Ischemic Cardiac Events during the Department of Health and Human Services Smallpox Vaccination Program, 2003


Ten ischemic cardiac events (ICEs) were reported among 37,901 initial US Department of Health and Human Services (DHHS) smallpox vaccinees. Symptoms developed a median of 10 days after vaccination (range, 0–28 days). The median age of case patients was 56 years (range, 42–65 years), and 60% were male. Seven (70%) of the case patients had ≥3 cardiac risk factors or probable coronary artery disease before vaccination. Two women, 55 and 57 years of age, experienced acute myocardial infarction and fatal cardiac arrests. Background rates of ICEs during a 3-week period for civilian populations that were age and sex matched to DHHS vaccinees were estimated. The observed number of myocardial infarctions exceeded estimated expectations (5 vs. 2) but remained within the 95% predictive interval (PI) (0.6–5.4). New onset angina was observed significantly less frequently than estimated expectations (1 vs. 10; 95% PI, 3.5–15.7). After persons with ≥3 cardiac risk factors or known heart disease were deferred from vaccination, no ICEs were reported among an additional 6638 vaccinees.

US smallpox vaccine uses the New York City Board of Health strain of live vaccinia virus, a less reactogenic strain that produces fewer adverse events (AEs) than strains historically used in Europe and elsewhere. Dry-vax (Wyeth Laboratories), derived from calf-lymph preparations, is the only licensed vaccine in the United States [1]. Ischemic cardiac events (ICEs) have been reported rarely after smallpox vaccination but were interpreted as unassociated events [2, 3].

In December 2002, the President of the United States announced a national program for smallpox vaccination, to enhance bioterrorism preparedness [4]. The US Department of Defense began vaccination on 13 December 2002 [5]. On 24 January 2003, the US Department of Health and Human Services (DHHS) civilian program began vaccinating health care and public health workers who volunteered for smallpox response teams.

The Centers for Disease Control and Prevention (CDC), the US Food and Drug Administration (FDA), and state health departments conducted surveillance for vaccine-associated AEs [6]. Reports of postvaccination myocarditis and pericarditis began in February 2003 and were augmented in March by reports of ICEs [7]. In response to concerns regarding possible causal relationships, the CDC and the Advisory Committee on Immunization Practices developed [7] and revised [8, 9] deferral criteria for prospective vaccinees with known
underlying heart disease or with ≥3 known major cardiac risk factors. Myocarditis and/or pericarditis (myo/pericarditis) among smallpox vaccinees is reported elsewhere [10, 11]. This article summarizes information on civilian vaccinees with ICEs.

METHODS

Case ascertainment. Health care workers, hospitals that care for vaccinees, local health departments, and state AE coordinators reported AEs to the Vaccine Adverse Event Reporting System (VAERS), jointly sponsored by the FDA and the CDC [6, 12]. The CDC also established the Clinician Information Line to enable AE consultation 24 h/day, 7 days/week between health care workers, AE coordinators, and CDC clinicians.

A standard data collection form was used to interview vaccinees potentially experiencing an ICE and their health care providers. Pertinent medical records and test results were reviewed. ICE cases were defined by a primary clinician diagnosis of symptoms consistent with myocardial infarction (MI) or angina pectoris supported by evidence of ischemia by electrocardiogram (EKG), serial cardiac enzyme testing, cardiac catheterization, or autopsy. A consulting cardiologist (L.S.S.) reviewed and adjudicated indeterminant cases. This article describes patients with ICEs that occurred within 6 weeks after vaccination.

Autopsy specimens were evaluated for the presence of vaccinia by use of PCR (orthopoxvirus hemagglutinin and type-A inclusion genes, followed by restriction-endonuclease fragment–length polymorphism analysis) [13–16]. Specimens were cultured and evaluated for viral cytopathic effect on B-SC-40 cell culture.

