Generalized Vaccinia, Progressive Vaccinia, and Eczema Vaccinatum Are Rare following Smallpox (Vaccinia) Vaccination: United States Surveillance, 2003

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Generalized vaccinia (GV), progressive vaccinia (PV), and eczema vaccinatum (EV) are adverse reactions following smallpox vaccination. We investigated all reports suggestive of GV, PV, or EV among United States civilian smallpox vaccinees during 2003 and applied standard case definitions. We identified 29 reports of possible GV among 38,440 vaccinees; 2 (7%) of the reports met the case definition. One case of GV was confirmed by identifying vaccinia from a lesion distant from the vaccine site using polymerase chain reaction. The other case was classified as probable GV, because confirmatory testing was not done. We identified 3 potential EV cases and 7 potential PV cases, none of which met the standard case definition. GV, PV, and EV were rare or absent following smallpox vaccination after careful screening of potential vaccinees. GV may be difficult to distinguish from other rashes, and confirmatory testing is recommended. Careful prevaccination screening probably contributed to the low incidence of these adverse reactions following smallpox vaccination.

As part of a national bioterrorism preparedness program, on 24 January 2003, the Department of Health and Human Services (DHHS) authorized voluntary smallpox vaccination of civilian health care workers and members of smallpox response teams identified by state and local health departments. These were individuals who might be called on to monitor or treat persons exposed to smallpox (variola) in the event of a bioterrorist attack [1]. The military began vaccinating against smallpox in December 2002 for bioterrorism preparedness [2]. In June 2001, the Advisory Committee on Immunization Practices (ACIP) recommended using smallpox vaccine to protect those working with orthopox viruses and to prepare for a possible terrorist attack [3].

The Centers for Disease Control and Prevention (CDC), together with state and local health departments, administered the DHHS smallpox preparedness and response vaccination program and established surveillance for adverse events following vaccination. Guidelines for prevaccination screening and postvaccination care were carefully planned and implemented in accordance with ACIP recommendations [4]. These guidelines were largely based on knowledge gained from previous routine vaccination in the United States during the 1960s [5–8] and an understanding of the pathophysiology of some of the adverse events [9, 10].

Generalized vaccinia (GV) following smallpox vaccination is the result of viremia [11]. Although rare and relatively benign, GV needs to be differentiated from other potentially more serious adverse events, such as eczema vaccinatum (EV) and progressive vaccinia (PV), as well as rashes that are not the result of a vaccinia viremia. GV can also be confused with varicella and smallpox. Skin lesions appear ∼1 week after smallpox vaccination and are similar in appearance to the lesion of the primary vaccination, but they are usually smaller and evolve more rapidly to scarring [11].

EV is a potentially serious illness that occurs in the skin of patients with atopic dermatitis (eczema) and other dermatitides that disturb the skin barrier. The skin becomes widely infected with vaccinia, possibly from a viremia or direct contact [11]. EV can occur if the atopic dermatitis is active or inactive at the time of vaccination, [12]. It often appears as pustular and
erosive lesions in confluent patterns in areas of the skin that are typically affected by the underlying skin disease. PV is the most severe adverse reaction associated with vaccinia and is life threatening. The first sign of PV is delayed healing or lack of healing of the vaccination site by day 15 following vaccination. The vaccinee usually appears well initially. Viremia can lead to secondary lesions on the body; the lesions can become necrotic, secondary infection may ensue, and the patient can become septic [10, 11]. EV and PV have known risk factors; prevenient vaccination screening recommendations target the prevention of these 2 adverse reactions [4].

A joint Smallpox Vaccine Safety Work Group (SVSWG) of the ACIP and Armed Forces Epidemiological Board (AFEB), in collaboration with the CDC, smallpox vaccine experts, and other medical specialists, developed surveillance case definitions for select adverse events following smallpox vaccination, which include GV, EV, and PV. We report the results of our surveillance activities using these case definitions during January 2003–December 2003 for GV, EV, and PV.

