Analysis of cases reported as generalized vaccinia during the US military smallpox vaccination program, December 2002 to December 2004

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Background: We evaluated military personnel who developed dermatologic reactions suggestive of generalized vaccinia (GV) after smallpox vaccination.

Methods: We conducted surveillance and retrospective analysis of cases from the Vaccine Adverse Event Reporting System (a passive reporting system managed by the Centers for Disease Control and Prevention), and the military's preventive medicine channels, vaccine healthcare centers, clinical laboratory network, dermatology clinics, and pathology departments from December 2002 to December 2004.

Results: Of 74 cases investigated in 753,226 vaccinations, 50 (67.6%) met the case definition of possible GV (rate 66/million), 95% confidence interval (49-88/million), consistent with historically reported rates. Cases of possible GV occurred more frequently in primary vaccinees (81/million) than in those revaccinated (32/million) (relative risk 2.6, 95% confidence interval 1.2-5.9, $P = .013$). None met the case definition of probable or confirmed GV, including 15 with virologically negative laboratory evaluations (eg, culture, skin biopsy, or polymerase chain reaction).

Limitations: The methods of case collection and retrospective nature of this study are its limitations. The clinical diagnosis of possible GV was made on the basis of the authors' interpretation of clinical notes and adverse events submitted by more than 100 different providers. Only 15 of the 74 cases of possible GV had laboratory attempts for virological confirmation.

Conclusion: GV is still a rarely reported complication of smallpox vaccination. True GV, strictly defined, may be even less common than previously reported. We named one self-limited dermatologic manifestation confused with GV "postvaccinial nonviral pustulosis." Properly screened individuals considering smallpox vaccination may be assured most exanthemata after vaccination are benign. (J Am Acad Dermatol 2006;55:23-31.)

Generalized vaccinia (GV) is a noteworthy adverse event associated with smallpox vaccination using live virus. Although GV is often dramatic in appearance, it typically resolves spontaneously without serious consequences.[1,2] Historically, this condition is said to present with widespread vesicular lesions and is believed to be caused by hematogenous spread of vaccinia virus as a result of vaccination. In the large epidemiologic surveys conducted in this country and elsewhere during the era of smallpox eradication (ie, the 1960s and 1970s), GV was identified as an infrequent,

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Abbreviations used:

CDC:	Centers for Disease Control and Prevention
DoD:	Department of Defense
EV:	eczema vaccinatum
GV:	generalized vaccinia
PCR:	polymerase chain reaction
PV:	progressive vaccinia
VAERS:	Vaccine Adverse Event Reporting System
VIG:	vaccinia immune globulin

usually benign, adverse event, occurring in a range between 23.4 to 238.2 cases per million vaccinations.[3-6] After the attacks of September 11, 2001, a campaign of smallpox vaccinations for biological defense preparedness among US military personnel and civilian healthcare workers began in December 2002. Adverse events, including suspected GV, have been closely monitored during the course of these vaccinations.

It is important to evaluate suspected cases of GV for several reasons. First, it is essential to recognize and differentiate GV from the more serious and potentially fatal dermatologic adverse events of eczema vaccinatum (EV) and progressive vaccinia (PV) with which it can sometimes be confused.[7-9] These latter conditions have stronger indications for intervention and treatment with the currently limited supply of vaccinia immune globulin (VIG), which is seldom necessary in cases of GV. However, some patients with GV, such as those with mild underlying immunodeficiencies, may become systemically ill or have recurrences of skin lesions over several months.[8-10] Such cases may warrant treatment with VIG or with nonapproved antivaccinial therapies, such as intravenous cidofovir. In addition, these patients theoretically present with live and, hence, potentially transmissible virus at sites distant from the vaccination.

The diagnosis of GV, although seemingly based on a simple clinical description, has been confusing to clinicians and difficult to apply consistently. This has been true since the earliest use of the term in the literature of the late 19th century.[7] As our understanding of the immunology of the virus used in smallpox vaccination has advanced, we are better able to differentiate among the dermatologic adverse events associated with this vaccine. These events include GV, EV, PV, inadvertent autoinoculation and contact inoculation (also termed accidental infection or implantation), and erythema multiforme. It appears that these events were often mistakenly diagnosed as GV because there were no generally accepted diagnostic criteria in the past. Furthermore, coincident exanthemata such as chickenpox or pustular impetigo must also be differentiated from GV.[3,9] Today, the wider availability of confirmatory laboratory techniques, including viral culture, immunohistology, and polymerase chain reaction (PCR) facilitates our ability to distinguish between postvaccination rashes, although clinical features are still important.

