

# Myopericarditis Following Smallpox Vaccination Among Vaccinia-Naive US Military Personnel

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**W**E REPORT THE FIRST 18 cases of probable myopericarditis following smallpox vaccination among otherwise healthy, young adult members of the US military who were vaccinated between mid-December 2002 and March 14, 2003 (N=326356; 230734 primary vaccinees and 95622 revaccinees). Despite decades as the standard vaccine for US civilian and military populations, the New York City Board of Health (NYCBOH) strain of vaccinia virus (Dryvax, Wyeth Laboratories, Marietta, Pa) has only rarely

**Context** In the United States, the annual incidence of myocarditis is estimated at 1 to 10 per 100000 population. As many as 1% to 5% of patients with acute viral infections involve the myocardium. Although many viruses have been reported to cause myopericarditis, it has been a rare or unrecognized event after vaccination with the currently used strain of vaccinia virus (New York City Board of Health).

**Objective** To describe a series of probable cases of myopericarditis following smallpox vaccination among US military service members reported since the reintroduction of vaccinia vaccine.

**Design, Setting, Participants** Surveillance case definitions are presented. The cases were identified either through sentinel reporting to US military headquarters surveillance using the Defense Medical Surveillance System or reports to the Vaccine Adverse Event Reporting System using *International Classification of Diseases, Ninth Revision*. The cases occurred among individuals vaccinated from mid-December 2002 to March 14, 2003.

**Main Outcome Measure** Elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and wall motion abnormalities on echocardiogram.

**Results** Among 230734 primary vaccinees, 18 cases of probable myopericarditis after smallpox vaccination were reported (an incidence of 7.8 per 100000 over 30 days). No cases of myopericarditis following smallpox vaccination were reported among 95622 vaccinees who were previously vaccinated. All cases were white men aged 21 years to 33 years (mean age, 26.5 years), who presented with acute myopericarditis 7 to 19 days following vaccination. A causal relationship is supported by the close temporal clustering (7-19 days; mean, 10.5 days following vaccination), wide geographic and temporal distribution, occurrence in only primary vaccinees, and lack of evidence for alternative etiologies or other diseases associated with myopericarditis. Additional supporting evidence is the observation that the observed rate of myopericarditis among primary vaccinees is 3.6-fold (95% confidence interval, 3.33-4.11) higher than the expected rate among personnel who were not vaccinated. The background incidence of myopericarditis did not show statistical significance when stratified by age (20-34 years: 2.18 expected cases per 100000; 95% confidence interval [CI], 1.90-2.34), race (whites: 1.82 per 100000; 95% CI, 1.50-2.01), and sex (males: 2.28 per 100000; 95% CI, 2.04-2.54).

**Conclusion** Among US military personnel vaccinated against smallpox, myopericarditis occurred at a rate of 1 per 12819 primary vaccinees. Myopericarditis should be considered an expected adverse event associated with smallpox vaccination. Clinicians should consider myopericarditis in the differential diagnosis of patients presenting with chest pain 4 to 30 days following smallpox vaccination and be aware of the implications as well as the need to report this potential adverse event.

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### Box. Myopericarditis Following Smallpox Vaccination: Adverse Event Surveillance Case Definitions

#### Confirmed Myopericarditis Following Vaccination

Patient with acute myocarditis\* with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease or toxic agent and, virus culture or detection† of vaccinia DNA by polymerase chain reaction identification of vaccinia virus infection from myocardial tissue or pericardial fluid (detection of viral nucleic acid in the myocardium is regarded as indicative of virus infection)

#### Probable Myopericarditis Following Vaccination

Patient with acute myocarditis\* with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease, or toxic agent

\*Clinical diagnosis of myocarditis is confirmed by detection of elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and abnormal findings on echocardiogram.