METHODS

Design and source of reports. We reviewed all adverse event reports with dermatological manifestations following smallpox vaccination during January 2003–December 2003 among US civilians. We then investigated those reports that were suspicious for GV, EV, and PV and assigned each report a working diagnosis for the suspected adverse reaction. Reports came from the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system established in 1990 that accepts reports of adverse events following any United States licensed vaccine from providers, health care workers, or the public [13]. Reports were also received through calls to the CDC Clinician Information Line, a toll-free number staffed 24 h per day, 7 days per week, by trained nurses to answer smallpox vaccine questions from providers or state health department personnel and, when necessary, triage these calls to clinical consultants at the CDC [4]. Some reports came directly to the CDC. We excluded reports regarding military vaccinees, and we referred such reports to the military smallpox vaccination program.

Study physicians contacted and interviewed the person reporting the adverse event and/or the health care provider who administered the vaccine. We used a standard questionnaire to collect information about the clinical details for the dermatological condition, demographic information, medical history, number of previous smallpox vaccinations, laboratory results, treatments, and the clinical outcome. We routinely requested digital photos. The coordinator for smallpox adverse events in each state often assisted in data collection. We consulted on the management of cases when asked to do so by the state coordinator. We always informed the state health department of outcomes. We kept all data confidential.

In February 2004, 20 reports with a working diagnosis of GV, EV, or PV were reviewed by the dermatology subgroup of the ACIP-AFEB SSVWG, which included dermatologists and smallpox vaccine experts. This group reviewed digital photographs and clinical data captured in our initial investigation. This review included all reports with a working diagnosis of GV that were accompanied by a photograph. The dermatology subgroup provided a final diagnosis for these reports.

Case definitions. Tables 1–3 present the standardized case definitions that we used to classify reports of GV, EV, and PV. These case definitions were agreed on by the ACIP-AFEB SSVWG on 8 April 2003, with input from the dermatology subgroup. We required laboratory evidence for vaccinia virus—either (1) by culture or (2) by PCR assay or antigen detection techniques, electron microscopy, or histopathological examination showing orthopox cytopathic changes—to confirm a case of GV, EV, or PV. Samples obtained from lesions needed to be distal from the vaccination site or from the likely site of inoculation (in a contact) when testing to confirm GV or EV.

Data management and analysis. We entered data into a database using Microsoft Access, version 10.0 (Microsoft), and we included clinical narratives. We completed descriptive analysis and calculated adverse reaction rates. We used the pre-event vaccination system (a registry for pre-event civilian smallpox vaccinees) [14] to determine the number of all smallpox vaccinees as a denominator to calculate rates and to determine the demographic distribution among all vaccinees.

RESULTS

Generalized vaccinia. Out of 38,440 civilian smallpox vaccine recipients, we identified and reviewed 29 reports of subjects who had received a working diagnosis of possible GV during January 2003–December 2003 (rate, 80 reports per 100,000 vaccine recipients). Most vaccinations were administered and 27 of the 29 reports of possible GV were received during February–April 2003 (figure 1). For the subjects with possible GV, the mean age was younger (37 years) and the percentage of females was greater (21 [72%] of 29 subjects), compared with all vaccinees (mean age, 47 years; female subjects, 64%). Thirteen (65%) of 20 subjects with known vaccination status were first-time vaccinees, whereas, among all vaccinees, only 24% were first-time vaccinees (table 4). The mean time to onset of the adverse event following vaccination was 11 days (median time to onset, 9 days; range, 2–20 days). Fifteen of the 29 reports included a digital photo of the rash. We concluded that, of the 29 reports, only 2 (7%) met the GV case definition, resulting in an incidence of 52 cases per 1,000,000 vaccinations (i.e., 2 cases per 38,440 vaccinations); 1 of these cases was confirmed
Table 1. Surveillance case definition for generalized vaccinia following smallpox vaccination, for use in smallpox vaccine adverse event monitoring and response.