The current case definition of the Centers for Disease Control and Prevention (CDC) of GV is "the spread of lesions to other parts of the body that are benign in appearance and occur as a result of viremia."[11] Table I illustrates some of the definitions and criteria used in the differential diagnosis of GV over time by various experts.

METHODS

The US Department of Defense (DoD) smallpox vaccination program used full-strength Dryvax (Wyeth Laboratories, Inc, Marietta, Pa), which contains the New York City Board of Health strain of vaccinia virus.[14] From December 2002 to December 2004, 753,226 DoD personnel were vaccinated with this virus. This study is a retrospective analysis of cases gathered through the Vaccine Adverse Event Reporting System (VAERS) (a passive reporting system managed by the CDC), the military's preventive medicine channels, the DoD vaccine healthcare centers, the military's clinical laboratory network (including the US Armed Forces Institute of Pathology), and military dermatology clinics and pathology departments from December 2002 to December 2004. We identified all cases that were reported as GV or in which the differential diagnosis included GV. In addition, we identified all cases that were described as a generalized, systemic, disseminated, or otherwise widespread cutaneous eruption composed of vesicles or pustules distant from the vaccination site, occurring within 1 month after the smallpox vaccination. In addition, we compared these cases with those recorded in the Defense Medical Surveillance System by the *International Classification of Disease, Ninth Revision* codes for GV (999.00) through both the inpatient and ambulatory data records.

RESULTS

In all, 74 putative cases of GV were identified. The mean age of the group of vaccinees suggested to have GV was 27.2 years, 5 (6.8%) were female, and 62 (83.8%) were vaccine naive (Table II). In comparison, the mean age of all military members vaccinated with smallpox vaccine to date was 27.9 years, 12% were women, and 70.5% were primary vaccinees. To analyze the presumed cases further, we adapted the case definitions distributed within DoD early in 2003 (Table III). Of the 74 cases that we

Table I. Historic definitions of generalized vaccinia

Jubb, 1943[12]	"It is only a papular rash that should raise suspicion of generalized vaccinia, and even then, the diagnosis should. . .be withheld unless the papules proceed to vesiculation. . .In diagnosis, the following considerations will be helpful: 1. Autoinoculation should be excluded. 2. The eruption does not appear earlier than the fourth, and seldom earlier than the ninth day after vaccination. 3. The eruption must be elsewhere than in the neighborhood of the vaccination site. 4. There must be a vesicular stage."
Barbero et al, 1955[7]	"There appear to be 3 conditions in which vaccinia virus gives clinical evidence of blood stream dissemination. . .it seems reasonable that a clinically convenient term be applied to each: GENERALIZED VACCINIA: Although applicable to all 3 clinical conditions [GV, eczema vaccinatum, and vaccinia necrosum/progressive vaccinia], it is suggested that this term be confined to those cases in which the primary site heals normally but in which vaccinal lesions erupt on the body between the sixth and the fourteenth day after vaccination. These lesions follow the same evolution as the primary site. . .and heal at the same time as the primary lesion without scarring."
Neff et al, national survey, 1967[4]	"Generalized vaccinial lesions that occur in the absence of eczema or other pre-existing skin lesions. . .. Although the spectrum of generalized vaccinia was variable the most common manifestation was satellite vesiculation around the vaccination site."
Lane et al, national surveillance, 1969[5]	"The clinical spectrum of generalized vaccinia was broad. . ..In most cases the clinical descriptions obtained were insufficient to distinguish patients with vesicular or pustular rashes from those with maculopapular or erythema-multiforme-like rashes. . .. We have preferred to call all such rashes except erythema multiforme 'generalized vaccinia.' It should be understood that 'generalized vaccinia' is a heterogeneous group."
Lane et al, 10 states, 1970[6]	"The diagnoses of the local physician was accepted in most instances of minor complications. . ..Generalized vaccinia comprised 19% of the primary-vaccination complications. Only patients with vesicular lesions away from the site of vaccination were included in this category. In the descriptions of some patients, it was difficult to distinguish generalized vaccinia from erythema multiforme, because of inadequate descriptions of the rash. The diagnosis by the reporting physician was accepted in such instances. . . .The techniques applied in these state surveys allowed many of the clinical details of cases to be lost. The surveys should be regarded as reports of diagnoses of the physicians, rather than as reports of proven disease entities."
Goldstein et al, 1975[13]	"Generalized Vaccinia. Diagnosis—This is a generalized erythematous maculopapular rash occurring in primary vaccinees on otherwise normal skin. The lesions often vesiculate and then umbilicate as would any vaccinial lesion. Generalized vaccinia probably results from the rare bloodborne dissemination of virus in normal individuals. Allergic rashes are commonly confused with this rare complication."
Fenner et al, 1988[3]	". . .[A] generalized vaccinial rash, sometimes covering the whole body, occurred 6-9 days after vaccination. The course of the individual skin lesions resembled that of the lesion at the vaccination site, but if the rash was profuse the lesions sometimes varied greatly in size. The generalized eruption usually did not have the 'centrifugal' distribution which was characteristic of the rash of smallpox. Generalized vaccinia was not associated with severe immunodeficiency, and the prognosis was good."