†Whether vaccinia myopericarditis is a direct viral cytopathogenic effect or an immune-mediated disease remains unclear.

been associated with myopericarditis following vaccination. Only 5 cases were reported in the medical literature between 1955 and 1986.<sup>1-8</sup>

Myocarditis and pericarditis following vaccination have been reported more commonly with other vaccinia virus strains,<sup>9-17</sup> may be associated with other adverse events following vaccination,<sup>2</sup> and may be asymptomatic.<sup>10,18-20</sup> In 1968, Price and Alpers<sup>14</sup> noted that minor cardiac complications after smallpox vaccination may be more common than is generally reported. Six years earlier, MacAdam and Whitaker<sup>21</sup> reported 3 cases of cardiac complications 5 to 14 days following smallpox vaccination and suggested that cardiac complications had been previously overlooked. In 1983, the incidence of myocarditis following vaccination among Finnish military conscripts who were hospitalized with mild myocarditis following vaccination with the Finnish strain of smallpox had been estimated to be as high as 1 per 10000.<sup>22</sup> As early as 1953, Mathieu and Hadot<sup>23</sup> recommended screening for cardiac risk factors before vaccination, especially in individuals aged 50 years or older.

## METHODS

### Surveillance for Adverse Events

A program to vaccinate up to 500 000 US military personnel was launched mid-

December 2002.<sup>24</sup> To detect adverse events after vaccination, the Department of Defense and the US Coast Guard require reporting to the Vaccine Adverse Event Reporting System (VAERS) using established guidelines. Additionally, the Department of Defense encourages clinicians to report all other clinically relevant adverse events after administration of any vaccine or medication to VAERS or MedWatch (US Food and Drug Administration Safety Information and Adverse Event Reporting Program). To heighten awareness of potential adverse events, including cardiac events, clinicians were provided extensive education and vaccinees were individually counseled and provided educational material. An Internet site providing access to a comprehensive array of materials and ongoing program status was established (<http://www.smallpox.army.mil/>).

A 3-pronged approach was implemented for surveillance and patient safety following vaccination, as described by Grabenstein and Winkler<sup>24</sup> elsewhere in this issue of THE JOURNAL. Standard documentation was used to record screening results, vaccination delivery, vaccination response, and adverse event management. Vaccination was recorded electronically as a component of the in-

dividual's longitudinal health record, which was maintained as part of the Defense Medical Surveillance System (DMSS).<sup>25</sup> This system integrates data from sources worldwide in a continuously expanding relational database that documents the military and medical experiences of service members throughout their careers. The DMSS allows nearly instantaneous assessments of the morbidity experiences of service members who share common characteristics, such as vaccination. Statistical analysis was performed using SAS version 8.02 (SAS Institute, Cary, NC).

### Case Identification

The cases presented herein were identified either through sentinel reporting to military headquarters and/or to the VAERS or through diagnostic surveillance among vaccinees at military treatment facilities using *International Classification of Diseases, Ninth Revision (ICD-9)*<sup>26</sup> coded diagnoses (420.90, 420.99, other and unspecified acute pericarditis; 422.90, 422.91, other and unspecified acute myocarditis; and 429.0 myocarditis unspecified) obtained from the DMSS. Fifteen cases were first identified from surveillance of military treatment facilities, and only 3 cases were first identified from the VAERS. The cases were classified based on surveillance case definitions shown in the BOX. Clinical diagnosis of myocarditis was based on detection of elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and wall motion abnormalities on echocardiogram.