Expected rates of ICEs. Data from 3 US population-based cohort studies (the Framingham Offspring Cohort Study, the Atherosclerosis Risk in Communities Study, and the Coronary Artery Disease Risk Development in Young Adults Study) were used to estimate expected rates of ICEs (CDC, unpublished data). On the basis of the age and sex distributions of civilian vaccinees as of 12 May 2003, the expected numbers of ICEs (fatal or nonfatal MI, new-onset angina, and sudden death) were determined for a 3-week period. For general surveillance purposes, a 6-week interval was used to increase sensitivity. The shorter 3-week window was used for the expected-rates analysis because 70% of reported postvaccination ICEs had symptom onset within 3 weeks after vaccination, and this time frame was thought by consulting cardiologists to be mechanistically most compatible with theoretical vaccine-induced ICEs. Postvaccination angina observed among persons previously diagnosed with coronary artery disease (CAD) was not included in this analysis, because the comparison expected rates derived from the cohort studies were based on incident (new-onset) angina.

RESULTS

Between 24 January and 31 October 2003, smallpox vaccine was administered to 37,901 civilian health care and public health workers in 55 jurisdictions, 31,263 (82.5%) of whom were vaccinated by 4 April 2003 [17] (figure 1). Overall, 64% of vaccinees were female, 76% had been previously vaccinated (i.e., were “revaccinees”), and the median age was 48 years.

Possible cardiac events. As of 31 October 2003, 203 persons with possible cardiac symptoms were investigated: 10 had an ICE, 21 met the case definition for myo/pericarditis [18], and 2 met the case definition for dilated cardiomyopathy [19]. Among the remaining 170 persons, 6 reported new-onset or
Table 1. Characteristics of patients with ischemic cardiac events following smallpox vaccination, 23 January–31 October 2003.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Time from vaccination to symptom onset, days</th>
<th>Diagnosis</th>
<th>Known clinical features at time of vaccination</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>F</td>
<td>5</td>
<td>MI/sudden death</td>
<td>Hypertension, hypercholesterolemia, smoking, history of chest tightness, and obesity</td>
<td>Died 23 March 2003</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>F</td>
<td>17</td>
<td>MI/sudden death</td>
<td>Hypertension, smoking until 1 year prior, and history of peripheral vascular disease and angina pectoris</td>
<td>Died 26 March 2003</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>M</td>
<td>2</td>
<td>MI</td>
<td>History of exertional dyspnea, smoking 20 years prior, and familial hyperlipidemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>M</td>
<td>0</td>
<td>MI</td>
<td>CAD, history of MI, hypertension, DM, hyperlipidemia, family history of CAD, and obesity</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>26</td>
<td>MI</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>F</td>
<td>10</td>
<td>MI</td>
<td>History of exertional chest pain, hypertension, DM, family history of CAD, hyperlipidemia, and obesity</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>4</td>
<td>Angina</td>
<td>History of exertional chest pain (not previously evaluated), hyperlipidemia, family history of CAD, and obesity</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>10</td>
<td>Angina</td>
<td>CAD, hypertension, and DM</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>M</td>
<td>21</td>
<td>Angina</td>
<td>Hypertension and obesity</td>
<td>Recovered</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>F</td>
<td>26</td>
<td>Angina</td>
<td>Hypertension, smoking, and obesity</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

NOTE.  CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction.

exacerbations of documented arrhythmias, 47 had palpitations without documented arrhythmias, 27 reported new-onset or exacerbations of hypertension, 107 had nonspecific or atypical chest pain, and 16 had dyspnea of unclear etiology (persons could report >1 symptom). One sudden cardiac death and 2 MIs that occurred >6 weeks after vaccination (from 10 weeks to 6 months after) are not included in this report.

**Ischemic events.** As of 31 October 2003, 10 ICEs were reported (6 acute MIs and 4 angina) (table 1). Vaccinees experiencing ICEs were ethnically diverse (8 white, 1 black, and 1 Native American). All were revaccinees, 60% were male, and the median age was 56 years (range, 42–65 years). Seven had successful vaccine reactions documented. Symptoms developed a median of 10 days (range, 0–28 days) after vaccination, and 7 vaccinees developed symptoms within 3 weeks after vaccination (figure 2). Two females, 55 and 57 years of age, died of cardiac arrest; both had atherosclerotic CAD and evidence of acute MIs at autopsy. Seven (70%) of the 10 case patients had ≥3 cardiac risk factors or clinical history consistent with ischemic cardiac disease, precluding vaccination after institution of deferral criteria [7, 8]. No ICEs were reported among persons vaccinated by the DHHS after 4 April 2003. Summary characteristics of vaccinees with ICEs, reported individually below, are shown in table 1.