Continued

Table I. Cont'd

Fulginiti et al, 2003[9]	"Generalized vaccinia is a specific syndrome resulting from viremic spread of virus from the vaccination site in presumably healthy individuals. . .it is almost always a benign complication of primary vaccination. Previous reports have mistaken EV, progressive vaccinia, and inadvertent inoculation syndromes for generalized vaccinia. . .Within a week after vaccination, lesions appear on unimmunized skin that appear to derive from viremia. Lesions are similar in appearance to those associated with primary vaccination. . .may occur on any part of the body and are seen most often on the trunk and abdomen. . .even more rarely lesions may recur for 4-6 week intervals. . .[T]his disorder must be differentiated from. . .erythema multiforme. . .EV. . .progressive vaccinia. . .chickenpox. . .and pustular impetigo. . .[V]irologic differentiation is essential [if patient is exposed to smallpox]. . .otherwise is seldom needed."

Table II. Characteristics of all patients in the military reported with possible generalized vaccinia after smallpox vaccination, December 2002 to December 2004

Characteristic	Patients with possible GV
Age, mean y (range)	27.2 (19-47)
Sex	
Male	69 (93.2%)
Female	5 (6.8%)
History of smallpox vaccination	
Primary vaccination (none)*	62 (83.8%)
Revaccination*	3 (4%)
Unknown	9 (12.2%)
History of hospitalization/isolation	
No	45 (60.8%)
Yes	12 (16.2%)
Unknown	17 (23%)
Patients with laboratory tests done†	22 (29.7%)
Skin biopsy/histology	19
DFA for HSV/VZV	4
Bacterial culture	4
Viral culture	4
Electron microscopy/HE stain	1
PCR for vaccinia	2
Patients with no or unknown laboratory tests done	52 (70.3%)

DFA, Direct fluorescent antibody; *GV*, generalized vaccinia; *HE*, hematoxylin-eosin; *HSV*, herpes simplex virus; *PCR*, polymerase chain reaction; *VZV*, varicella zoster virus.

*Patient was presumed to have primary vaccine if age $\leq$ 28 years and presumed to be a revaccinee if age $\geq$ 41 years at time of vaccination.

†Totals are greater than number of patients because some patients had multiple laboratory tests done.

investigated, 24 (32.4%) were promptly eliminated because the clinical description did not mention any lesions compatible with vesicles or pustules. Only 50 (67.6%) of the reported cases met the case definition for possible or suspected GV based on clinical description of the rash (Table IV). Only 15 of these 50 cases had any laboratory tests (eg, culture, histopathology, or PCR for vaccinia) completed to assist with diagnosis. Of these 15, none had laboratory evidence of vaccinia. None of the 74 cases met our case definition of probable or confirmed GV.