Overview

Generalized vaccinia is a disseminated vesicular or pustular rash appearing anywhere on the body ≥4 days after smallpox vaccination and may be accompanied by fever. Generalized vaccinia can also appear as a regional form that is characterized by extensive vesiculation around the vaccination site or as an eruption localized to a single body region. The skin lesions of generalized vaccinia are thought to contain virus spread by the hematogenous route. Primary vaccinees are at higher risk for generalized vaccinia than revaccinees. Generalized vaccinia is usually self-limited among immunocompetent hosts. VIG might be beneficial in the rare case in which an immunocompetent person appears to be systemically ill. Generalized vaccinia is often more severe among persons with underlying immunodeficiency, and these patients might benefit from early intervention with VIG.

Comments

1. Systemic symptoms may be present
2. At early onset of some cases, skin lesions may be macules or slightly elevated papules; in late cases, lesions may have developed scabs
3. History or clinical signs of eczema/atopic dermatitis or Darier disease or severe illness should prompt evaluation for eczema vaccinatum
4. Presence of acute or chronic exfoliative, erosive, or blistering skin disease (e.g., acute burn or epidermolytic hyperkeratosis) should prompt consideration of multiple inadvertent inoculations
5. A vaccinial skin eruption characterized by grouped vesicles or pustules close to or surrounding the vaccination site but which do not appear to be satellite lesions (e.g., on the basis of the presence of a large number of lesions and/or evidence that the lesions are due to hematogenous spread of vaccinia) may constitute a regional form of generalized vaccinia

Case definition

A probable case of generalized vaccinia occurs in persons recently vaccinated or in a close contact of a recent vaccinee who meet the following criteria:

- Vesicular or pustular eruption at ≥1 body area distant from the vaccination site or inadvertent inoculation site
- Skin eruption occurring ~4–19 days following smallpox vaccination or contact with someone vaccinated against smallpox
- Lesions follow approximately the same morphological progression as a primary vaccination site (i.e., papule, vesicle, pustule, scab, and scar)
- Unlikely that autoinoculation accounts for skin eruption
- Other likely etiologies have been excluded

A confirmed case of generalized vaccinia occurs in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and for whom there is laboratory evidence of vaccinia infection (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site [if identifiable] in a close contact of a known vaccinee or in a patient who is not known to be a close contact), as follows:

- Demonstration of vaccinia virus by culture, or
- Histopathologic examination showing typical orthopox cytopathic changes and either PCR assay or antigen detection techniques (e.g., direct fluorescent antibody testing) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus, which are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture

NOTE. VIG, vaccine immune globulin.
Table 2. Surveillance case definition for eczema vaccinatum following smallpox vaccination, for use in smallpox vaccine adverse event monitoring and response.

Overview

Eczema vaccinatum is a localized or generalized papular, vesicular, pustular, or erosive rash syndrome that can occur anywhere on the body, with a predilection for areas currently or previously affected by atopic dermatitis lesions. Persons with a history of atopic dermatitis are at highest risk for eczema vaccinatum. Onset of the characteristic lesions can be noted either concurrently with or shortly after the development of the local vaccinial lesion in vaccinees. Eczema vaccinatum cases resulting from secondary transmission usually appear with skin eruptions ~5–19 days after the suspected exposure. Eczema vaccinatum lesions follow the same dermatological course (i.e., progression) as the vaccination site in a vaccinee, and confluent or erosive lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are frequently systemically ill. Eczema vaccinatum tends to be most severe among first-time vaccinees, young children, and unvaccinated close contacts of vaccinees. Prior to the availability of VIG, this condition had a high mortality; establishing the diagnosis early and treating with VIG is crucial in reducing mortality.