**Case 1: MI and sudden death.** A 55-year-old Native American woman with a history of hypertension, hypercholesterolemia, smoking, and obesity was vaccinated on 18 March 2003. Several previous hospitalizations for chest tightness and shortness of breath or for near syncope and diaphoresis culminated in a November 2001 diagnosis of angina pectoris despite normal cardiac enzymes, EKGs, persantine Cardiolite (sestamibi) stress test, and echocardiogram. She attributed recurring prevaccination diaphoresis and lightheadedness to hypoglycemia. At the time of vaccination, her medications included atenolol, hydrochlorothiazide, diltiazem, and valsartan. After vaccination, she reported minor arm soreness. On 22 March, after attending a traditional Native American sweating ceremony, she complained of acute onset of malaise, abdominal pain, vomiting, and diarrhea. That evening, she was observed to be improved and sleeping. The next morning, she was found unresponsive and pronounced dead on arrival at the hospital. An autopsy was conducted at the Office of the Chief Medical Examiner, Department of Health, Virginia. Tissues also were examined at the Department of Defense Armed Forces Institute of Pathology and the Infectious Disease Pathology Activity, National Center for Infectious Disease, CDC. Autopsy showed focal severe coronary arteriosclerosis, an acute plaque rupture and occlusive thrombosis in the right coronary artery (RCA), and softening and focal microscopic acute ischemic changes in the posterior left ventricle but no evidence of myocarditis or coronary arteritis. PCR and immunohistochemistry detected vaccinia virus at the vaccination site but not in multiple other organs tested, including the myocardium, lung, kidney, brain, and liver.

**Case 2: MI and sudden death.** A 57-year-old white woman with a history of hypertension, peripheral vascular disease, and a right carotid endarterectomy in 1998 for carotid stenosis was vaccinated on 27 February 2003. She smoked for 40 years but stopped 1 year before vaccination. In December 2001, after an
exercise stress test reproduced chest pain accompanied by ST-segment and T-wave changes in the inferolateral leads, cardiac catheterization at that time demonstrated mild luminal irregularities and an RCA with an abnormal posterior origin. Medical therapy was advised; at the time of vaccination, medications included amlodipine, losartan, hydrochlorothiazide, and raloxifene. One day after vaccination, she complained of malaise, myalgia, fatigue, dizziness, fever (temperature, 102.6°F), and nausea. Five days after vaccination, she was admitted to the hospital with nausea, shortness of breath, and a cough producing green sputum, but she denied chest pain. EKG was normal. She was treated with bronchodilators, fluids, and antibiotics and was discharged the next day. Seventeen days after vaccination, she complained of nausea and left chest pain and collapsed with ventricular fibrillation. She was resuscitated, intubated, and admitted to a cardiac care unit. EKG showed ST-segment elevations in leads V1–V3 and in the AVF lead consistent with an acute inferior MI. An echocardiogram showed mild inferior-wall hypokinesis, and cardiac enzymes were elevated (peak troponin I, 24.72 ng/mL [normal, <0.6 ng/mL]; peak creatinine kinase MB [CK-MB] fraction, 172 ng/mL [normal, 0–5 ng/mL]). She remained comatose and died with multisorgan failure 11 days after admission. Autopsy performed by the local coroner’s office and tissues examined at the CDC showed a large healing infarct involving the posterior left ventricular wall and interventricular septum with moderate-to-severe coronary artery atherosclerosis especially involving the RCA and the left anterior descending (LAD) artery. There was no evidence of myo/pericarditis or coronary arteritis. PCR and immunohistochemistry detected vaccinia virus at the vaccination site but not in any other tissue, including multiple myocardium sections.

**Case 3: MI.** A 64-year-old white man with a history of familial hyperlipidemia, a 20-year history of smoking, and several months of exertional dyspnea and cough was vaccinated on 21 March 2003. Two days after vaccination, he had 2 dizzy spells 30 min apart, the first associated with sudden onset of fullness in his chest. After hospital admission, an EKG showed inferior ST-segment depression and T-wave inversion, and cardiac enzymes were elevated (troponin I, 3.7 ng/mL [normal, <0.4 ng/mL]; CK-MB fraction, 9.3 ng/mL [normal, 0–8 ng/mL]). An echocardiogram showed moderate inferior wall hypokinesis. Cardiac catheterization on 25 March showed 80% stenosis of the first diagonal branch and 50% stenosis of the second diagonal branch of the LAD coronary artery, total occlusion of the middle portion of the circumflex coronary artery, and 90% stenosis proximally and 50% stenosis diffusely through the remainder of the RCA. He received balloon atherectomy. Stents were placed in his LAD and right proximal coronary arteries. He returned to work on 31 March.

