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The US Department of Defense requested that the Advisory Committee on Immunization Practices–Armed Forces Epidemiological Board joint Smallpox Vaccine Safety Working Group define the likelihood that smallpox vaccination played a causal role in the fatal illness of an Army reservist. Reported serious adverse events for which there was no a priori reason to discount the existence of a causal association with smallpox vaccine were reviewed to assess whether they were signals of constellations of vaccine-associated adverse events. A causal relationship between the immunization experience and the index patient’s death was favored, but the implication of an individual vaccine was precluded. No new smallpox vaccine–associated clinical syndromes were identified. The data supported neutrality regarding the hypothesis that dilated cardiomyopathy was causally associated with smallpox vaccine–induced myocarditis. This review of sentinel cases augmented the ongoing safety review process and was transparent, but it shares limitations with other case-based causality-assessment methods.

In December 2002, the President of the United States recommended a national smallpox vaccination program. On 16 December 2002, the US Department of Defense (DoD) reinstated a smallpox vaccination program among military personnel. On 24 January 2003, the US Department of Health and Human Services (DHHS) authorized voluntary smallpox vaccination of health care and public health workers who might serve as members of smallpox response teams.

In January 2003, the Institute of Medicine (IOM) Committee on Smallpox Vaccination Program Implementation recommended the establishment of an independent external review board charged with Data and Safety Monitoring Board–like responsibility for safety oversight of the US National Smallpox Pre-Event Vaccination Program [1, 2]. A joint Smallpox Vaccine Safety (SVS) Working Group (WG) of the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) and the DoD’s Armed Forces Epidemiological Board (AFEB) (henceforth referred to as the “SVS WG”) was created to meet this need.

On 4 April 2003, a young, previously healthy female
Army reservist died of an unexplained illness. During the week of 2 March, she had received multiple vaccinations, including vaccines to prevent smallpox, typhoid, anthrax, hepatitis B, and measles, mumps, and rubella, as routine preparation for deployment. After vaccination, she experienced onset of an unexplained illness with a progressively deteriorating clinical course [3]. Autopsy and extensive review by clinicians at Walter Reed Army Medical Center and through the CDC's Unexplained Deaths Project [4] failed to define the illness etiology.

Faced with similar challenges of unexplained illness after anthrax vaccination in the military, the DoD had requested that an independent civilian panel be created to help assess the likelihood of a causal relationship between anthrax vaccination and these illnesses [5, 6]. In response, the Division of Vaccine Injury Compensation, Health Resources and Services Administration, DHHS, which conducts similar causality assessments for adverse events after routinely recommended childhood vaccinations, organized the Anthrax Vaccine Expert Committee [5, 6]. In April 2003, the Assistant Secretary of Defense (Health Affairs) requested that the SVS WG develop a similar process to assess the likelihood of a causal relationship between smallpox vaccination and the death of this Army reservist (the "index patient").

Whenever an adverse event follows a medical intervention, the question of whether a causal relationship exists between the 2 arises [7, 9]. In pharmacovigilance, case reports of adverse events in persons exposed to medical products are reviewed systematically, and the degree of certainty that a causal relationship exists between product exposure and the adverse event is classified [9] by experts in immunization safety. Historically, various methods ranging from global introspection to branched logic tree algorithms to Bayesian analysis [10–14] have been used to improve the ability to make causal inferences about the relationship between a specific exposure and subsequent adverse events.

Rarely, an adverse event can be definitively causally linked to a prior exposure or intervention by virtue of the presence of a pathognomonic laboratory or clinical finding (e.g., isolation of vaccine strain virus) [15]. Occasionally, responses to dechallenge or rechallenge may reinforce the likelihood of causal relationship [16]. However, most adverse events do not have such unusual features permitting easy conclusions regarding causality [15]. In the absence of such findings, well-conducted clinical trials or epidemiologic studies that demonstrate a significantly increased rate of the adverse event among persons who have experienced that exposure, compared with that in control populations, combined with fulfillment of several tenets of causal relationship first outlined by Hill [17], are needed. Because most adverse health outcomes are multifactorial in etiology, even when an elevated risk for an adverse event among vaccinated persons can be demonstrated at the population level, uncertainty remains about whether such a causal relationship exists in a specific individual instance if no pathognomonic conditions are present.

Review of case reports is most useful for identifying adverse events that may signal a previously unrecognized causal association between vaccination and adverse event syndromes that can be evaluated in future studies. Furthermore, identification of adverse event signals is better achieved by reviewing case series, rather than individual reports, and is best accomplished by universal systematic review of all similar or related reports [7, 8, 15, 18–28].

The CDC coauthors of the present article (L.E.C., J.K.I., and R.T.C.) reviewed historical approaches to and expert critiques of causality-assessment methods, as well as the experiences of the Anthrax Vaccine Expert Committee [5, 6], Health Canada's Advisory Committee on Causality Assessment [18], and the IOM Immunization Safety Review Committee [7, 8, 19]. They noted that a causality-assessment exercise could not determine whether smallpox vaccination played a causal role in the index patient's death, because pathognomonic findings, epidemiologically demonstrated statistical associations, and challenge/rechallenge observations were all absent.

Further, the inherent conditions necessary for assessing causal relationships between smallpox vaccine and reported adverse events for other vaccines are missing for most Vaccine Adverse Event Reporting System (VAERS) reports [7, 8, 15, 18–28]. VAERS is a passive reporting system for adverse events following vaccination, operated jointly by the CDC and the US Food and Drug Administration (FDA). VAERS served both the CDC and DoD as a principle surveillance tool for identification of adverse events following smallpox vaccination.