## RESULTS

Clinical and diagnostic details for the 18 cases of probable myopericarditis following smallpox vaccination reported among 230 734 primary vaccinees (71% of vaccinees) are presented in the TABLE. No cases were detected among 95 622 vaccinees who were previously vaccinated. All cases were military personnel in active duty who received vaccination with the NYCBOH strain of vaccinia

MYOPERICARDITIS FOLLOWING SMALLPOX VACCINATION AMONG US MILITARY PERSONNEL

**Table.** Relevant Findings Among 18 Primary Vaccinee Cases With Probable Myopericarditis Following Smallpox Vaccination Among US Military Personnel

Case	After Vaccination, d	Smallpox and Other Vaccines Administered Within 30 d	Viral Prodrome	Chest Pain	ECG Findings	ECHO Findings	Cardiac Enzyme Positive Peak Levels*	Infectious Disease Laboratory Evaluation Results†
1	11	1/25/03: smallpox 1/23/03: meningococcal and anthrax 1/29/03: MMR	Myalgias, arthralgias, lymphadenopathy	Substernal	ST-segment elevation	Low normal LV systolic function; EF, 50%-55%	CK-MB, 48.6; troponin I, 14.76	Serum: hepatitis panel negative; CBC and metabolic panel normal; elevated liver enzymes: AST, 94 (normal, 5-45 IU/L); ALT, 66 (normal, 7-56 IU/L); ESR elevated: 30 (normal, 0-15 mm/h) CSF: none Other: none
2	7	1/31/03: smallpox	Fever (38.5°C), chills, headache, stiff neck, myalgias	Better with bending forward	Normal	EF, 50%; improved later to 59%	CK-MB, 8.0; troponin I, 1.31	Serum: coxsackie A and B virus, HIV, hepatitis A, B, and C, Lyme Ab, ANA, RF, ASO: negative, acute, and convalescent; Adenovirus CF Ab unremarkable; DNase B Ab unremarkable CSF: viral culture negative, Shell vial culture for Enterovirus, HSV, and CMV negative Other: nasal wash viral culture negative
3	8	2/05/03: smallpox, anthrax, influenza, typhoid (parenteral)	Fever (subjective), sore throat, myalgias	Squeezing, pleuritic, reproduced by touch	ST-segment elevation	Normal	CK-MB, 22.3; troponin I, 3.0	Serum: influenza A and B, RPR, ANA, HIV, hepatitis profile, RF, viral cultures, PPD, CBC, metabolic panel normal, C-reactive protein, 1.1 (normal <1 mg/dL), ESR, 26 (normal 0-15 mm/h) CSF: none Other: none
4	11	2/08/03: smallpox	Fever (subjective), myalgias, arthralgias, headache	Radiation to neck	ST-segment elevation	Pericardial effusion = 4 mm	CK-MB, 133	Serum: baseline laboratory results (chem7, CBC, LFT, and coagulation studies) normal; C-reactive protein, 42 (normal 0-1 mg/dL) CSF: none Other: normal cardiac catheterization
5	10	2/13/03: smallpox 2/07/03: anthrax 2/26/03: anthrax	Recent upper respiratory tract symptoms	Pleuritic	ST-segment elevation	Normal	CK-MB, 33; troponin T, 1.3	Serum: CBC, ESR, and metabolic panel normal; PCRs and cultures for enteroviruses and vaccinia negative CSF: none Other: none
6	7	2/27/03: smallpox and anthrax	Chills, night sweats	Worse with movement	ST-segment elevation	Mild global hypokinesia; LVEF, 50%-55%	CK-MB, 55; troponin I, 97.2	Serum: C3/C4, CH <sub>50</sub> levels, C1q assay, Raji cell assay for circulating immune complexes, RF, ANA, all normal; PCRs and cultures for enteroviruses and vaccinia, negative CSF: none Other: none
7	11	2/27/03: smallpox	Fever (subjective), chills, sweating	Pleuritic	ST-segment elevation	Small pericardial effusion	CK-MB, 46.4	Serum: hepatitis panel negative except for HBs Ab positive (previous hepatitis B vaccine); CBC normal CSF: none Other: none
8	10	2/13/03: smallpox 2/06/03: anthrax 2/20/03: anthrax	Myalgias, fever (subjective), arthralgias	Pleuritic	ST-segment elevation	Normal	Troponin I, 7.7	Serum: C-reactive protein and ANA normal, Lyme titers negative CSF: none Other: none