**Case 4: MI.** A 46-year-old white man with a history of a previous MI and angioplasty in 1997, hypertension, diabetes mellitus, hyperlipidemia, obesity, sedentary lifestyle, and a family history of CAD was vaccinated on 19 March 2003. He had mild intermittent chest pain during the 3 days before vaccination. The night after vaccination, chest pain worsened, he developed diaphoresis, and he presented to the local emergency department. EKG demonstrated a sinus tachycardia of 103 beats/min but no evidence of ischemia; initial cardiac enzymes were normal. The next morning, his creatine phosphokinase (CPK) level was 256 U/L, CK-MB fraction was 19 ng/mL, and troponin I was 5.8 ng/mL; a non-Q wave MI was diagnosed. Cardiac catheterization showed significant obstructive lesions in the obtuse marginal branch of the left circumflex artery and the posterolateral and posterior descending branches of the RCA. Angioplasty and stent placement were performed. The patient returned to work.

**Case 5: MI.** A 49-year-old, slightly obese white man with no recognized cardiac risk factors was vaccinated on 12 March 2003. Twenty-six days after vaccination, he developed burning substernal chest pain, which resolved spontaneously. The next day, the pain recurred, worsened, and radiated to his neck and arms and was associated with diaphoresis and nausea. An EKG demonstrated Q waves in leads V1–V4 and an inferior ST-segment wave depression. Cardiac enzymes were elevated (CPK, 1285 U/L [normal, <170 U/L]; troponin I, 12.7 ng/mL [normal, <0.1 ng/mL]). An acute anterior MI was diagnosed. Cardiac catheterization showed a proximal occlusion of the LAD artery and 2 50%–60% occlusions in the RCA. Catheterization identified elevated left ventricular end diastolic pressures, anterolateral and apical akinesia, and an estimated ejection fraction of 35%. He underwent a successful percutaneous transluminal coronary angioplasty procedure with 2 stents placed in his LAD artery. During hospitalization, he reported a history of borderline, untreated hypertension. A lipid profile showed total cholesterol of 207, with high-density lipoprotein of 34 and low-density lipoprotein of 130. He was discharged after 5 days.
Case 6: MI after atrial fibrillation. A 54-year-old white woman with a history of exertional chest pain, diabetes mellitus, hypertension, hyperlipidemia, family history of premature coronary disease, and obesity was vaccinated on 3 March 2003. Several months of exertional chest pain resolved spontaneously 7 months before vaccination. Ten days after vaccination, the patient noted chest discomfort, a rapid irregular pulse, and dizziness. Blood pressure was 165/112. EKG showed atrial fibrillation, ventricular rate of 160, and ST-segment depression of inferior and lateral leads. She was treated with metoprolol and aspirin; 3–4 hours after symptom onset, both her rhythm and EKG returned to normal. Serial cardiac enzymes showed a peak CPK of 197 IU/L (normal, 6–250 IU/L), CK-MB fraction of 14 ng/mL (normal, 0–5 ng/mL), and troponin 10.3 ng/mL (normal, 0.0–0.4 ng/mL). Two-dimensional time-motion doppler echocardiography demonstrated indirect evidence of left ventricular diastolic dysfunction, mild mitral and tricuspid regurgitation, and a left atrial dimension estimate of 4–4.5 cm (normal dimension, 1.9–4.0 cm). Cardiac catheterization showed severe CAD. Left ventriculography demonstrated mild posterobasal hypokinesis, normal systolic function elsewhere, and a left ventricular ejection fraction of 75%. After 4-vessel coronary artery bypass graft surgery, she returned to work.