Comments

1. Although a history consistent with eczema/atopic dermatitis or Darier disease is included in the surveillance definition for eczema vaccinatum, clinicians evaluating vaccinees or close contacts of recent vaccinees with a presentation consistent with eczema vaccinatum who do not report having 1 of these dermatologic conditions should still consider eczema vaccinatum as a clinical diagnosis and assess for treatment with VIG.

2. Lesions of eczema vaccinatum are in approximately the same stage of morphologic development as each other and progress.

3. Darier disease, also known as keratosis follicularis, is a rare, dominantly inherited, keratinizing skin disorder, characterized by innumerable crusts and epidermal fissures, most prominent on seborrheic areas (e.g., behind ears and on the neck and sternum). The clinical manifestations, once evident, are lifelong but can wax and wane in severity.

Case definition

A probable case of eczema vaccinatum occurs in a person recently vaccinated or in a known close contact of a recent vaccinee who meets the following criteria:

- A history of or current exfoliative skin condition consistent with a diagnosis of eczema/atopic dermatitis or Darier disease
- AND
- Multiple skin lesions that Developed in a vaccinated person either concurrently or soon after lesion at vaccination site or in a close contact of a recent vaccinee up to 3 weeks after exposure, if time of relevant exposure is known, and
  - Are distant from the vaccination or the likely inoculation site (i.e., they are unlikely to be satellite lesions), and
  - Are or become multiple vesicular/pustular sometime during their evolution (i.e., do not remain macular or papular). Erosive or ulcerative lesions may be seen.
- AND
- Other likely etiologies have been excluded, such as eczema herpeticum (which can be particularly difficult to distinguish), smallpox, chickenpox, disseminated herpes zoster, or pustular (bacterial) impetigo

A confirmed case of eczema vaccinatum occurs in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and for whom there is laboratory evidence of vaccinia infection (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site [if identifiable] in a close contact of a known vaccinee or in a patient who is not known to be a close contact), as follows:

- Demonstration of vaccinia virus by culture, or
- PCR assay or antigen detection techniques (e.g., direct fluorescent antibody testing) revealing vaccinia, histopathologic examination showing typical orthopox cytopathic changes, and electron microscopy of biopsy specimens revealing orthopox virus, which are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture

NOTE. VIG, vaccine immune globulin.
**Table 3. Surveillance case definition for progressive vaccinia, for use in smallpox vaccine adverse event monitoring and response.**

### Overview
Progressive vaccinia refers to continued vaccinia virus replication, with progressive infection of skin surrounding the vaccination site or inadvertent inoculation site and sometimes the development of secondary metastatic lesions in a person with underlying immune deficit (humoral or cellular). The condition is rare, severe and often lethal. The description of the vaccination site lesion is usually that of a necrotic lesion; however this is not the only presentation described with progressive vaccinia. Lesions can appear “clean”, fungated, piled-up, or have bacterial superinfection.

### Case definition

A **suspected case** of progressive vaccinia occurs in persons recently vaccinated or in a known close contact of a recent vaccinee who meets the following criteria:

- A known or suspected depressed or defective immune system (suspicion may first arise as result of clinical suspicion of progressive vaccinia)
- AND
- A vaccination site lesion or inadvertent inoculation site with 1 of the following criteria:
  - No or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion
  - Progressive expansion ≥15 days after vaccination
  - Failure to heal or failure of lesion to regress ≥15 days after vaccination
- AND
- Other likely etiologies, such as bacterial superinfection, have been excluded

A **probable case** of progressive vaccinia occurs in persons recently vaccinated or in a known close contact of a recent vaccinee who meets the following criteria:

- A known or suspected depressed or defective immune system
- AND
- A vaccination site lesion or inadvertent inoculation site with 1 of the following criteria:
  - No or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion
  - Progressive expansion ≥21 days after vaccination
  - Failure to heal or failure of lesion to regress ≥21 days after vaccination
- AND
- Other likely etiologies, such as bacterial superinfection, have been excluded

