriousb</td>
<td>712</td>
</tr>
</tbody>
</table>

**NOTE.** Cases are those under investigation or completed as of 31 December 2003; nos. and classifications of adverse events are updated regularly in *Morbidity and Mortality Weekly Report* as more information becomes available.

- **Serious** includes events that result in hospitalization, permanent disability, life-threatening illness, or death. These events are temporally associated with vaccination but are not necessarily causally associated with vaccination.
- **Nonserious** includes expected self-limited response to smallpox vaccination (e.g., fatigue, headache, pruritis, local reaction at vaccination site, regional lymphadenopathy, lymphangitis, fever myalgia and chills, and nausea); additional events are temporally associated with smallpox vaccination but are not necessarily causally associated with vaccination.
cination, on the basis of review by 2 independent panels of civilian physicians. Additional information on this case is available at http://www.smallpox.mil/event/panelreport.asp. Another case involved the sudden death of a 26-year-old soldier given smallpox and influenza vaccines 16 days earlier; in this case, evidence of parvovirus B19 was found in his heart tissue. The other deaths involved the following diagnoses (1 each, except as noted): myocardial infarction, atherosclerotic coronary vascular disease (2), pulmonary embolism, heat injury, and benzodiazepine overdose. These deaths were judged to be unrelated to vaccination, on the basis of individual factors such as preexisting disease, incidence among unvaccinated people, and lack of physical evidence to implicate a vaccine [46].

Detection and Reporting
The CDC clinical rash illness algorithm has been widely disseminated and was included in the mailing to US physicians in 2003. From January 2002 through 31 December 2003, the CDC received 36 reports about patients suspected to have smallpox. All of these were categorized as low [32] or moderate [4] risk for smallpox. Twenty-four of the patients had laboratory specimens collected and evaluated to assist in the diagnosis, and the remainder had a clinical diagnosis only. Varicella infection accounted for 16 (47%) of the cases, and no one had smallpox [48]. A prospective, multicenter study examined the performance of this algorithm for patients with an acute, generalized vesicular or pustular rash (AGVPR) admitted to emergency departments and inpatient units of 12 acute-care hospitals in 6 states. Of 26,747 patients (3.5% of all admissions) with rash-like conditions screened, 89 (1.2 patients per 10,000 admissions) had an AGVPR. Physicians or study staff classified none of 73 enrolled patients as being at high risk for smallpox; 72 (99%) were classified as being at low risk, and 1 was classified as being at moderate risk. The discharge diagnosis for 55 (75%) of these 73 participants was varicella illness [21].

As of June 2007, 83 LRN laboratories can perform rapid assays to support the rash illness testing algorithm for varicella, vaccinia, and orthopoxvirus, which can be used in combination to rule out variola (smallpox) virus infection. A number of these same laboratories have the facilities and trained personnel needed to perform variola virus–specific testing. All LRN reference laboratories (>160) have the contact information needed to quickly refer suspect specimens to the closest LRN laboratory if their laboratory is unable to perform variola virus–specific testing.

Protection of the Public from Smallpox
Enough smallpox vaccine is presently available to vaccinate the entire US population. In addition to the Dryvax smallpox vaccine currently being used in both the military and civilian responder vaccination programs, ~85 million doses of stored vaccine were discovered by Aventis Pasteur. This latter vaccine has also been shown to be immunogenic if diluted 1:5. Acambis, under its contract with the US government, has delivered 192.5 million doses into the Strategic National Stockpile. The vaccine was approved by the US Food and Drug Administration on 31 August 2007 [25].