(continued)

**Table.** Relevant Findings Among 18 Primary Vaccinee Cases With Probable Myopericarditis Following Smallpox Vaccination Among US Military Personnel (cont)

Case	After Vaccination, d	Smallpox and Other Vaccines Administered Within 30 d	Viral Prodrome	Chest Pain	ECG Findings	ECHO Findings	Cardiac Enzymes Positive Peak Levels*	Infectious Disease Laboratory Evaluation Results†
9	12	2/28/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, polio (IPV), meningococcal, typhoid (parenteral)	Recent upper respiratory tract symptoms	Pleuritic	ST-segment elevation	Mild LV dysfunction; LVEF, 45%	Troponin I, 22.5	Serum: metabolic panel, CBC, C1q assay, C3/C4, CH50 levels, ANA, RF, all normal; C-reactive protein, 3 (normal, 0-1 mg/dL) CSF: none Other: none
10	12	3/05/03: smallpox	None reported	Pleuritic and positional	ST-segment elevation	Normal	Troponin T, 0.395	Serum: CBC, metabolic panel, LFTs, TSH, all normal; ESR, 35 (normal, 0-15 mm/h) CSF: none Other: none
11	19	3/08/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, typhoid (VICPs) 3/24/03: anthrax	Fever, arthralgias, dry cough	Positional	ST-segment elevation	Low EF, 37%	Troponin T, 9.2	Serum: multiple heart biopsy specimens negative by PCR for vaccinia CSF: none Other: cardiac biopsy pathological results consistent with eosinophilic myocarditis
12	12	3/13/03: smallpox 1/16/03: typhoid (VICPs)	Myalgias	Pleuritic	ST-segment elevation	Low normal LVEF, 50%-55%	CK-MB, 76.6; troponin I, 150	Serum: acute and convalescent viral titers negative; C3/C4, C1q assay, CH50, interleukin-6, Raji cell assay, C-reactive protein, negative CSF: none Other: none
13	14	1/30/03: smallpox 1/17/03: anthrax	Recent upper respiratory tract symptoms	Substernal	ST-segment elevation	Normal	Troponin I, 30	Serum: CBC, metabolic panel, INR, lipid panel, protein electrophoresis, TSH, normal; C-reactive protein, 12 (normal, 0-1 mg/dL) CSF: none Other: none
14	7	3/06/03: smallpox	None reported	Left axillary	Normal	Normal	Troponin I, 0.73	Serum: none CSF: none Other: none
15	7	3/14/03: smallpox	Headache, fatigue	Substernal	ST-segment elevation	Low normal LVEF, 50%	Troponin I, 15	Serum: CBC normal CSF: none Other: none
16	8	3/14/03: smallpox	Chills, adenopathy	Substernal with radiation down both arms	ST-segment depression	Inferior wall hypokinesis	Troponin I, 1.99	Serum: CBC, metabolic panel, lipid panel, drug assays/toxicology, normal CSF: none Other: none
17	12	3/04/03: smallpox 2/18/03: anthrax 2/06/03: anthrax 2/03/03: meningococcal	None reported	Substernal	ST-segment elevation	Normal	Troponin I, 139; CK-MB, 93	Serum: CBC, metabolic panel, normal CSF: none Other: none
18	11	2/14/03: smallpox and anthrax	Muscle aches, elevated temperature	Substernal with radiation to right scapula	ST-segment elevation	Small pericardial effusion with mild inferior hypokinesis	Troponin I, 3.23	Serum: CBC, metabolic panel, ANA, anti-DNA, anti-cardiolipin, serum electroimmunoelectrophoresis, normal; C-reactive protein, 8.03 (normal, 0-0.94 mg/dL) CSF: none Other: none