Additionally, extensive CDC and DoD systems for prospective monitoring of smallpox vaccination–associated adverse events already in place [2, 29, 30] had been sensitive enough to identify previously underrecognized smallpox vaccine–associated adverse events [2, 29, 31–41]. Rereviewing adverse event reports previously reviewed under this safety oversight system as part of a causality-assessment exercise would be an unjustifiable use of resources, duplicating efforts while contributing marginal gain. One alternative, superimposing a limited causality-assessment exercise on the existing safety review process, would lose the value of universal uniform review.

The CDC concluded that a traditional causality-assessment exercise could not determine whether smallpox vaccination played a causal role in this death. Instead, the specific review needs raised by this case would be best served by augmenting the existing prospective safety review process with a systematic retrospective case review process designed to identify adverse events of unusual nature, severity, or frequency ("sentinel cases"). Whether these sentinel cases were signals of unrecognized vaccine-associated syndromes could be clarified through systematic
critical review of data that supported or refuted a causal relationship. The SVS WG and the Assistant Secretary of Defense (Health Affairs) concurred.

The present article describes the Sentinel Case Review Process for Signal Clarification (henceforth referred to as the “Sentinel Review Process”) developed at the CDC and used by the SVS WG to assess the significance of the index patient’s death and other adverse events identified after smallpox vaccination conducted between December 2002 and June 2004. This process adapted and incorporated lessons from the Anthrax Vaccine Expert Committee [5, 6], the Advisory Committee on Causality Assessment [18], and the IOM [7, 8, 19]. It also benefited from published critiques of prior causality-assessment efforts and specific critiques offered by expert consultants during our process development [5–8, 18–26]. This process was intended to meet the needs of the US smallpox vaccination program at a specific point in time, rather than to serve as a general model for adverse event signal clarification or for vaccine safety case assessment. The present article also summarizes the clinical cases reviewed by the SVS WG using this Sentinel Review Process and the outcome of these independent deliberations.

METHODS

Smallpox Vaccine Adverse Events Monitoring and Response System

The extensive prospective monitoring of adverse events for the US National Smallpox Pre-Event Vaccination Program has been described elsewhere [2, 29, 30, 42]. In brief, reports received through VAERS [43–45], the CDC Clinician Information Line [4, 42], DoD health care providers, or by other means were reviewed and systematically categorized according to case definitions [2]. Per federal regulations, VAERS reports are classified as “serious” if the reported event resulted in hospitalization, permanent disability, life-threatening illness, or death [43–45]. Summaries of total VAERS reports, “serious” reports, and reports fitting case definitions received between 16 December 2002 and 30 June 2004 were shared with the SVS WG, made available on CDC and DoD Web sites, and published in Morbidity and Mortality Weekly Report (http://www.cdc.gov/mmwr/).

ACIP-AFEB SVS WG

The SVS WG functioned as a joint working group of the CDC’s ACIP and the DoD’s AFEB and was composed of health profession content experts (Appendix A). The SVS WG reported directly to the ACIP and through it to the director of the CDC, issued regular reports to the AFEB and through it to the Assistant Secretary of Defense (Health Affairs), and consulted with the IOM committee. The ACIP-AFEB joint SVS WG was supported by the CDC National Immunization Program.

A task force of medical epidemiologists reviewed medical records and studied reports of individual sentinel events (including all deaths) for evidence of temporal clustering after vaccination and for increases in observed rates relative to background. During weekly teleconferences with the SVS WG, the CDC and DoD provided results from these investigations and ongoing analyses of summary data for review. Analyses were made available to the public through publication, presentation at appropriate scientific forums, and reports to the ACIP during 3 open public meetings annually (http://www.cdc.gov/nip/ACIP/default.htm), and, when needed, an emergency teleconference meeting of the ACIP [2, 31].

Sentinel Case Review for Signal Clarification

CDC staff conducted a systematic retrospective review of all serious adverse events after smallpox vaccination that were reported to VAERS, to identify sentinel cases that might represent signals of unrecognized causal association between vaccination and clinical adverse events. The SVS WG then examined these sentinel cases in depth to clarify, as much as possible, potential associations between these sentinel cases and the smallpox vaccine.

Identification of sentinel cases and potential clusters for review. In 2003, VAERS reports were systematically organized using the Coding Symbol for Thesaurus of Adverse Reaction Terms (COSTART) codes [43–46]. A frequency analysis of COSTART codes associated with all VAERS reports involving smallpox vaccine was conducted, seeking patterns suggestive of vaccine-associated syndromes (e.g., temporal clustering and apparent increases above background rate). Reported events that did not meet the VAERS “serious” criteria but that might represent the less-severe end of a spectrum resulting in disabling or life-threatening disease were also reviewed. Lastly, CDC immunization safety staff used established statistical techniques to detect adverse event clusters and used “signal-detection techniques” to seek additional cases appropriate for review [47, 48].

Identified sentinel cases were organized in 6 categories (table 1) as follows: Category 1 includes events etiologically associated with smallpox vaccine by pathognomonic clinical or laboratory findings (e.g., progressive vaccinia, eczema vaccinatum, fetal vaccinia, inadvertent inoculations, and contact transmissions). Most dermatologic conditions reported to VAERS were included in this category. Category 2 includes events etiologically associated with smallpox vaccine through statistically significant epidemiologic studies (e.g., myocarditis and/or pericarditis [hereafter referred to as “myo/pericarditis”]). Category 3 includes events and syndrome clusters already extensively reviewed by the SVS WG or designated experts, about which determinations regarding causality had been reached (e.g., all possibly cardiogenic events, including ischemic cardiac events, hypertension, dysrhythmias, and nonspecific chest pain, as well as dermatologic conditions reported to VAERS that lacked pathognomonic findings and therefore did not qualify for cate-
Table 1. Categories of sentinel events.