The Defense Medical Surveillance System relational database showed that 16 individuals were hospitalized with a first-time, primary diagnosis of GV (*International Classification of Disease, Ninth Revision* code 999.00) during the surveillance period addressed. Interestingly, the ambulatory data record also recorded 2120 first occurrences with this primary diagnosis in outpatient visits during the same period. If all 74 cases reported as GV through VAERS and other passive methods (similar to the studies of the 1960s and 1970s) were counted in the numerator, the military's rate of GV would be 74/753,226 or 98 cases per million vaccinations (or one case in 10,178 vaccinations). Based on our analysis of reported cases in this study, the rates of possible GV, primary vaccinees versus revaccinees, and men versus women are compiled in Table V. Table VI illustrates the relative risk for being reported as a possible patient with GV in primary vaccinees versus revaccinees and in men versus women. Overall, the relative risk of being reported as having possible GV was significant for primary vaccinees; men were more likely than women to be reported as having possible GV but the difference was not statistically significant.

DISCUSSION

The classic epidemiologic studies on adverse reactions to the smallpox vaccine[4-7] reported widely varying rates of GV that ranged from 18.9 to 212.1 cases per million primary vaccinees age 20 years and older (95% confidence interval ranging from 6.9-482/million primary vaccinees), with a summary risk of 39.9 per million primary vaccinees.[15] Using the rates we calculated for possible cases of GV, our experience with GV overall and in primary vaccinees is well within the historic range. It is, however,

Table III. Case definitions for generalized vaccinia after smallpox vaccination applied to assess reported cases of generalized vaccinia (Military Vaccine Agency, US Department of Defense, 2003)

Possible or suggested generalized vaccinia
- All of the following must be present:
1. A generalized eruption occurring beyond the local vaccination site consisting of lesions with a vesicular or pustular presentation or having a mixture of papules and vesicles or pustules

AND

2. Eruption occurred within 1 month of vaccination

AND

3. No plausible explanation for an adverse reaction

Probable generalized vaccinia
- At least 1, 2, and 3 must be present:
1. A generalized eruption distant from the vaccination site
   A. Vesicles or pustules appear on normal skin, with morphology consistent with vaccinia
   B. Lesions occur on at least 3 regions of the body (each extremity and both anterior and posterior torso count as separate regions)

AND

2. Eruption occurred within 6-9 days after vaccination

AND

3. At least 12 individual lesions in the same stage of development and evolving through normal vaccination stages, typically over several days or a week
4. Fever, myalgias, and related symptoms may be present

Confirmed generalized vaccinia
- All of the clinical criteria for probable generalized vaccinia, above

AND

- Laboratory confirmation of vaccinia or orthopoxvirus by at least one of the following methods:
1. Conventional histology
2. Electron microscopy
3. Viral culture
4. Polymerase chain reaction

slightly higher than the 9 cases per million of GV reported in the 1990s by the Israeli Defense Forces, who used the Lister vaccine in their military recruits.[16] The rate of GV in DoD revaccinees inferred based on age was significantly lower in comparison with the reported rate of GV in those naive to vaccinia, also consistent with past experience. However, our case rate of 32 per million vaccinations is somewhat higher than the rates historically reported in the 1960s and 1970s.[4-6] This may be a result of intense surveillance with the current campaign, overreporting, misclassification, or a combination of these because we had no probable or confirmed cases identified. In addition, given that it has been decades since most individuals were originally vaccinated, our group of revaccinees may have been somewhat more likely to immunologically respond similarly to a vaccine-naive person. The actual rate of GV today, determined from our experience, is probably much lower than previously reported if we apply the strictest criteria for GV, in which live vaccinia virus is detected in lesions distant from the vaccination site (although this confirmatory test was seldom used).

We examined the consistency of the case definition of GV in place during the 1960s and 1970s versus the definition in use today. The current case definition used by the DoD is more stringent than the previous case definition of 40 years ago, because of the additional requirement for confirmation of vaccinia. During the eradication era, reports of GV relied primarily on clinical impression. At that time, the main effort of surveillance was to identify cases of severe vaccination reactions, especially those that were potentially life-threatening or that required the administration of VIG. Exanthemata that were clinically benign or inconsequential were not scrutinized to the degree that they may be currently.

We queried the authors of the classic epidemiologic studies (J. M. Lane, J. M. Neff, and V.A. Fulginiti) about these discrepancies, and with their permission, we list their comments and reflections on the earlier surveillance definitions of GV (Table VII). They acknowledge that many of the cases once categorized as GV were probably not caused by viremia and lacked virus in the distant skin lesions. Hence, they would not be characterized as GV today by the case definition we used.