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; ASO, anti-streptolysin O; AST, aspartate aminotransferase; C3/C4, complement factor 3/complement factor 4; CBC, complete blood cell count; CFS, cerebrospinal fluid; CF, complement fixation; CK-MB, creatine kinase MB isoenzyme; CH50, total hemolytic complement; ECG, electrocardiogram; ECHO, echocardiograph; EF, ejection fraction; ESR, erythrocyte sedimentation rate; HBSAg, hepatitis surface antigen; HIV, human immunodeficiency virus; INR, international normalized ratio; IPV, injectable polio vaccine; LFT, liver function tests; LV, left ventricular; LVEF, left ventricular ejection fraction; MMR, measles-mumps-rubella; PCR, polymerase chain reaction; RF, rheumatoid factor; TSH, thyrotropin; VICPs, Vaccine Injury Compensation Programs.

\*Troponin I and troponin T activity and CK-MB are reported in ng/mL.

†Metabolic panel includes serum sodium, potassium, chloride, CO<sub>2</sub>, blood urea nitrogen, creatinine, glucose, and calcium concentrations. Hepatitis panel includes hepatitis B surface antigen, hepatitis C antibody, hepatitis B surface antibody, and hepatitis B core antibody. Chem 7 includes sodium, potassium, chloride, CO<sub>2</sub>, blood urea nitrogen, creatinine, and glucose.

virus in various regions of the United States, Europe, and the Middle East. All cases were white (73% of total vaccinees), men (78% of total vaccinees), aged 21 years to 33 years (mean age, 26.5 years; 59% of total vaccinees were aged 21-35 years), with disease onset 7 to 19 days following vaccination (mean, 10.5 days). Typical clinical presentation involved prodromal myalgias; arthralgias; subsequent pleuritic, precordial chest pain; and variable shortness of breath and/or dry cough. All vaccinees had elevated serum cardiac enzyme levels; 15 of the 18 cases had ST-segment elevation changes on electrocardiogram, and 11 of the 18 cases had abnormal echocardiogram findings (ie, wall motion abnormalities). Biopsy of myocardial tissue was performed in only 1 case; the results revealed histological evidence of eosinophil infiltration of the myocardium, eosinophil degranulation, secretion of major basic protein in close apposition to myocyte necrosis, and IL-5 generation. No cases were confirmed by viral diagnosis. All cases had a characteristic primary vaccination response at the inoculation site as defined by the World Health Organization.<sup>27</sup> Results of serologic laboratory tests, when done, did not indicate the presence of other infectious etiologies or host conditions predisposing to myopericarditis. All cases survived and all returned to duty or are on short-term convalescent leave. Longer-term follow-up to detect possible sequelae is underway.

The 18 cases among 230 734 primary vaccinees represent an incidence of 7.80 per 100 000 over a 30-day observation window. The background incidence of myopericarditis in all service members on active duty is 2.16 cases (95% confidence interval, [CI], 1.90-2.34; Poisson distribution) per 100 000 over any 30-day period. This incidence was calculated using 2002 calendar year DMSS data for all services for the above described 5 myopericarditis ICD-9 diagnoses among a population of 1 399 739 persons. When stratified by age, race, and sex, the background incidence rates in all service members of myopericarditis were not statistically significant,

with 2.18 expected cases per 100 000 for ages 20 years to 34 years (95% CI, 1.90-2.34); 1.82 expected cases per 100 000 for whites (95% CI, 1.50-2.01), and 2.28 expected cases per 100 000 for males (95% CI, 2.04-2.54).

The expected number of myopericarditis cases in the population of 230 734 primary vaccinees was calculated by applying the background rate estimate of 2.16 to this population, which yielded 4.98 expected cases (95% CI, 4.38-5.40). The 18 cases reported herein represent an unadjusted estimate of relative risk (RR) of 3.61 (95% CI, 3.33-4.11; Poisson distribution) over the expected incidence of myopericarditis.