<table>
<thead>
<tr>
<th>Category</th>
<th>Nature of sentinel events</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Events etiologically associated with smallpox vaccine by pathognomonic clinical or laboratory findings</td>
<td>Contact transmissions</td>
</tr>
<tr>
<td>2</td>
<td>Events etiologically associated with smallpox vaccine through statistically significant epidemiologic studies</td>
<td>Myocarditis and/or pericarditis</td>
</tr>
<tr>
<td>3</td>
<td>Events and syndrome clusters about which determinations regarding causality had previously been reached by expert review</td>
<td>Ischemic cardiac events</td>
</tr>
<tr>
<td>4</td>
<td>Events for which an a priori reason to discount causal association exists</td>
<td>Death due to traumatic injury</td>
</tr>
<tr>
<td>5</td>
<td>All neurological adverse events</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>6</td>
<td>All other adverse events</td>
<td>Self-explanatory</td>
</tr>
</tbody>
</table>

gory 1). Category 4 includes events for which an a priori reason to discount association existed. Deaths and hospitalizations due to trauma or injury and other events with an established diagnosis independent of vaccination, such as appendicitis and cholecystitis, were included in this category. Category 5 includes all neurological adverse events. Category 6 includes all other adverse events.

Events in categories 1–4 were reviewed, reported separately [2, 32–36, 42], and excluded from the Sentinel Review Process because causality ascertainment was complete. Events in category 5 were referred to a neuroepidemiologist for prereview and are reported separately [49, 50]. Dermatologic conditions, including generalized vaccinia, were also reviewed and reported separately [51, 52]. Only events in category 6 were reviewed by the SVS WG using the Sentinel Review Process and summarized herein.

**Review subgroups.** Subgroups of the SVS WG were assigned to review the following category 6 sentinel events: subgroup A, previously unreviewed deaths; subgroup B, clinical syndromes characterized by chest pain, dyspnea, and fever; and subgroup C, dilated cardiomyopathy (DCM). The goals were to assess evidence supporting or refuting the likelihood that the identified individual cases represented varying manifestations of a common syndrome and that identified cases or syndromes might be causally associated with vaccination. The outcomes of these subgroup reviews were brought to the whole SVS WG for critique and concurrence.

Sentinel Case Pre-Review, Re-Review, and Cluster Assessment Forms were created for the purpose of this review process (Appendices B–D). These forms were used to ensure a systematic thought process and to facilitate the development of written reports. Language adapted from the Anthrax Vaccine Expert Committee, the Advisory Committee on Causality Assessment, and the IOM’s review processes was incorporated into these forms [5, 6, 18, 19].

Government physicians who were not members of the SVS WG collected and collated relevant medical information and completed a Sentinel Case Pre-Review Form (Appendix B) for each case. The members of the SVS WG (identified in Appendix A, all of whom are private-sector independent experts) signed appropriate nondisclosure agreements and received all unredacted medical and other relevant records as well as the completed Sentinel Case Pre-Review Forms. The SVS WG members independently reviewed all records and completed a Sentinel Case Re-Review Form (Appendix C) for each case and 1 Syndrome Cluster Assessment Form (Appendix D) for each subgroup. Each SVS WG subgroup reported conclusions from deliberations on the cases under its review.

The SVS WG chair led all subgroup deliberations, the overall SVS WG critique, and the finalization of all reports. The outcomes of subgroup reviews were brought to the whole SVS WG for critique and concurrence.

The final reports were provided to the parents of all affected cases. The results of the review were shared with other appropriate parties. After release, reports were available to the public through a DoD Web site.

**RESULTS**

As of 6 August 2003, 1767 adverse events temporally associated with smallpox vaccination had been reported to VAERS. More than 90% of these reported events, including all events potentially belonging to the spectrum of adverse events causally associated with smallpox vaccination (categories 1–3 and a subset of reports in category 5), had undergone extensive review by government medical epidemiologists in consultation with outside experts. The outcomes of these reviews had been previously...
presented to the SVS WG and are not discussed here. Below, we discuss the outcome of SVS WG independent deliberation using the Sentinel Review Process.

Subgroup A: Unreviewed Deaths—Report Released 7 November 2003

Ten fatal events temporally associated with smallpox vaccination were reported to VAERS. For completeness, all 10 fatal events reported to VAERS are included in table 2.

Five deaths due to autopsy-confirmed ischemic cardiac disease had been extensively examined during an investigation of ischemic cardiac events among recent smallpox vaccinees. The evidence did not support an increased rate of ischemic events among recent vaccinees, compared with the expected background rate. These 5 deaths were excluded from the Sentinel Review Process because no benefit would be gained by further review.

Three previously unreviewed deaths were attributed to leukemia, hyperthermia, or illicit drug overdose (table 2). In each instance, the cause of death was clearly documented by laboratory testing or temperature measurement and was supported at autopsy. The medical records and other documentation available for review were complete and sufficient in each instance, and the evidence favored rejection of a causal relationship between vaccination and any of these 3 deaths. Only the third (illicit drug overdose) underwent the formal Sentinel Review Process (table 2).