Table IV. Analysis of 74 cases reported as generalized vaccinia between December 2002 and December 2004

Cases reported as GV or possible GV* (No. presumed to be revaccinees, ie, born ≤ 1971)	74 (12)
Cases with vesicular or pustular lesions	50 (7)
Possible or suggested GV	50 (7)
Location	
Trunk/back/chest	36
Upper extremities only	6
Diffuse	2
Unspecified	5
Laboratory confirmation sought†	15
Viral culture performed	4‡
Bacterial culture performed	4§
Skin biopsy performed	12‖
EM/HE stain performed	1¶
DFA for HSV/VZV performed	3#
PCR for vaccinia performed	2**
Probable GV	0 (0)
≥3 Regions involved	34 (2)
Above + within 6-9 d of vaccination	8 (1)
Above + >12 lesions morphologically like smallpox	0 (0)

DFA, Direct fluorescent antibody; *EM*, electron microscopy; *GV*, generalized vaccinia; *HE*, hematoxylin-eosin; *HSV*, herpes simplex virus; *PCR*, polymerase chain reaction; *VZV*, varicella zoster virus.
*Classification of rashes by description and location and other symptoms were based on clinician description in written notes or reports.
†Total number of laboratory tests performed is greater than the number of patients because in some cases multiple tests were done for a single patient.
‡One viral culture grew HSV-1, the rest were negative.
§One bacterial culture grew coagulase-negative staphylococci, the other 3 were negative.
‖Spongiosis = 3; superficial/mild epidermal perivascular/chronic dermal inflammation = 7; ruptured milia = 1; folliculitis = 2.
¶Negative for vaccinia.
#All were negative.
**Both were negative.

Table V. Analysis of rates of generalized vaccinia in specific populations

	No. of 74 reported cases	Rate (per million vaccinees)	95% CI (per million vaccinees)
Possible GV	50	66	49-88
Primary vaccinees	43	81	59-109
Revaccinees	7	32	13-65
Male	47	70	52-94
Female	3	35	7-10

CI, Confidence interval; *GV*, generalized vaccinia.

Table VI. Analysis of relative risk of being reported as having possible generalized vaccinia in this study

	Relative risk of possible GV	95% CI	χ^2	*P*
Primary vaccinee vs revaccinee	2.6	1.2-5.9	6.1	.013
Male vs female	2.0	0.63-6.48	0.96	.32

CI, Confidence interval; *GV*, generalized vaccinia.

The strategy behind current smallpox vaccination programs is to perform a thorough prevaccination screening to exclude all potential vaccinees who are at identifiable risk for clinically significant adverse reactions, especially EV and PV.[8,11] As a result, relatively few adverse reactions seen today are clinically significant. Most dermatologic reactions today would have been regarded 50 years ago as benign and inconsequential. Still, more recent guidance distributed to clinicians regarding the management of postvaccination adverse reactions can still leave room for confusion. Thus, under the current vaccination program, healthcare workers and public health officials conscientiously detect and report adverse events, to the extent that a generalized rash occurring soon after smallpox vaccination may be hastily identified as GV, based only on a cursory clinical diagnosis. The fact that 2120 ambulatory reports in the Standard Ambulatory Data Record were coded as GV but not otherwise reported through VAERS suggests that this was used as a general-purpose code for any dermatologic adverse reaction after smallpox vaccination. We are reviewing a sample of these records to characterize and identify potential misclassification further.

Jubb,[12] reviewing the literature and experience from the early periods of widespread vaccination, noted that rashes postvaccination were frequent, and could appear as "papular, pustular, punctuate, erythematous, morbilliform, urticarial, roseolar, eczematous, and macular," and he considered erythema multiforme one of the more frequent manifestations (although few of these would today be considered true erythema multiforme). In the early stages of the smallpox preparedness program after September 11, 2001, Frey et al[17] noted, when testing clinical responses to diluted and undiluted vaccine, that 14.3% of their 665 participants had rashes in a part of the body other than the vaccination site, with pustular or vesicular rashes on the chest and back being most common. None were considered to be GV or yielded live virus and all resolved spontaneously. Based on our observations, many of the vesicopustular rashes seen since 2002 appear to be an entity that probably existed earlier but was not definitively described