#### Etiologic Summary of Cases

The lack of clinical suspicion for myopericarditis following vaccination, no standard evaluation protocol, and the varied capability of the medical sites where these cases presented resulted in variable diagnostic workup for etiologic causes. In none of the cases was infection of myocardial tissue or pericardial fluid with the vaccinia virus confirmed using virus culture or by detection of vaccinia DNA by polymerase chain reaction. Among this case series, when serologic testing was done, findings have been negative for coxsackie A and B viruses, as well as hepatitis B and C, HIV, *Borrelia burgdorferi*, and *Streptococcus pyogenes* (by antistreptolysin O and anti-DNAse B). Viral cultures of nasal wash from 1 patient recovered no adenovirus or influenza viruses. Results of cerebrospinal fluid viral cultures from the same patient were negative, including a shell viral culture that tests specifically for enteroviruses, herpes simplex viruses, and cytomegalovirus. Results of serum antinuclear antibody from 6 patients and rheumatoid factor from 4 patients also were negative. To address the variability in etiologic diagnosis given the unexpected occurrence of these probable cases of myopericarditis following vaccination, the Department of Defense Vaccine Healthcare Center Network is developing clinical

guidelines for evaluating patients and clinical policy to increase clinician awareness.

#### COMMENT

Viral myocarditis is an inflammatory disorder of the myocardium characterized by injury of myocytes with associated inflammatory infiltrate.<sup>28</sup> Often pericarditis and myocarditis are observed in tandem, hence the term *myopericarditis*.<sup>29</sup> Clinical diagnosis is suggested by detection of elevated serum levels of myocardial enzymes (creatine kinase-MB isoenzyme, troponin I, and troponin T), usually in the presence of nonspecific electrocardiographic changes and/or focal or generalized wall motion abnormalities on echocardiography.<sup>18,30</sup> In most cases, an etiology is not determined, but in cases in which a causative infectious agent has been identified, viral agents are most common, particularly the enterovirus group (predominantly coxsackie B virus), adenoviruses, and influenza A.<sup>31</sup> Diagnosis may be confirmed using histopathological and/or viral identification by polymerase chain reaction from endomyocardial biopsy or autopsy specimens.<sup>28,30</sup> Whether myopericarditis following smallpox vaccination is a direct viral cytopathic effect or an immune-mediated phenomenon remains unclear.

#### Association of Myopericarditis With Vaccinia Virus

Vaccinia virus has long been associated with myopericarditis.<sup>28,29,32</sup> However, only 1 previous report has described the pathological characteristics of myopericarditis following smallpox vaccination; the histological changes included a mixed mononuclear infiltrate.<sup>33</sup> This case series of probable myopericarditis associated with the New York City Board of Health strain of vaccinia virus serves to establish an expected baseline rate for myopericarditis following vaccination in primary vaccinees. The cases reported herein occurred only in otherwise healthy, young, white adult men who were carefully screened for conditions that might

preclude vaccination. The cases reported were moderate to severe in clinical presentation, and our observed incidence of myopericarditis likely represents a minimum, with milder cases unrecognized.

The close temporal clustering following vaccination (7 to 19 days; mean 10.5 days), the wide geographic and temporal distribution during the vaccination program, and the lack of alternative diagnoses, provide epidemiologic evidence for an association between smallpox vaccination and myopericarditis. Additional supporting evidence is the absence of myopericarditis in revaccinees and the observation that the observed rate of myopericarditis among primary vaccinees is 3.6-fold higher than the expected rate among personnel on active duty who were not vaccinated. However, some covariates could confound this rate comparison, and a multivariate statistical model in a case-control study design is needed. Myopericarditis due to a synergistic inflammatory effect of multiple vaccines cannot be excluded. Exertion may have predisposed these military personnel to viral myocarditis, as exertion has been associated with increased viral titer and inflammation of the heart in experimental animal models.<sup>34,35</sup> It is possible that the occurrence of myopericarditis following vaccination may represent coincidental outcomes; however, the data linking myopericarditis with smallpox vaccine seem the most likely explanation.