A fatal pulmonary embolic event had been reported to VAERS prior to 6 August 2003 and was reviewed by the SVS WG through a less formal process. Key portions of the medical records for this pulmonary embolic event, including the medical history at the time of illness onset and records describing personal medical history prior to deployment, were not available for review. However, results of an extensive and well-documented postmortem examination were available to the reviewers. This postmortem examination documented pulmonary emboli arising from a deep venous thrombosis in the leg as the cause of death, as well as evidence of a heterozygous state for factor V Leiden mutation R506Q, which is associated with a propensity for a hypercoagulable state. This case did undergo the formal Sentinel Review Process, performed by subgroup A, and the available records were considered to be sufficient to support the conclusions drawn. Multiple risk factors for hypercoagulable states were identified and were judged to be convincingly responsible for the outcome. No evidence implicated either smallpox or anthrax vaccine in the onset of deep venous thrombosis that led to the fatal pulmonary embolic event.

The 10th fatal event, the death of the index patient that initiated the Sentinel Review Process, prompted a search for cases that might constitute an unrecognized syndrome characterized by chest pain, dyspnea, and fever and was referred to subgroup B.

In conclusion, 4 deaths attributable to leukemia, hyperthermia, illicit drug overdose, or pulmonary emboli were reported to VAERS after vaccination, but all appear to be unrelated to either each other or to any vaccine exposure. The evidence favors rejection of a causal relationship between vaccination and any death reported to VAERS in temporal association with smallpox vaccination among those reported in table 2, with the exception of the index patient reviewed by subgroup B below.

Subgroup B: Syndromes Characterized by Chest Pain, Dyspnea, and Fever—Report Released 7 November 2003

An analysis of VAERS reports searching for the COSTART terms “fever” AND “chest pain” AND “dyspnea” identified a total of 13 reports. Four of these were referred to subgroup C for the Sentinel Review Process. One identified event was a myocardial infarction included in the previous extensive review of ischemic adverse events, for which no etiologic association with smallpox vaccination was demonstrated. An additional 4 events were cases of myocarditis. Causal association between smallpox vaccination and myo/pericarditis had been established [32]. The remaining 4 instances of illness of undefined etiology charac-

Table 2. Deaths reported to the Vaccine Adverse Event Reporting System in temporal association with smallpox vaccination.

<table>
<thead>
<tr>
<th>Reported cause of death</th>
<th>No. of reports</th>
<th>Included in formal sentinel review?</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic cardiac disease</td>
<td>5</td>
<td>N</td>
<td>Available data do not support causal association; possibility cannot be absolutely rejected</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1</td>
<td>N</td>
<td>Causal relationship rejected</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>1</td>
<td>N</td>
<td>Causal relationship rejected</td>
</tr>
<tr>
<td>Illicit drug overdose</td>
<td>1</td>
<td>Y: subgroup A, previously unreviewed deaths</td>
<td>Causal relationship rejected</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>1</td>
<td>Y: subgroup B, previously unreviewed deaths</td>
<td>Causal relationship rejected</td>
</tr>
<tr>
<td>Lupuslike syndrome* (index patient)</td>
<td>1</td>
<td>Y: subgroup B, clinical syndromes characterized by chest pain, dyspnea, and fever</td>
<td>Causal relationship with immunization experience favored but evidence not definitive</td>
</tr>
</tbody>
</table>

* Fever, diffuse serositis, indeterminant rheumatologic testing in female of childbearing age.

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Table 3. Subgroup B: clinical syndromes characterized by chest pain, dyspnea, and fever.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4 (index patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category, years</td>
<td>40–60</td>
<td>&gt;60</td>
<td>40–60</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Vaccination status</td>
<td>Revaccinee</td>
<td>Primary</td>
<td>Revaccinee</td>
<td>Primary</td>
</tr>
<tr>
<td>Simultaneous other vaccinations?</td>
<td>None recorded</td>
<td>1 additional</td>
<td>None recorded</td>
<td>4 additional plus PPD</td>
</tr>
<tr>
<td>First symptoms, days after vaccination</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Symptom(s)</td>
<td>Hospitalized with CP, SOB, tachycardia, and dizziness 2 days after vaccination</td>
<td>Fall with loss of consciousness, left hip injury; 1-min palpitations the following day</td>
<td>CP radiating to neck and arm; headache, fatigue, dizziness, nonproductive cough, myalgias, nausea</td>
<td>CR SOB, fever, weakness, confusion</td>
</tr>
<tr>
<td>Symptom pattern</td>
<td>Discharged with Dx of new-onset HTN and tachycardia; cardiac cath results WNL 12 days after vaccination</td>
<td>Onset of bilateral swollen feet 1 month after vaccination; 2 months after vaccination, experienced 1.5 h of palpitations, dyspnea, weakness, and CP that precipitated hospitalization and Dx of new-onset atrial fibrillation, CHF, and HTN resulting in DOE</td>
<td>Presented to ED 3 days after vaccination with CP, anxiety, tachycardia, and DOE; results of serial cardiac evaluations and ECHOs over 2 months remained WNL, but fever, CP, and SOB lingered</td>
<td>Continuous and progressive worsening of symptoms suggestive of fulminate autoimmune or lupuslike syndrome</td>
</tr>
<tr>
<td>Outcome at last follow-up</td>
<td>Persistent intermittent pleuritic CP and DOE with negative evaluation &gt;3 months after vaccination</td>
<td>Atrial fibrillation, CHF, and DOE prevent return to work</td>
<td>Persistent fevers, CP, and DOE despite repeatedly negative results of cardiac evaluations 2 months after vaccination</td>
<td>Death on day 15 after vaccination; autopsy documented diffuse alveolar damage, pericarditis, and anoxic encephalopathy</td>
</tr>
</tbody>
</table>

**NOTE.** Cath, catheterization; CHF, congestive heart failure; CP, chest pain; DO, dyspnea on exertion; Dx, diagnosis; ECHO, echocardiogram or echocardiography; ED, emergency department; HTN, hypertension; PPD, purified protein derivative; SOB, shortness of breath; WNL, within normal limits.
terized by chest pain, dyspnea, and fever, with 1 fatality, were reviewed by subgroup B and are described in table 3.