A **confirmed case** of progressive vaccinia occurs in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a suspected case and for whom there is laboratory evidence of vaccinia infection (on the basis of testing skin lesions ≥15 days after vaccination or likely time of inoculation in a close contact of a recent vaccinee or in persons with no known contact with a vaccinee), as follows:

- Demonstration of vaccinia virus by culture, or
- Histopathologic examination showing typical orthopox cytopathic changes and either PCR assay or antigen detection techniques (e.g., direct fluorescent antibody testing) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus, which are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture

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A revaccinee presented with generalized red papules on the face, trunk, arms, thighs, and neck 8 days after smallpox vaccination. She also had systemic symptoms of headache, nausea, and vomiting that resolved by day 10 following vaccination. The rash persisted and progressed to pustules and scabs at various stages on her body. On day 21 following vaccination, the rash had resolved except for 1 scab on her leg. This scab dropped off. No laboratory tests or digital images were obtained. This case was not reviewed by the dermatology subgroup of the ACIP-AFEB SVSWG, because there were no images available. We classified this case as probable GV because no other etiology for the rash was identified.

**EV and PV.** We identified and reviewed 7 reports that had received a working diagnosis of possible PV and 3 that had received a working diagnosis of possible EV. All 10 reports were received during March–May 2003. Six of the 10 patients had laboratory testing of material taken from the lesions, and all test results were negative for vaccinia. We received digital images for 7 of these cases. Of the 7 reports of possible PV, 5 received a final diagnosis of delayed healing of the vaccination site (time to complete healing after vaccination, 27–75 days), and 2 were classified as nonspecific rashes. One laboratory test in a case of possible EV confirmed a diagnosis of varicella zoster virus infection in a 6-year-old boy who was a close contact of a vaccinee. One case of possible EV was determined to be an eczematous dermatitis unrelated to vaccinia and another was determined to be a nonspecific rash. None of these reports met the case definition for either PV or EV.
DISCUSSION

The rates of GV, EV, and PV that we found are much lower than those reported in the studies conducted in the 1960s in the United States [5–8]. There are several differences between the recent pre-event vaccination program and the vaccination activities in the 1960s. First, the recent program vigorously screened prospective vaccinees with a detailed multistage protocol that eliminated persons having or living with patients with immunodeficiencies, atopic dermatitis, or other exfoliative skin conditions [4, 16]. Second, the program followed recommendations to preferentially include previously vaccinated persons [16], who have lower rates of adverse events than do primary vaccinees [5–7, 17, 18]. Third, children, who have a higher rate of adverse events associated with vaccinia [5, 7, 8], were excluded from vaccination [4, 16]. Fourth, the program recommended scrupulous vaccination site care, including covering the site with a semipermeable membrane that reduces shedding of vaccinia into the environment and thus reduces transmission of the virus [3, 4, 16]. Finally, the program included vigorous efforts to educate members of the medical profession and prospective vaccinees about adverse events that can occur following vaccination, which probably increased the effectiveness of screening and the care of vaccination sites. All of these measures were improvements over the laissez-faire approach common in the 1960s.

There are no known preventive measures that decrease the risk of developing GV after smallpox vaccination. An as-yet-

Table 4. Characteristics of patients receiving a working diagnosis of generalized vaccinia (GV), progressive vaccinia (PV), or eczema vaccinatum (EV) after smallpox vaccination, United States, 2003.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GV (n = 29)</th>
<th>PV (n = 7)</th>
<th>EVa (n = 3)</th>
<th>All smallpox vaccinees (n = 38,440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (range)</td>
<td>37 (20–65)</td>
<td>45 (31–66)</td>
<td>32 (6–63)</td>
<td>47 (18 to &gt;70)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>4</td>
<td>0</td>
<td>24,502</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>13,938</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>5</td>
<td>0</td>
<td>NA</td>
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<tr>
<td>Black</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>Laboratory tests performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
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<td>13</td>
<td>5</td>
<td>0</td>
<td>NA</td>
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<td>0</td>
<td>0</td>
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<td></td>
<td></td>
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</tr>
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<td>15</td>
<td>5</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>History of smallpox vaccination</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>20</td>
<td>3</td>
<td>2</td>
<td>38,181</td>
</tr>
<tr>
<td>First vaccination</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>9003</td>
</tr>
<tr>
<td>Revaccination</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>29,178</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available.