Case 7: Angina. A 60-year-old white man with hyperlipidemia, obesity, and a family history of early CAD was vaccinated on 12 February 2003. He was taking atorvastatin and aspirin. He had no known history of CAD but, both 10 and 2 days before vaccination, reported brief episodes of substernal chest pressure during strenuous exercise. One day after vaccination, he developed myalgias, arthralgias, low-grade fever, and headache that persisted. On the third day, he sought evaluation for a brief episode of exertional chest pressure but declined further evaluation after EKG showed no acute changes. The following day, he was admitted to the hospital for more-severe chest pain with minimal exertion and at rest. Nonspecific ST-segment and T-wave abnormalities on EKG were unchanged from May 2002. Cardiac enzymes were normal (CPK, 86 U/L [normal, 30–174 U/L]; troponin I, <0.3 ng/mL [normal, 0–1.9 ng/mL]). Cardiac catheterization on 17 February showed LAD artery luminal irregularities, a proximal 90% lesion in a large circumflex vessel, and an occluded RCA but normal left ventricular function. He was treated with angioplasty and the placement of 2 stents. Recurrent chest pain the following day led to recatheterization. The stents were patent. Chest pain was attributed to distal embolization to a small posterior left ventricular branch of the RCA. He remained pain free and resumed normal activities.

Case 8: Angina. A 65-year-old black man with a history of known CAD, hypertension, and diabetes mellitus was vaccinated on 3 March 2003. In 2002, syncope was evaluated with cardiac catheterization that identified a distal lesion of his LAD artery that was not amenable to surgery. His medications included ramipril, aspirin, and glyburide. He attributed occasional left chest pain and arm paresthesias during extreme exercise in the months before vaccination to cervical disc disease. Five days after vaccination, fatigue, myalgias, and malaise not responsive to ibuprofen began. Ten days after vaccination, a papular chest rash developed, exercise tolerance decreased, and he experienced left-chest discomfort. His symptoms worsened. On day 23 after vaccination, he was admitted to the hospital after a 25-min episode of severe chest pain. An EKG showed no acute changes. Serial CPK and CK-MB fraction were slightly elevated (peak total CK, 220 U/L [normal, 55–170 U/L]; CK-MB fraction, 5.1 ng/mL [normal, 0.0–5.0 ng/mL]), but troponin T was <0.04 ng/mL (normal, 0.0–0.10 ng/mL). A thallium stress test elicited similar symptoms and demonstrated anterior ischemic changes consistent with his prior coronary catheterization. A beta-blocker and a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor were added to his medical regimen, his dose of angiotensin-converting enzyme-1 inhibitor was increased, and he was discharged with a diagnosis of angina. Four months after vaccination, fatigue and reduced exercise tolerance persisted.

Case 9: Angina. A 57-year-old white man with a history of obesity, hypertension controlled with nadolol, and low-dose aspirin therapy but no symptoms of CAD was vaccinated on 27 February 2003. Twenty-one days after vaccination, 15 min of pressuring chest discomfort and weakness occurred while he was gardening and resolved with rest. Exertional chest pain relieved by rest continued over the next week. EKG was normal.

Table 2. Observed versus expected numbers of incident cardiac events among US civilian vaccinees, 24 January–31 October 2003.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. observed</th>
<th>No. expected</th>
<th>95% Predictive interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>5</td>
<td>2</td>
<td>0.6–5.4</td>
</tr>
<tr>
<td>Angina</td>
<td>1</td>
<td>10</td>
<td>3.5–15.7</td>
</tr>
<tr>
<td>Myocardial infarction and death</td>
<td>2</td>
<td>1</td>
<td>0–2.96</td>
</tr>
</tbody>
</table>

**NOTE.** Persons with onset >3 weeks after vaccination and persons with angina with pre-existing symptoms were excluded. Source: CDC, unpublished data derived from data provided by the National Heart, Lung, and Blood Institute and the Atherosclerosis Risk in Communities, Framingham Offspring Cohort, and Coronary Artery Risk Development in Young Adult studies.
and cardiac enzyme levels were not determined during an emergency department evaluation on 1 April. Cardiac catheterization on 3 April identified a totally occluded circumflex artery, high-grade stenosis of the middle and distal RCA, and high-grade stenosis of the LAD artery with normal left ventricular systolic function. He was symptom free after coronary artery triple-bypass graft surgery.