**Summary consensus.** The reviewers concluded that the medical records available for review were complete and sufficient for all cases. It was the consensus of subgroup B that, although some of these cases share common signs and symptoms, they do not present a pattern that justifies recognition of a new possibly vaccine-associated clinical syndrome apart from the inflammatory syndrome already recognized as myo/pericarditis associated with smallpox vaccination.

**Patient 1:** a woman 40–60 years of age hospitalized with chest pain, shortness of breath, new-onset hypertension, and tachycardia 2 days after vaccination. All reviewers found that the evidence favored rejection of a causal relationship.

**Patient 2:** a woman >60 years of age with palpitations and loss of consciousness 5–6 days after vaccination, diagnosis of new-onset atrial fibrillation, congestive heart failure, and hypertension 2 months after vaccination. The interpretation of this case was confounded by the patient’s having received anthrax vaccination on the same day as the primary smallpox vaccination. Two reviewers felt that the documented medical condition, atrial fibrillation, was highly unlikely to be caused by the smallpox vaccination and, thus, favored rejection of a causal relationship. The patient had preexisting medical conditions associated with increased risk for atrial fibrillation, and atrial fibrillation had not been associated with receipt of either anthrax or smallpox vaccine either historically or during the current military experience. Furthermore, because the initial self-reported episode of palpitations 19 days after vaccination was not medically evaluated or documented, these reviewers felt that the documented onset of atrial fibrillation >30 days after vaccination was not compatible with a causal association due to the extended latency of symptom onset.

The third reviewer felt that the evidence could not exclude a causal relationship. The initial symptoms were reported by the patient within 6 or 19 days of vaccination, which falls within the 1–3-week postvaccination interval associated with elevated risk of myo/pericarditis. The patient’s comorbid conditions could be implicated in the etiology of the atrial fibrillation. Therefore, a causal relationship between the receipt of the vaccine and the atrial fibrillation could not be excluded.

**Patient 3:** a woman 40–60 years of age who presented to the emergency department 3 days after vaccination, with chest pain, anxiety, tachycardia, and dyspnea on exertion. Although all reviewers agreed that the vaccination-event interval was compatible with an association between smallpox vaccination and the clinical events that followed, nevertheless, the evidence was inadequate to accept or reject a causal association between smallpox vaccination and the clinical outcome.

**Patient 4, the index patient:** a woman <30 years of age with onset, on day 2 after vaccination, of continuous, progressive symptoms suggestive of fulminate lupuslike syndrome that resulted in death 15 days after vaccination. The analysis of this case was complicated by the highly complex clinical presentation encompassing multiple signs and symptoms rather than one predominant symptom. Further, assessing attribution of causality was complicated by the history of concurrent immunizations, in addition to purified protein derivative placement. The primary adverse events reported occurred rarely; similar events were known to occur in association with other diseases. The patient had not had similar symptoms in the past. In fact, no concomitant or preceding medical conditions or other contributing factors were identified during the review. The vaccination-event interval was compatible with an association between the immunization experience and the clinical events that followed, and pericarditis has been described in association with smallpox vaccination. However, the entire spectrum of disease experienced by this patient has not been described in association with any vaccine. In addition, the multiplicity of clinical events, as well as the concurrent immunizations received, confounded assessment of this case. There were too many symptoms, too many concurrent exposures, and insufficient information to allow a simple direct answer to the question of whether this event could be related to any 1 vaccine. Similarly, the data were insufficient to allow assessment of whether the event was explainable by the biological properties of any vaccination received.

The available evidence was insufficient either to definitively establish or to definitively reject a causal association between smallpox vaccination and the clinical outcome. The consensus of the reviewers was that the weight of the evidence favored acceptance of a causal relationship between the immunization experience and the disease. However, the history of concurrent immunizations precluded specific implication of smallpox or any other individual vaccine.

**Subgroup C: Dilated Cardiomyopathy—Report Released 2 February 2004**

Two cases of DCM first diagnosed after vaccination and previously reviewed by the SVS WG were initially identified for systematic sentinel case review. Prior to completion of the Sentinel Review Process, an additional 3 cases of DCM were identified. These 5 cases underwent a formal sentinel case review, are described in subgroup C’s narrative report below, and are those of the first 5 patients described in table 4. Two additional patients with DCM identified after the Sentinel Review Process was complete are also included in table 4.

Subgroup C reviewed 5 smallpox vaccine recipients who subsequently developed DCM. Each patient had ≥1 risk factor for cardiac disease, none of which appeared, in the opinion of the group, likely to represent a primary etiologic factor for the
Table 4. Subgroup C: dilated cardiomyopathy (DCM).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients reported before and included in Sentinel Review Process</th>
<th>Case patients reported after Sentinel Review Process</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
<tr>
<td>Age category, years</td>
<td>30–40</td>
<td>40–60</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Vaccination status</td>
<td>Revaccinee</td>
<td>Revaccinee</td>
</tr>
<tr>
<td>Retrospective history: first possibly associated symptoms, weeks after vaccination</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Initial symptoms(s)</td>
<td>Bandlike CP, low-grade fever</td>
<td>Nausea, fatigue, dyspnea, CP</td>
</tr>
<tr>
<td>Symptom pattern</td>
<td>Intermittent</td>
<td>Intermittent, progressing to continuous</td>
</tr>
<tr>
<td>DCM diagnosis, weeks after vaccination</td>
<td>23</td>
<td>22a</td>
</tr>
<tr>
<td>Precipitant of diagnostic evaluation</td>
<td>Collapsed while running</td>
<td>Fatigue, SOB, CP</td>
</tr>
<tr>
<td>Initial ECHO EF, %</td>
<td>35</td>
<td>10–15</td>
</tr>
<tr>
<td>Follow-up ECHO EF, %</td>
<td>48 (March 2004)</td>
<td>10–20 (pretransplant)</td>
</tr>
<tr>
<td>Symptoms resolved?</td>
<td>Y</td>
<td>After cardiac transplant</td>
</tr>
<tr>
<td>Back to work?</td>
<td>Y</td>
<td>Disability discharge</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>Orthopedic limitations</td>
<td>&lt;4 METs before transplant</td>
</tr>
<tr>
<td>Cardiac disease risk factors</td>
<td>No CAD by cath; HTN; elevated HDL</td>
<td>Nonobstructive CAD by cath; childhood asthma; mild emphysema; history of 1–3 ETOH drinks/month</td>
</tr>
</tbody>
</table>