*a One report of EV involved a 6-year-old child who was not vaccinated but who had contact with a vaccinee.
unknown immunologic defect may enhance susceptibility to GV [11]. We found only 2 cases of GV among 38,440 civilian smallpox vaccinees (a rate of 52 cases per 1,000,000 vaccinees), which is one-fifth of the rate reported in the 10-state physician survey conducted by Lane et al. [8] in 1968 (a rate of 241.4 cases per 1,000,000 vaccinees). There have been rates reported for GV of 20.8–241.4 cases per 1,000,000 vaccinees [6, 8]. We chose to compare our rate with that found in the physician survey conducted by Lane et al. [8], because the methodology made it possible to capture more of the less-serious adverse reactions (such as GV) than can be captured by studies using less-active surveillance techniques. We had laboratory support, input from dermatologists and smallpox vaccine adverse event experts, and, frequently, digital photographs, all of which increased the specificity of the diagnosis. More than 75% of reports of possible GV received a final diagnosis of hypersensitivity reaction or nonspecific rash after review by the dermatology subgroup of the SVSWG or because the laboratory results were negative for vaccinia and other orthopox viruses. In the 1968 survey, PCR testing was not available, no standard case definition was employed, and a meticulous dermatologic review of each case was not possible [8]. An overdiagnosis of GV almost certainly inflated the rates in the 1968 physician survey, which accepted the diagnosis of the reporting physician when it was not possible to determine the cause of the rash by description [8]. It may be difficult to distinguish the rash associated with GV from erythema multiforme or hypersensitivity rashes without virologic testing or skin biopsy [8, 18, 19]. Varicella, which is more common in children (who were excluded from the 2003 pre-event program), may have been confused with GV in the past [11, 20]. Varicella is now much less common because of the availability of varicella vaccine. Pustular impetigo or other bacterial skin infections may also be difficult to distinguish from GV without cultures. Physicians unfamiliar with hypersensitivity rashes, which can present with multiple morphologies, may label any generalized rash after smallpox vaccination as GV. The vast majority of GV reported in 1963 and 1968 studies were nonspecific rashes that were not sufficiently investigated to rule out GV (J. Michael Lane, John Neff, and Vincent Fulginiti, personal communication), which resulted in much higher rates than those found in our study.

The 2 patients with probable or confirmed GV raise several interesting research and clinical laboratory diagnostic questions. There were no samples obtained to document viremia in either patient. Digital photos of the probable case were not available, and no specimens were obtained for virologic testing. Although this case met the case definition for probable GV, the diagnosis relied entirely on the clinical examination. This patient may have had folliculitis or hypersensitivity reaction. The patient with confirmed GV reported symptoms starting 2 days after vaccination, which is unusual, because GV typically starts ∼1 week after vaccination. This patient was a revaccinee; revaccinees tend to respond to vaccination earlier and more mildly than do primary vaccinees [21], possibly accounting for the early symptoms, but GV is rare among revaccinees [11]. This health care worker could have been exposed to vaccinia even before vaccination, and the rash could represent an inadvertent inoculation that would also have positive laboratory results. Recurrent rash is rare in cases of GV but can occur, usually at 4–6-week intervals for up to 1 year after vaccination [11]. Even with 1 confirmed case of GV, the rate we found is still low, and because it is relatively benign, we think GV is unlikely to be of importance in a mass vaccination campaign.