The CDC issued guidance in its smallpox response plan for large-scale use of smallpox vaccine, with estimated resource requirements to vaccinate 1 million people in 10 days [26]. An October 2003 survey by the Association of State and Territorial Health Officials indicated that 30 (60%) of 50 states responding to the survey reported that they could vaccinate their populations against smallpox in 10 days [49]. Reporting in response to the 2005 PHEP guidance for smallpox mass vaccination capability has been incomplete, and further assessments are under way. However, all states were funded and tasked to enhance mass vaccination capability in preparation for an influenza pandemic [50]. In 2007, ≥80% of PHEP grantees reported capability for mass vaccination in the setting of an influenza pandemic, including adequate staffing, clinic locations, security, vaccine storage, and monitoring of adverse events (CDC, unpublished data).

To address mass vaccination capability, grantees continue to (1) train public health responders in smallpox vaccination roles, (2) work with local health departments to ensure that all have a smallpox response plan, (3) conduct exercises of state and local smallpox response plans, and (4) improve smallpox vaccination electronic tracking systems. For example, the North Carolina Division of Public Health has developed and promoted an algorithm for smallpox mass vaccination clinics and has established standing orders for smallpox vaccine for use in local health departments. In addition, they have provided smallpox vaccination refresher certification courses for medical volunteers as needed, conducted training and drills with Public Health Regional Surveillance Teams on rapid case-tracing methodology using handheld PC technology, and maintained up-to-date information on their cache of smallpox vaccine.

The New York City Department of Health and Mental Hygiene (NYC DOHMH) has maintained surveillance for suspected smallpox cases by maintaining awareness among health care providers who need to report patients with suspicious rashes. In addition, it has developed protocols and provided staff training and patient simulation drills at all hospital emergency departments and primary care clinics, regarding appropriate triage of patients presenting with fever and rash symptoms. The NYC DOHMH has continued to conduct smallpox vaccination technique training, and, as of June 2007, a total of 1021 individuals from hospitals, New York City agencies, and the NYC DOHMH has received smallpox vaccination training. At least 5 clinical staff members from 57 New York City hos-
pitals have received training. An additional 13 hospitals have 1–4 staff members trained. As of 31 October 2005, >291,400 vaccine doses have been released to state health departments for the civilian smallpox responder program. Much of the unused vaccine is in storage in the states and offers an additional state preparedness measure, since the vaccine could be used to begin vaccinations in response to a public health threat involving smallpox until additional vaccine can be delivered from the Strategic National Stockpile.

**Collaboration with Partners**
The CDC held regular conference calls with state and local public health departments and health care provider partners to review program implementation issues, pending policy changes, and program progress. These occurred 3 times per week initially, then once per week through 2003 and as necessary.

**Program Evaluation**
The IOM Committee on Smallpox Vaccine Program Implementation reports addressed all facets of the vaccination program, including vaccination screening materials and processes, surveillance for adverse events, and information systems. The active surveillance system for adverse events was implemented following this committee’s recommendation [16]. The committee concluded that they were uncertain whether preparedness for a smallpox outbreak had been enhanced [27]. Their major concerns included the lack of a clear definition of preparedness; an apparent primary focus on numbers of persons vaccinated; poor communication to health care workers and potential responders, as well as to the public, about the goals of the program; and lack of information about how performance indicators for states were being developed and implemented [27].

The CDC, in addition to conducting program evaluation of training, vaccination, adverse-events monitoring, and rash illness surveillance described above, conducted surveys of health care workers, first responders, and program coordinators in hospitals and local health departments. These surveys assessed predictors of smallpox vaccination and nonvaccination. Health departments had higher vaccination rates than hospitals, as did facilities that invited <10 employees to be vaccinated [29]. The leading reason for vaccination was preparation for participation in a smallpox response team [30]. Leading reasons for nonvaccination were the belief that the risk of smallpox was not high enough to warrant the risks of vaccination and concern about vaccine adverse events [28, 30]. Hispanic, black, and Asian individuals were significantly more likely than white individuals to be somewhat or very concerned about vaccine adverse events [28].