NOTE. CAD, coronary artery disease; cath, catheterization; CP, chest pain; DM, diabetes mellitus; DOE, dyspnea on exertion; ECHO, echocardiogram or echocardiography; EF, ejection fraction; ETOH, ethyl alcohol; HDL, high-density lipoprotein level; HTN, hypertension; MET, metabolic equivalent; NA, not available; SOB, shortness of breath.

a Troponin I level, 0.6 mg/L (normal, <0.05 mg/L).
cardiomyopathy. Several patients did have prior illnesses that can lead to myocardial dysfunction: obesity and borderline hypertension in one; hypertension, hypercholesterolemia, and diabetes in a second; borderline hypertension and mild proteinuria in a third; childhood asthma, emphysema, and minimal alcohol use in a fourth; and mitral valve prolapse in a fifth (table 4). However, these illnesses and conditions are common in the general population in this age group, and none appeared to be severe enough or long-standing enough to account for the development of DCM.

The 5 clinical courses varied in the type of symptoms, the timing of the onset of relevant symptoms or of diagnosis of DCM after smallpox vaccination, the clinical course after diagnosis, and the evidence of recovery to date. Some have improved considerably and appear likely to recover completely, whereas 2 developed markedly symptomatic heart failure with no sign of recovery and underwent successful cardiac transplantation. The other cases had a more benign and self-limited course. Variability in clinical course is common among patients who develop DCM from any cause.

The documentation of DCM occurred 30–163 days (mean, 106 days; median, 99 days) after vaccination. However, patients had frequently reported symptoms prior to this documentation, including fatigue and dyspnea. The earliest symptoms noted in the materials available for review that were potentially referable to a cardiac cause were described as occurring 5–141 days (mean, 35 days; median, 9 days) after vaccination. However, the history was very limited for some patients, and symptoms may have occurred earlier in some without documentation. A number of patients reported symptoms that could have reflected preexisting myocarditis—for example, chest pain (table 4). At least 1 patient had evidence of elevated troponin levels, suggesting an active myocarditis at the time of onset of DCM. The others lacked this finding, but this may be due to variability in testing at the time of onset of symptoms or to the possibility that asymptomatic myocarditis preceded the symptoms of DCM. None of these patients had ever had cardiac symptoms prior to vaccination. Although 3 of these patients received simultaneous vaccinations, 2 did not, which suggests that the multiplicity of simultaneous immunizations per se was not etiologically implicated in this clinical outcome.

In all cases, diagnostic testing had been performed to determine whether ischemia could be a cause of the DCM. Four of the 5 patients underwent cardiac catheterization, and the fifth underwent an adenosine pharmacologic stress test (table 4). In no instance was sufficient coronary artery disease identified to suggest ischemia as a cause of DCM. One patient had normal coronary arteries, and 3 had no more than minimal irregularities of the coronary arteries, with no obstruction. The adenosine stress test was negative for ischemia.

Despite the clinical variability among the individual cases, these 5 patients all had cases of DCM; therefore, their conditions represented a common syndrome. There are multiple known causes of DCM, and it is frequently not possible to definitively identify a specific cause of DCM in individual cases, as in these 5 cases. The available evidence is presently inadequate to accept or reject a definitive causal association between the smallpox vaccine and this clinical outcome. However, this cluster group does present a pattern of 5 reasonably healthy people who, within a period after smallpox vaccination that is both temporally and mechanistically compatible with an etiologic association, developed DCM, a documented outcome of myocarditis. (Of note, none of these 5 persons or of the additional 2 described in table 4 had received diagnoses of myocarditis prior to the diagnosis of DCM.) These observations suggest a possible causal association between smallpox vaccination and DCM that is worthy of further study.

Observations, including epidemiologic evidence, have documented a statistically significant excess of myo/pericarditis among recent recipients of the smallpox vaccine [32–37]. However, to date, DoD data suggest no progression from myocarditis to DCM in the 84 cases followed for a median interval of 15 months. Although this is reassuring, symptoms of DCM following subclinical myocarditis may not be clinically apparent for many months. There are no published data regarding pathognomonic findings, positive challenge/rechallenge observations, or epidemiologic evidence of statistically significantly elevated rates of DCM among smallpox vaccinees, compared with comparable but nonvaccinated persons in the general population. On the basis of data reported to VAERS as of 30 December 2003, if there is an association between smallpox vaccination and the development of DCM, it would appear to be infrequent, in the range of 3 cases of DCM per 40,000 civilian vaccinees at 1 year of follow-up. Because there is not active follow-up of all vaccinees, it is not possible to be certain that all cases have been ascertained by this passive reporting system. The integrated health system for military personnel has identified 4 cases of DCM among 710,000 military vaccinees, with a median interval of 18 months elapsed since vaccination.