On the basis of 1960s rates, we might have expected to find 1–2 cases of EV among the 38,440 individuals vaccinated in the 2003 pre-event program [6, 8]. The rate of EV during the 1960s among the United States population was ∼1 case per 25,000 vaccinations, and the prevalence of atopic dermatitis was unknown. Many of the EV cases at that time were among close contacts of recently vaccinated individuals, most of whom were <18 years of age [6, 7]. Secondary transmission to unvaccinated children with atopic dermatitis tended to occur in the home, where skin-to-skin contact was more frequent [22]. There is no biological marker that predicts the occurrence or severity of EV in persons with atopic dermatitis. The risk for EV in predisposed populations is unknown. There are reports of successful smallpox vaccination of affected individuals with minimal sequelae [23, 24]. Only a subset of patients with atopic dermatitis, such as those who experience disseminated molluscum contagiosum or herpes virus infections, may be at highest risk for EV [25]. The worldwide prevalence of atopic dermatitis has increased during the past 40 years [26–28]; therefore, more individuals are presumed to be at risk for the development of EV after smallpox vaccination. Despite this increased prevalence, we found no cases of EV. The 2003 pre-event vaccination program followed the ACIP recommendation of vigilantly screening out individuals with a history of active or inactive atopic dermatitis and covering the vaccination

Table 5. Final diagnosis for patients receiving a working diagnosis of generalized vaccinia after smallpox vaccination, United States, 2003.

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>No. of patients (n = 29)</th>
<th>No. of patients with laboratory-confirmed diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized vaccinia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Nonspecific rash</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Varicella</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3 ±</td>
<td>1 ±</td>
</tr>
</tbody>
</table>

* Erythema multiforme minor, poison oak, and viral infection.
* Erythema multiforme minor, confirmed by histopathological examination.
site until the scab separates [4]. As a result, no cases of EV or civilian-to-civilian transmission of vaccinia were detected.

Our surveillance during the 2003 pre-event vaccination program was, in many ways, more intensive than past surveillance. First, VAERS allows reporting of adverse events by anyone, including health care providers and vaccine recipients, and accepted reports by mail or online. Second, the Clinician Information Line, with its widely publicized toll-free number and 24-h staffing, provided timely and easy access for clinicians and health department personnel to notify the CDC. Third, state smallpox vaccine adverse event coordinators identified and reported adverse events. Finally, the public and the medical profession were extensively educated about adverse events through training programs, internet sites, and videotapes. With these mechanisms in place, the system was sensitive. Furthermore, we believe that the system was specific. We only classified reports after individual follow up by CDC clinicians and frequent consultation with subject matter experts (i.e., dermatologists and smallpox vaccination experts). Laboratory testing and digital photos were obtained for several cases and provided further documentation. Not all cases were reviewed by the dermatology subgroup, and samples for laboratory testing were not always obtained (including skin biopsies). Nevertheless, we feel that the surveillance during the 2003 pre-event program was sensitive and specific and that our rates represent true rates for the surveillance during the 2003 pre-event program was sensitive and specific and that our rates represent true rates for pre outbreak vaccination with vigorous screening. Although methods of surveillance differed, the Department of Defense used similar screening and educational tools for the smallpox vaccination pre-event program. Consistent with our findings, the Department of Defense also found no cases of EV or PV, and only 1 case met their definition of probable GV out of 800,000 vaccinees to date (John D. Gravenstein, personal communication).

In the event of a widespread smallpox outbreak, a substantial proportion of the United States’ population may be targeted for vaccination. We might expect an increase in the rate of these adverse reactions, particularly EV and PV, unless at-risk individuals can be quickly identified and easily sequestered as an alternative to vaccination. Even if sequestering is possible, the age range and residual immunity from prior vaccination will be different from that found in the recent pre-event program. We must expect higher rates of adverse events among first-time vaccinees and children [5–8]. Because we know the risk factors for PV and EV, we may be able to implement measures that can protect individuals at risk from developing these adverse reactions following vaccination during a smallpox outbreak. The current research to develop a less reactogenic smallpox vaccine may also reduce the risk of serious adverse events [29].

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