**DISCUSSION**
We believe that the smallpox preparedness program with the accomplishments outlined in this article has strengthened preparedness and the public health infrastructure. The clinician education component of the program reached out to all public health departments and to all physicians and nurses in the United States. The program also included the first effort at large-scale organized civilian smallpox vaccination since 1971. Although the number of persons vaccinated was small in comparison with the initial proposed target, the infrastructure developed to support the vaccination effort, such as plans, educational materials, adverse-events surveillance systems, and vaccination monitoring, was substantial. This infrastructure laid the groundwork for subsequent preparedness activities, such as those for pandemic influenza preparedness [51].

The small numbers of vaccinations in comparison with the larger numbers projected by state and local health departments in their initial plans likely reflect the voluntary nature of the program, concerns about adverse events after vaccination, and, possibly, the fact that standard provisions for compensation for illness from those adverse events were not put in place until after the program began [27]. Uncertainty about the likelihood of a smallpox outbreak has also been cited as a reason for limited vaccination uptake [28, 30]. Both the DHHS SPRP and Department of Defense vaccination programs have been conducted with rigorous safety measures and have resulted in rates of adverse events similar to or lower than those historically observed. In the DHHS SPRP, there were no reports of contact transmission of vaccinia virus. However, both in this program and in the military, myo/pericarditis was newly recognized as an adverse event caused by the NYCBOH vaccinia vaccine strain, with probable cases occurring at the rate of ~116–541 cases/1,000,000 vaccinees.

The rates of successful vaccination (take rates) of 93%–93.5% documented among civilian vaccinees were slightly lower than that reported among military vaccinees, 95%. These differences may have been attributable to very conservative take readings in the civilian program. In August 2003, the CDC issued revised guidance to improve take readings and assessment of immunity after vaccination [52].

The relatively few inquiries to the CDC about febrile patients with rash illnesses that might be smallpox suggested that widespread dissemination of the rash illness algorithm has been successful in assisting clinicians and public health staff in evaluating such patients at the local level. Alternatively, it may be that physicians did not seriously consider smallpox in the differential diagnosis of potentially compatible clinical illnesses.

In collaboration with external partners, the CDC established performance indicators for the PHEP grantees in 2005, including many relevant to smallpox preparedness [33]. These
indicators had 4 goals, corresponding to 4 phases of public health emergencies: (1) pre-event planning and infrastructure development, including the development of emergency plans, formalizing of networks and mutual collaborative relationships, workforce development, and vulnerability assessment; (2) systems for early detection and reporting of illnesses related to biological, chemical, and radiological agents, to recognize opportunities for early intervention; (3) response and containment, including the marshalling of resources and systems for the escalation of public health capacity during an emergency; and (4) recovery, including mental health services, remediation of community risk, and incorporating lessons learned into emergency plans and procedures. These indicators address 2 of the concerns of the IOM committee, in that general preparedness for urgent health threats has been addressed, beyond the narrow focus of preparedness for a smallpox outbreak, and that performance indicators are in place and utilized.

The purposes of the indicators were to (1) define and establish a fundamental level of preparedness against which grantees can measure their progress; (2) help the CDC identify technical assistance needs for the grantees; (3) serve as the foundation for future evaluations of grantee preparedness programs; (4) help the CDC develop milestones, targets, and standards to be used in future CDC guidance; and (5) help quantify the resources—human and fiscal—necessary to be fully prepared at the local, state, and federal levels. To date, assessments of implementation have been incomplete, but more are under way.

These indicators were derived from the concentrated effort in the smallpox program and facilitated the evolution of current thinking about general preparedness for responding to all public health emergencies attributed to all hazards. Many of the specific program and policy efforts during the DHHS SPPR initiative were successful in leading to an improved public health response to emergencies such as the severe acute respiratory syndrome and monkeypox outbreaks [27, 33]. The capacity to move vaccine into communities and build up the infrastructure to conduct mass campaigns is a major strategy for containment of the transmission of many biological threats to health, including pandemic influenza [54]. By maintaining and exercising emergency response plans for smallpox, the public health community has improved the local capacity to respond to infectious disease threats.

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