Clinicians should be alert to the potential occurrence and implications of myopericarditis among adult primary vaccinees after receiving smallpox vaccination, and they should report these adverse events to the VAERS. Patients with a clinical suspicion of myopericarditis based on decreased ventricular function on echocardiography, a markedly elevated troponin levels suggestive of significant myocyte injury or a cardiac magnetic resonance imaging positive scan for myocarditis may be indicated to undergo endomyocardial biopsy. Biopsy specimens should be tested for the presence of vaccinia virus.

### Study Limitations

Potential bias exists for both underreporting and overreporting of cases. Although extensive efforts have been made to identify all cases, underreporting bias may result from incomplete ascertainment of cases with myopericarditis following smallpox vaccination, considering the reported mild-to-moderate acute presentation and clinical course,<sup>10</sup> and the necessity of an index of suspicion to pursue an association. The generalized lack of clinical suspicion, exemplified by only 3 cases initially being reported through the VAERS, argues against overreporting of myopericarditis among vaccinees resulting from a case-ascertainment bias of clinicians. Ascertainment bias among vaccinees that resulted in overreporting (eg, the inference that individuals with chest pain after smallpox vaccination may be more likely to seek care) also is unlikely, given the moderate-to-severe clinical presentation of the reported cases. The absence of cases in this study among revaccinees, females, and nonwhite males is difficult to explain from a purely epidemiologic perspective. The Centers for Disease Control and Prevention (CDC) has reported myopericarditis following smallpox vaccination in females, although the CDC case definition differed from that used to classify the cases reported herein.<sup>36</sup> Although revaccinees might be expected to be more aware of the potential adverse effects from this vaccine and thus be less likely to seek care, given the extended time (decades) from their initial vaccination, and the acutely ill presentation of the reported cases, this seems to be an unlikely explanation.

These cases were diagnosed prior to the press release from the CDC on March 25, 2003, which changed the vaccine eligible screening criteria and highlighted the concerns for potential cardiac adverse effects after smallpox vaccination.<sup>37</sup> Recognition of potential cardiac adverse events led to development of a case definition for myocarditis and pericarditis and increased awareness by clinicians of this potential adverse event following smallpox vaccination.<sup>38</sup> Future

reports will include additional cases recognized subsequent to the change in case definition along with follow-up of these cases and a case-control study examining risk factors among the cases reported herein.

The generalizability of these findings from young adult military vaccinees to the general US population is limited. Similar populations, such as police, firefighters, or other first-responders, are prescreened and periodically evaluated for good overall health and therefore may be the most appropriate comparison group. Further investigation is ongoing to better define the occurrence of myopericarditis following smallpox vaccination. It also will be important to closely monitor the longer-term health of these cases, as studies have indicated that viral myocarditis may result in long-term or permanent damage to the heart.<sup>29,30</sup>

### Implications

Implications of these findings for older individuals, or individuals with preexisting cardiac morbidity, are unclear.<sup>39</sup> Clinicians treating patients with other complications from smallpox vaccination (eg, encephalitis, generalized vaccinia, or eczema vaccinatum) may want to evaluate patients for occult myopericarditis.<sup>2</sup> Based on reports of cardiac events following smallpox vaccination among military and civilian vaccinees, the CDC has recommended additional exemptions based on known cardiac disease or potential risk factors for cardiac disease.<sup>40</sup>

These findings are relevant to current policies and guidelines for vaccinating military and civilian populations against smallpox. Although these cases all recovered clinically from their acute illness, the potential long-term consequences must be evaluated to know the true significance of myopericarditis following vaccination. Furthermore, these findings suggest that myopericarditis following smallpox vaccination is an expected adverse event. We project a morbidity estimate of at least 78 cases of clinical myopericarditis per million primary vaccinees in com-

parable adult populations. Myopericarditis following vaccination should be considered in the differential diagnosis of patients with chest pain 4 to 30 days following smallpox vaccination.

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