We 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 been reported to cause myopericarditis. Although many viruses have been identified as causes of myocarditis, 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.
Adverse events following vaccination,2 the Finnish strain of smallpox had been associated with myocarditis following vaccination. Six years earlier, MacAdam and Whitaker21 reported 3 cases of cardiac complications after smallpox vaccination may be more common than is generally reported. Six years earlier, MacAdam and Whitaker21 reported 3 cases of cardiac complications 4 to 14 days following smallpox vaccination and suggested that cardiac complications had been previously overlooked. In 1968, Price and Alpers14 noted that minor cardiac complications after smallpox vaccination may be more common than is generally reported. Six years earlier, MacAdam and Whitaker21 reported 3 cases of cardiac complications 4 to 14 days following smallpox vaccination and suggested that cardiac complications had been previously overlooked. In 1968, Price and Alpers14 noted that minor cardiac complications after smallpox vaccination may be more common than is generally reported. 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Table. Relevant Findings Among 18 Primary Vaccinee Cases With Probable Myopericarditis Following Smallpox Vaccination Among US Military Personnel

<table>
<thead>
<tr>
<th>Case</th>
<th>After Vaccination, d</th>
<th>Smallpox and Other Vaccines Administered Within 30 d</th>
<th>Viral Prodrome</th>
<th>Chest Pain</th>
<th>ECG Findings</th>
<th>ECHO Findings</th>
<th>Cardiac Enzymes Positive Peak Levels</th>
<th>Infectious Disease Laboratory Evaluation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>1/25/03: smallpox 1/23/03: meningococcal and anthrax 1/29/03: MMR</td>
<td>Myalgias, arthralgias, lymphadenopathy</td>
<td>Substernal</td>
<td>ST-segment elevation</td>
<td>Low normal LV systolic function; EF, 50%-55%</td>
<td>CK-MB, 48.6; troponin I, 14.76</td>
<td>Serum: hepatitis panel negative; CBC and metabolic panel normal; elevated liver enzymes: AST, 94 (normal, 5-45 IU/L); ALT, 68 (normal, 7-56 IU/L); ESR elevated: 30 (normal, 0-15 mm/h)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>1/31/03: smallpox</td>
<td>Fever (38.5°C), chills, headache, stiff neck, myalgias</td>
<td>Better with bending forward</td>
<td>Normal</td>
<td>EF, 50%; improved later to 59%</td>
<td>CK-MB, 8.0; troponin I, 1.31</td>
<td>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</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>2/03/03: smallpox, anthrax, influenza, typhoid (parenteral)</td>
<td>Fever (subjective), sore throat, myalgias</td>
<td>Squeezing, pleuritic, reproduced by touch</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>CK-MB, 22.3; troponin I, 3.0</td>
<td>Serum: influenza A and B, RPR, ANA, HIV, hepatitis profile, RF, viral cultures, PPD, CBC, metabolic panel normal, C-reactive protein, 1.1 (normal &lt;1 mg/dL), ESR, 26 (normal 0-15 mm/h)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>2/08/03: smallpox</td>
<td>Fever (subjective), myalgias, arthralgias, headache</td>
<td>Radiation to neck</td>
<td>ST-segment elevation</td>
<td>Pericardial effusion = 4 mm</td>
<td>CK-MB, 133</td>
<td>Serum: baseline laboratory results (chem7, CBC, LFT, and coagulation studies) normal; C-reactive protein, 42 (normal 0-1 mg/dL)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>2/13/03: smallpox 2/07/03: anthrax 2/26/03: anthrax</td>
<td>Recent upper respiratory tract symptoms</td>
<td>Pleuritic</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>CK-MB, 33; troponin T, 1.3</td>
<td>Serum: CBC, ESP, and metabolic panel normal; PCRs and cultures for enteroviruses and vaccinia negative</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>2/27/03: smallpox and anthrax</td>
<td>Chills, night sweats</td>
<td>Worse with movement</td>
<td>ST-segment elevation</td>
<td>Mild global hypokinesis: LVEF, 50%-55%</td>
<td>CK-MB, 55; troponin I, 97.2</td>
<td>Serum: C3/C4, CH50 levels, C1q assay, Raj cell assay for circulating immune complexes, RF, ANA, all normal; PCRs and cultures for enteroviruses and vaccinia, negative</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>2/27/03: smallpox</td>
<td>Fever (subjective), chills, sweating</td>
<td>Pleuritic</td>
<td>ST-segment elevation</td>
<td>Small pericardial effusion</td>
<td>CK-MB, 46.4</td>
<td>Serum: hepatitis panel negative except for HBs Ab positive (previous hepatitis B vaccine); CBC normal</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>2/13/03: smallpox 2/06/03: anthrax 2/20/03: anthrax</td>
<td>Myalgias, fever (subjective), arthralgias</td>
<td>Pleuritic</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>Troponin I, 7.7</td>
<td>Serum: C-reactive protein and ANA normal, Lyme titers negative</td>
</tr>
</tbody>
</table>