**Case 10: Angina.** In 1998, a 42-year-old white woman with hypertension, a history of smoking, and obesity had burning chest pain radiating down her arms, but an Adenoscan (adenosine) Myoview (technetium-99 m-tetrofosmin) stress test and echocardiography were normal. The pain, believed to be gastrointestinal, resolved with famotidine therapy. When vaccinated on 4 March 2003, she was taking losartan, potassium, hydrochlorothiazide, and cardiazem. She experienced burning chest pain similar to her 1998 pain, relieved by ranitidine, about the time of her smallpox vaccination. On 1 April, 26 days after vaccination, she reported new-onset crushing retrosternal chest pain not relieved by ranitidine that radiated to her throat, was associated with shortness of breath and dyspnea on exertion, and continued intermittently until 9 April, when an EKG demonstrated nonspecific ST depression in the inferolateral leads and poor R-wave progression. Benazepril and atorvastatin were prescribed. An Adenoscan Myoview stress test was consistent with reversible ischemia of the anterior segment of the left ventricle. Cardiac catheterization demonstrated a 99.9% occlusion of the proximal circumflex coronary artery with no other significant lesions and normal left ventricular function. The patient returned to normal activities after percutaneous transluminal coronary angioplasty with stent placement.

**Expected numbers of ICEs.** Three persons (MI case 5 and angina cases 9 and 10) who had ICEs >3 weeks after smallpox vaccination and 1 person (angina case 8) who had known CAD before vaccination were not included as observed case patients in this analysis. The number of observed MIs (5) exceeded the expected point estimate (2) but not the upper 95% PI (0.6–5.4). The 1 patient with angina was significantly less than the expected point estimate (10; 95% PI, 3.5–15.7). The number of persons with sudden death (2) exceeded the expected point estimate (1) but remained within the 95% PI (0–2.96) (table 2).

**DISCUSSION**

We report 10 persons who experienced ICEs after smallpox vaccination during the 2003 US civilian program. Whether these events were causally associated with vaccination is unknown. All cases had >1 risk factor for CAD; 70% had ischemia-like symptoms before vaccination. Although the observed numbers of MIs exceeded the expected point estimate, they remained within the 95% PI. No ICEs were reported among persons vaccinated after the implementation of deferral recommendations in late March 2003.

Myocarditis and pericarditis after smallpox vaccination were reported during the smallpox-eradication era, most commonly in Europe and Australia [20–22], and during the current US vaccination campaigns [7, 8, 10, 11]. ICEs have rarely been reported after smallpox vaccination. Eight MIs or ischemia seen on EKG associated with 5 deaths were reported after smallpox vaccination during a 1955 French campaign. Seven case patients were male, 53–83 years of age, and 3 had known preexisting cardiac disease. Symptom onset was 7–10 days after vaccination. These observed events may have been expected to be due to chance alone, since 25 million people were vaccinated [2]. In another report, a 57-year-old German man had an MI after receiving a killed smallpox vaccine, followed 8 days later by a live smallpox vaccine [3].

No ICEs were reported from the 1963 national survey [23], the 1963 4-state survey [24], the 1968 national survey [25], or the 1968 10-state survey [26] that described smallpox vaccine AEs in the United States. Several European studies documented EKG changes in persons after vaccination that were attributed to silent myocarditis rather than ischemia [27, 28].

Cases of sudden death after smallpox vaccination that were reported from Europe, Australia, and the United States all had evidence of severe myocarditis without ischemic disease at autopsy [20–22, 29]. A review of US death certificates covering 1959–1966 and 1968 identified 84 deaths after smallpox vaccination; none appeared to be cardiac in origin, although no autopsy was performed for 1 elderly patient who died shortly after vaccination [30].

The expected-rates analysis should be interpreted cautiously. Numbers of both expected and observed events are low. It is not possible to be confident that the populations in cohorts used to estimate expected rates had cardiac risk profiles similar to those of the 2003 vaccinees. Passive surveillance was used to identify ICEs after smallpox vaccination. Persons in the comparison cohort studies were more actively followed, possibly resulting in ICE ascertainment differences. The reporting sensitivity of VAERS varies by the severity and acuity of the AEs. Only 3% of hypotonic-hyporesponsive episodes after administration of diphtheria-tetanus toxoid-pertussis vaccine were reported to VAERS. Reporting of severe AEs, such as poliomyelitis after oral polio vaccine, was higher (68%) [31].