Without further evidence, the data remain insufficient to move clearly away from neutrality to favor or reject a causal association between smallpox vaccination and DCM. Idiopathic cardiomyopathy is a rare event, making it hard to determine true statistical association. Epidemiologic data assessing the statistical frequency of DCM among smallpox vaccinees, compared with the usual baseline rate of DCM observed in this population without vaccination, would be valuable, but the expected rate of DCM in a population of this age range is unknown. This is the missing evidence that could move opinion toward or away from neutrality, if it were sufficiently different from what has been seen among smallpox vaccinees, but it is not available at present.
There are biological mechanisms supporting the hypothesis that an association exists between smallpox vaccination and DCM, possibly via intervening myocarditis, and this should continue to be evaluated. A history of smallpox vaccination should be sought in all cases of apparent idiopathic DCM, and symptoms that may represent DCM in smallpox vaccinees should be vigorously investigated, regardless of the duration that has passed between vaccination and onset of symptoms. If subsequent epidemiologic evidence suggested that the occurrence of this number of cases within this period after vaccination exceeded the usual range by statistically significant amounts, this evidence would favor acceptance of a causal relationship with smallpox vaccination. If we are to continue to vaccinate substantial numbers of individuals, consideration should be given to supporting further epidemiologic studies to evaluate the possible association between smallpox vaccination and DCM.

Note. After the DCM Sentinel Review was completed, 2 additional cases of DCM in smallpox vaccine recipients were identified. These are the last 2 patients described in table 4 and do not change the conclusions of this review.

DISCUSSION

This Sentinel Review Process is a new method for case-based assessment of adverse events following immunization. It met the needs of the DoD and CDC for review of cases of special concern and had several additional strengths. It provided a forum that allowed multiple experts to independently assess the likelihood that the most concerning adverse events reported during this vaccination program bore a causal relationship to the vaccine. It provided discussion of these conclusions in an open, transparent forum through presentations by the chair to the ACIP. Most significantly, it provided the best determination possible of the degree of confidence that the family members of these patients, the general public, and future vaccinees can place in the likelihood that smallpox vaccination contributed to the observed adverse clinical outcomes. Findings were shared with multiple interested parties, including the families of affected individuals.

This Sentinel Review Process identified no pattern that justified recognition of a new possibly smallpox vaccine–associated clinical syndrome. Although identified biological mechanisms support a hypothesized causal association between smallpox vaccination and DCM via intervening myocarditis, subgroup C reviewers determined that the data remain insufficient to support any action other than maintaining a stance of neutrality regarding such a causal association. They did encourage further observation to assess the possibility of linkage.

DCM, recognized among smallpox vaccine recipients at an estimated rate of 3 cases per 40,000 vaccinees, was judged to be “infrequent.” However, Rotashield (Wyeth), an earlier rotavirus vaccine, was withdrawn from the US market on the basis of an incidence of intussusception of ∼1 case per 10,000 vaccinees. Thus, were evidence supporting a causal association to be identified, the rate at which DCM was recognized among smallpox vaccine recipients is similar to rates of vaccine-associated adverse events judged to merit regulatory action in the past. The decision to take regulatory action in response to the linkage of adverse events to pharmaceutical products is complex, however. The frequency with which the adverse event follows exposure is only one influence, inadequate by itself to define appropriate action, because the relationship between risk and benefit differs among products.

This review suggested a need to look at the biological response of adults to concurrent exposure to multiple immune stimulants, such as vaccines, as a potential risk factor for rare serious adverse events [53, 54]. A working group of the National Vaccine Advisory Committee independently identified as a priority the investigation of the possibility of health risk associated with multiple concurrent vaccinations of adults [53, 54]. A CDC Vaccine Analytic Unit investigation of whether concurrent vaccinations (>2 vaccinations on consecutive days) are associated with hospitalization found no evidence of elevated risk for hospitalization even among US military personnel who received ≥5 concurrent vaccinations [54]. The index patient in this review received multiple immunizations within a short period, followed by onset of a rapidly progressive, clinically complex, and ultimately fatal illness characterized by chest pain, dyspnea, and fever. Acceptance of a causal relationship between the immunization experience and this disease was favored, but the history of multiple simultaneous immunizations precluded specific implication of any individual vaccine.

Limitations of this Sentinel Review Process are shared with other case-based methods of causality assessment. As with all nonepidemiologic “study designs,” this process is not able to account for confounding (e.g., by multiple immunizations) at the individual case level. Inherent uncertainty remains in the causal inferences determined by the group deliberations.

VAERS reports, which served as the basis for case finding, are inherently limited and may contain inaccuracies. For this process, these limitations of reviewed cases were largely overcome by accessing the full medical records. However, compliance with follow-up requests for additional data on cases reported to VAERS cannot be mandated, limiting the ability to assess for accuracy or completeness of information contained in the reports.

Our use of references to “biological plausibility,” a term borrowed from processes used by the IOM in earlier vaccine safety reviews, resulted in some unintended confusion in interpretation. Statements in this report that the association of a given outcome with smallpox vaccination might be biologically plausible were not intended to convey a determination that the
vaccine was likely to have caused the outcome. Rather, such statements acknowledged that hypotheses existed that could plausibly link biological aspects of the vaccination or the host response to the clinical outcome. In each instance in which the phrase “biological plausibility” was used in this review, connections between the hypothesized biological pathways and the clinical outcome have not been demonstrated by experimental or laboratory evidence and remain hypothetical. The IOM has since chosen to refer to “biological mechanisms” rather than “biological plausibility,” to avoid similar confusion in subsequent reports, and subgroup C also adopted this phrase in an attempt to more clearly communicate intent.