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### MYOPERICARDITIS FOLLOWING SMALLPOX VACCINATION AMONG US MILITARY PERSONNEL

<table>
<thead>
<tr>
<th>Case</th>
<th>After Vaccination, d</th>
<th>Smallpox and Other Vaccines Administered Within 30 d</th>
<th>Viral Prodrome</th>
<th>Chest Pain</th>
<th>ECG Findings</th>
<th>ECHO Findings</th>
<th>Cardiac Enzymes Positive Peak Levels</th>
<th>Infectious Disease Laboratory Evaluation Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2/29/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, polio (IPV), meningococcal, typhoid (parenteral)</td>
<td>12</td>
<td>Recent upper respiratory tract symptoms</td>
<td>Pleuritic</td>
<td>ST-segment elevation</td>
<td>Mild LV dysfunction; LVEF, 45%</td>
<td>Troponin I, 22.5</td>
<td>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</td>
</tr>
<tr>
<td>10</td>
<td>3/03/03: smallpox</td>
<td>12</td>
<td>None reported</td>
<td>Pleuritic and positional</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>Troponin T, 0.396</td>
<td>Serum: CBC, metabolic panel, LFTs, TSH, all normal, ESR, 35 (normal, 0-15 mm/h) CSF: none Other: none</td>
</tr>
<tr>
<td>11</td>
<td>3/08/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, typhoid (VCPs) 3/24/03: anthrax</td>
<td>19</td>
<td>Fever, arthralgias, dry cough</td>
<td>Positional</td>
<td>ST-segment elevation</td>
<td>Low EF, 37%</td>
<td>Troponin T, 9.2</td>
<td>Serum: multiple heart biopsy specimens negative by PCR for vaccinia CSF: none Other: cardiac biopsy pathological results consistent with eosinophilic myocarditis</td>
</tr>
<tr>
<td>12</td>
<td>3/13/03: smallpox 1/18/03: typhoid (VCPs)</td>
<td>12</td>
<td>Myalgia</td>
<td>Pleuritic</td>
<td>ST-segment elevation</td>
<td>Low normal LVEF, 50%-55%</td>
<td>CK-MB, 76.6; troponin I, 150</td>
<td>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</td>
</tr>
<tr>
<td>13</td>
<td>1/30/03: smallpox 1/17/03: anthrax</td>
<td>14</td>
<td>Recent upper respiratory tract symptoms</td>
<td>Substernal</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>Troponin I, 30</td>
<td>Serum: CBC, metabolic panel, INR, lipid panel, protein electrophoresis, TSH, normal; C-reactive protein, 12 (normal, 0-1 mg/dL) CSF: none Other: none</td>
</tr>
<tr>
<td>14</td>
<td>3/06/03: smallpox</td>
<td>7</td>
<td>None reported</td>
<td>Left axillary</td>
<td>Normal</td>
<td>Normal</td>
<td>Troponin I, 0.73</td>
<td>Serum: none CSF: none Other: none</td>
</tr>
<tr>
<td>15</td>
<td>3/14/03: smallpox</td>
<td>7</td>
<td>Headache, fatigue</td>
<td>Substernal</td>
<td>ST-segment elevation</td>
<td>Low normal LVEF, 50%</td>
<td>Troponin I, 15</td>
<td>Serum: CBC-normal CSF: none Other: none</td>
</tr>
<tr>
<td>16</td>
<td>3/14/03: smallpox</td>
<td>8</td>
<td>Chills, adenopathy</td>
<td>Substernal with radiation down both arms</td>
<td>ST-segment depression</td>
<td>Inferior wall hypokinesis</td>
<td>Troponin I, 1.99</td>
<td>Serum: CBC, metabolic panel, lipid panel, drug assays/toxicology, normal CSF: none Other: none</td>
</tr>
<tr>
<td>17</td>
<td>3/04/03: smallpox 2/19/03: anthrax 2/06/03: anthrax 2/03/03: meningococcal</td>
<td>12</td>
<td>None reported</td>
<td>Substernal</td>
<td>ST-segment elevation</td>
<td>Normal</td>
<td>Troponin I, 159; CK-MB, 93</td>
<td>Serum: CBC, metabolic panel, normal CSF: none Other: none</td>
</tr>
<tr>
<td>18</td>
<td>2/14/03: smallpox and anthrax</td>
<td>11</td>
<td>Muscle aches, elevated temperature</td>
<td>Substernal with radiation to right scapula</td>
<td>ST-segment elevation</td>
<td>Small pericardial effusion with mild inferior hypokinesis</td>
<td>Troponin I, 3.23</td>
<td>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</td>
</tr>
</tbody>
</table>