Although the cases of ICEs after smallpox vaccination reported here may have been coincidental, biologic mechanisms by which vaccine could be causally associated can be hypothesized. Inflammation plays a decisive role in the pathophysiology of acute thrombotic events, including unstable angina and acute MIs [32]. Local effects of inflammation on atherosclerotic lesions and systemic inflammatory responses may increase thrombotic risk [32]. Good evidence supports the oc-
currence of systemic inflammation and extremely elevated cytokine levels after smallpox vaccination. In a 60-subject study of dose-related smallpox vaccination effects, vigorous cytotoxic T cell and IFN-γ responses occurred in 94% of persons who developed vesicles after vaccination [33]. In another study of 107 vaccinia-naïve individuals vaccinated with 1 of 3 smallpox vaccine dilutions, levels of IFN-γ, IL-10, and TNF-α were significantly increased [34]. No specific mechanism has yet been postulated by which specific cytokines could induce ICEs; however, the presence of inflammatory mediators is of interest. Systemic reactions, including fever, are common after vaccination [35] and could increase metabolic demand in patients at risk for ICEs.

Case 6 may be an example of ischemia induced by the increased oxygen demand of a rapid heart rate from atrial fibrillation in the setting of preexisting CAD. Arrhythmias after smallpox vaccination were previously recognized only in association with myocarditis and pericarditis. A 57-year-old patient was reported with pericarditis, fever, and atrial fibrillation 14 days after vaccination in Great Britain [36].

Many of the tests used to diagnose myocarditis, pericarditis, and ICEs, such as echocardiography and sensitive cardiac enzyme testing, were not available during previous smallpox vaccination campaigns, possibly resulting in underrecognition of cardiac events. Furthermore, since ascertainment of vaccine-associated AEs relies on provider suspicion that an event may be casually associated with the vaccine, cardiac events may have been underreported [23–26]. Historically, the majority of vaccinees were children in whom cardiac events were less likely to occur or to be recognized. Press coverage of cardiac events during the current campaign may have increased both detection and reporting.

In conclusion, we report 10 cases of ICEs during the civilian smallpox vaccination program. Causal association remains uncertain; these events may have coincidentally followed vaccination. All persons described in this report had underlying risk factors for atherosclerotic CAD; most had symptoms before vaccination. These people were at increased risk of developing ICEs, regardless of any theoretical contribution from smallpox vaccination. Since deferral of persons at increased risk of cardiac disease from smallpox vaccination, no vaccinated persons have reported ICEs.

It may be worthwhile to determine expected rates of clinical events such as MI before initiation of future vaccination campaigns, to avoid undue concern if events occur that are coincidental to the vaccination. In the case of an actual biologic attack with smallpox virus, it may be necessary to vaccinate individuals despite cardiac risk factors but to monitor at-risk persons for cardiac events. It is difficult to consider eliminating the cardiac deferral criteria in the pre-event setting. Regardless of whether there is an association between ICEs and smallpox vaccination, inclusion of persons with significant medical histories or risk factors on response teams in either pre- or post-event settings warrants careful consideration.

Lastly, the current smallpox vaccine (New York City Board of Health strain) is a relatively impure live vaccine product derived from calf lymph. It is important not to generalize speculation about this vaccine to other nonsmallpox vaccines in routine current use.

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Acknowledgments

We gratefully acknowledge the case patients, health care providers, state and local health department officials, Vaccine Adverse Event Reporting System reporters, and State Adverse Event Coordinators for their assistance in identification, evaluation, reporting, and follow-up of adverse events after smallpox vaccination. We also thank Jan Phillips, Constance Marin, Susan Smith, Jerry Gibson, and Linda Bell of the South Carolina Department of Health and Environmental Control and Gayle Guidash and Claude Dharamraj of the Pinellas County Health Department, Florida.

Supplement sponsorship. This article was published as part of a supplement entitled “Posteradication Vaccination against Smallpox,” sponsored by the National Center for Immunization and Respiratory Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), and by the Coordinating Office for Terrorism Prevention and Emergency Response, CDC.

Potential conflicts of interest. All authors: no conflicts.

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Ischemic Events and Smallpox Vaccination • CID 2008;46 (Suppl 3) • S241