Table VII. Recent opinions from authors of classic smallpox studies

V. A. Fulginiti, MD (written communication, December 10, 2004)	"GV is [the] viremic spread of lesions which have the very characteristic appearance of a primary vaccination at the secondary sites and which usually, but not always heal rapidly whether we treat them or not. Rarely, crops occur at intervals for up to one year. . . [W]e recovered virus from the site(s). . .and in a few instances from the blood. Our belief then and now is that this is a very rare complication, and is probably a mild immunodeficiency which we could not ascertain in those days. . .Rashes which do not have the typical pustular, primary-like appearance, are not GV to me."
J. M. Lane, MD, MPH (written communication, December 10, 2004)	"[T]he vast majority of the cases [of GV] in our tables in the 1968 data were [non-descript benign] rashes. . . [A] modest macular rash with minimal constitutional symptoms is simply part of the normal spectrum of primary vaccinia, and [should] not [be] label[ed]. . . as 'adverse events'."
J. M. Neff, MD (written communication, December 9, 2004)	"[C]ases that were reported in the 1960s represented a hodge podge of conditions. Physicians reported these cases using the definition of the appearance of a post vaccinial vesicular rash in the absence of eczema or immune deficiency. . ..By the late 1960s we began to question the frequency of this condition and think that most of these cases reported as GV were hypersensitivity reactions or a hodge podge of vesicular conditions, some auto inoculations or folliculitis."

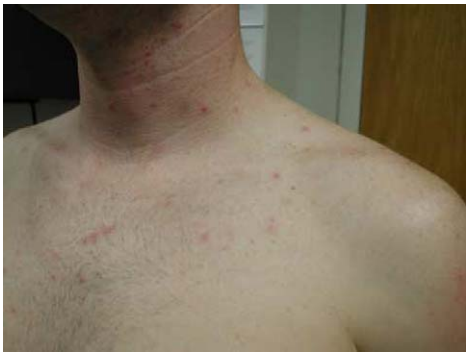

Fig 1. Postvaccinial nonviral pustulosis occurring on neck, shoulders, and upper aspect of chest of young man. Photograph courtesy of Melinda A. Cavicchia, LTC, MC, USA.

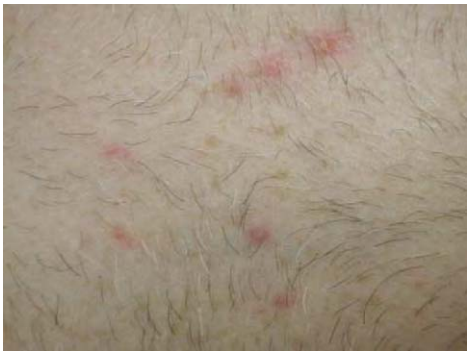

Fig 2. Typical lesions are perifollicular papules and pustules with surrounding erythema. Photograph courtesy of Melinda A. Cavicchia, LTC, MC, USA.

40 years ago. We call this entity postvaccinial nonviral pustulosis. This phenomenon was readily evident to military dermatologists by early 2003, but was first described in print as focal and generalized folliculitis after smallpox vaccination.[18] Two other compatible cases from the recent military campaign have since been described in the literature.[19] In brief, this entity is primarily a truncal eruption composed of follicular and perifollicular papules and pustules, each surrounded by a small edematous, red areola approximately 3 to 4 mm in diameter (Fig 1). Lesions are usually discrete, clustered on the upper aspect of the back and chest, and occur principally in young adults approximately 1 to 2 weeks (range 5-30 days, mean 11.2 days) after primary vaccination (Fig 2). Some patients report mild pruritus, but patients with postvaccinial nonviral pustulosis are not toxic. The condition is self-limiting and requires no further care other than symptomatic relief. In all 15 cases that we examined where laboratory confirmation was sought, the lesions were virologically negative by histology, culture, and PCR for vaccinia. The differential diagnosis for this eruption includes GV, bacterial folliculitis, pityrosporum folliculitis, and varicella zoster (eg, varicella or disseminated zoster) or herpes simplex virus infection.