**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; CPS, cerebrospinal fluid; CF, complement fixation; CK-MB, creatine kinase MB isoenzyme; CH50, total hemolytic complement factor 4; CBC, complete blood cell count; CPS, cerebrospinal fluid; CF, complement fixation; CK-MB, creatine kinase MB isoenzyme; CH50, total hemolytic complement factor 4; 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; LFTs, liver function tests; LV, left ventricular; LVEF, left ventricular ejection fraction; MMR, measles-mumps-rubella; PCR, polymerase chain reaction; RF, rheumatoid factor; TSH, thyrotropin; VCPs, Vaccine Injury Compensation Programs. |
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.22 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 per 100 000 (95% confidence interval, [CI], 1.90-2.34) per 100 000 (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) per 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.28 Often pericarditis and myocarditis are observed in tandem, hence the term myopericarditis.29 Clinical diagnosis is suggested by detection of elevated serum levels of myocardial enzymes (creatinine 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.18,30 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 viruses, adenoviruses, and influenza A).31 Diagnosis may be confirmed using histopathological and/or viral identification by polymerase chain reaction from endomyocardial biopsy or autopsy specimens.28,30 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.28,29,32 However, only 1 previous report has described the pathological characteristics of myopericarditis following smallpox vaccination; the histological changes included a mixed mononuclear infiltrate.33 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

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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 revaccinates 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. It is possible that the occurrence of myopericarditis following vaccination may represent coincidental outcomes; however, the data linking myopericarditis with smallpox vaccine seems 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, 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 revaccinates, 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. Although revaccinates 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. 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. 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 long-term health of these cases, as studies have indicated that viral myocarditis may result in long-term or permanent damage to the heart.

Implications

Implications of these findings for older individuals, or individuals with preexisting cardiac morbidity, are unclear. Clinicians treating patients with other complications from smallpox vaccination (eg, encephalitis, generalized vaccinia, or eczema vaccinatum) may want to evaluate patients for occult myopericarditis. 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.

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 compli-
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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