Even with the likelihood of overdiagnosis and misclassification, GV is a rare event, and true GV is probably rarer still. This is supported by a 2004 study that showed that viremia is an uncommon occurrence with the New York City Board of Health strain of vaccinia. Investigators took periodic blood samples from 28 recently vaccinated primary vaccinees for viral analysis by culture, rapid PCR, and electroluminescence antigen detection assay. In a total of 220 samples obtained over 3 weeks after vaccination,

viremia was not detected in any vacinee.[20] In addition, a 2005 parallel study of 38,440 civilian smallpox vaccinees reported two cases of exanthemata meeting the case definition of GV (an incidence rate of 52/1,000,000 vaccinations), and one case of GV confirmed by PCR.[21] In 1960, Kempe[22] reported that he and another individual were separately unable to confirm viremia after routine vaccination in a total of 131 otherwise healthy people. Blattner et al[23] noted failure to confirm virus in the blood of 7 vaccinated people, although he did find "bound" virus in the blood of two patients admitted for the apparent complication of inadvertent inoculation. Viremia has been documented in fatal cases of cutaneous complications after vaccination in individuals who are immunocompromised[24] and is implied by the existence of vaccinia osteomyelitis and fetal vaccinia, but these examples are also rare.[2,3,7-9] European authors during the first part of the 20th century have been cited as finding vaccinia in the blood in the first week after routine vaccination with virus strains other than New York City Board of Health.[23,24]

The recent medical literature includes 4 articles that report GV after smallpox vaccination. We believe that these cases warrant further scrutiny. Two of the reports describe virologic confirmation of GV; however, the same patient is described in both reports.[25,26] Furthermore, in this patient, the ectopic vaccinial lesions appeared less than 48 hours after vaccination, whereas several earlier definitions of GV suggested that it occurred not sooner than 4 to 6 days after inoculation.[3,7,12] Based on the consensus of the Bioterrorism Taskforce of the American Academy of Dermatology, and after conferring with the author of the report, the patient described in a 2004 *Journal of Emergency Medicine* article[27] is more correctly given the diagnosis of classic erythema multiforme *sensu stricto*. Meanwhile, the images used to illustrate a purported case of GV in another 2004 article fail to demonstrate a definitive morphology or distribution of the patient's lesions.[28] On further review of these cases and discussions with their authors, we believe that these reports would mislead one to believe that GV is more prevalent than it actually is. More importantly, readers of these reports might infer that generalized eruptions after smallpox vaccination that appear similar to the articles' photographs should be diagnosed as GV, without the need for laboratory confirmation.

Our study was primarily limited by our methods of case collection, especially with respect to cases identified through VAERS, which relies on spontaneous reporting of adverse events. The retrospective nature of our study was also a limitation, particularly as it related to the inability to quickly follow up and request a more exhaustive laboratory workup for the patient. It was challenging to definitively interpret or corroborate the clinical description of the primary care providers (the majority of whom were not dermatologists, immunologists, or infectious disease physicians), as only a few patients had photographs taken of the acute rash; thus, the written description of the rash was largely the basis for our classification of the rashes. In some cases, the description on the VAERS report was simply "generalized vaccinia" with no further elaboration. Nonetheless, we believe this study contributes to the smallpox literature as a further refinement of the postvaccinial reactions that fall in the benign spectrum. We further recommend that future diagnosis of GV, particularly when the use of VIG is being considered as a therapy, be confirmed with laboratory studies and not be established solely on the clinical picture. Furthermore, in all cases where GV is in the differential diagnosis, the clinician should seek to rule out the other possible diagnoses, some of which may be of more concern than GV, such as PV, EV, and others with lesser import, including inadvertent inoculation, the sterile postvaccination pustular eruption described here and by Talbot et al,[18] and diseases unrelated to vaccinia (eg, bacterial folliculitis, pityrosporum folliculitis, and varicella zoster or herpes simplex virus infection). Consultation with a dermatologist, immunologist, or infectious disease physician should be pursued, as should laboratory assays such as bacterial and viral cultures, direct fluorescent antibody against vaccinia and herpesviruses, or skin biopsy. PCR confirmation of vaccinia should be sought only after these avenues have been exhausted, because of the increased likelihood of false-positive rates in patients at low risk for GV.[26]

Significance of our findings

The very low incidence of GV helps us marshal our limited supplies of VIG. Properly screened individuals who are considering smallpox vaccination can be further assured that most exanthemata after vaccination are benign entities.

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