Lastly, this Sentinel Review Process was deliberately designed to meet the specific review needs presented to the DoD, CDC, and the ACIP-AFEB joint SVS WG at the time of this review and may not be generalizable.

There is an ongoing need for case-based assessment methods, because very rare adverse events are technically and logistically difficult to study epidemiologically. General guidance for case-level assessment would fill a key unmet vaccine safety need. Development of such guidelines is currently being supported by the CDC through the Clinical Immunization Safety Assessment Network [55]. This Sentinel Review process may provide a model for other attempts at case-based safety assessments tailored to address situation-specific needs.

**Acknowledgments**

We thank Neal Halsey, Vito Caserta, Rob Pless, Gina Mootrey, John Grabenstein, Rick Riddle, and Roger Gibson, for insightful critiques of previous causality-assessment models and for critical review of our efforts; Jim Sejvar, for neuroepidemiological review; Karen Goldenhal and colleagues at the US Food and Drug Administration, for critical review of this article and contributions to the Vaccine Adverse Event Reporting System and the Smallpox Vaccine Safety Working Group; and innumerable military and civilian health care professionals; state territorial, county, city, or local health department professionals; and other colleagues in the Department of Defense and Department of Health and Human Services, whose observations and cooperation enabled these efforts.

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**Potential conflicts of interest.** J.N. serves on the data and safety monitoring board for Acambis. T.M. serves on the data and safety monitoring board for VaxGen. G.P. served as principal investigator on a smallpox clinical study sponsored by Acambis and serves on the scientific advisory board for Dynport. All other authors: no conflicts.

**APPENDIX A**

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Member and affiliation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>John F. Modlin, MD, Dartmouth Medical School, Lebanon, NH (ACIP), Chair, January–March 2003</td>
</tr>
<tr>
<td>Smallpox/variola</td>
<td>John Neff, MD, University of Washington, Seattle, WA, Cochair, January–March 2003, Chair, March 2003–October 2004</td>
</tr>
<tr>
<td>Public health</td>
<td>Guthrie S. Birkhead, MD, New York State Department of Health, Albany, NY (ACIP), Cochair, March 2003–October 2004</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>Pierce Gardner, MD, Stony Brook University School of Medicine, Stony Brook, NY (AFEB)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Gregory Poland, MD, Mayo Clinic, Rochester, MN (AFEB, ACIP)</td>
</tr>
<tr>
<td>Infection control</td>
<td>W. Dana Flanders, MD, Emory University, Rollins School of Public Health, Atlanta, GA</td>
</tr>
<tr>
<td>Tobacco control</td>
<td>Robert Shope, MD, University of Texas at Galveston, Galveston, TX (AFEB) (deceased)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Gregory C. Gray, MD, University of Iowa College of Public Health, Iowa City, Iowa, IA (AFEB)</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Fernando A. Guerra, MD, San Antonio Metropolitan Health District, San Antonio, TX (NVAC [National Vaccine Advisory Committee])</td>
</tr>
<tr>
<td>Veterinary Medicine</td>
<td>Louisa E. Chapman, MD, MSPH, and John K. Iskander, MD, MPH, were detailed to the CDC Smallpox Vaccine Adverse Events Monitoring and Response Activity,</td>
</tr>
<tr>
<td></td>
<td>where Dr. Chapman served as CDC ex-officio representative to the SVS WG and Dr. Iskander led the Surveillance Team. Robert T. Chen, MD, was chief of the Immunization Safety Branch, Epidemiology and Surveillance Division, National Immunization Program, during the period when this work was accomplished.</td>
</tr>
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**NOTE.** The Centers for Disease Control and Prevention (CDC) coauthors were responsible for development and reporting of the Sentinel Review Process methodology and were not members of the ACIP-AFEB joint SVS WG and did not contribute to the subgroup review outcomes reported here. Louis E. Chapman, MD, MSPH, and John K. Iskander, MD, MPH, were detailed to the CDC Smallpox Vaccine Adverse Events Monitoring and Response Activity, where Dr. Chapman served as CDC ex-officio representative to the SVS WG and Dr. Iskander led the Surveillance Team. Robert T. Chen, MD, was chief of the Immunization Safety Branch, Epidemiology and Surveillance Division, National Immunization Program, during the period when this work was accomplished.
APPENDIX B

1. Identifying information:

1.1. Case VAERS #□□□□□□□□□□ 1.2. Date of pre-review: ____/____/____ (MM / DD / YY)

1.3. Pre-Reviewer Name: ____________________  CDC □  DoD □

1.4. Date of Smallpox vaccination: ____/____/____ (MM / DD / YY)

1.5. Primary event reported: ____________________

VAERS serious? □ Yes □ No

1.6. Onset date: ____/____/____ (MM / DD / YY) Duration: ____________________

1.7. Current status:
□ Recovered to baseline □ Partially recovered □ Permanently disabled □ Dead

1.8. Do you agree with reported diagnosis? □ Yes □ No □ Insufficient data to assess

If no, your diagnosis: ____________________

1.9. Is this case part of a syndrome cluster? □ Yes □ No  If yes:

1.9.1. Sentinel Case Cluster Identification #: □□□□□□□□□□

1.9.2. number of cases in cluster □□□

2. Questions regarding the primary event reported:

2.1. Frequency of occurrence of adverse event? □ Rare □ Intermediate □ Common

2.2. Similar events known to occur with other disease? □ Yes □ No □ Insufficient data

2.3. Event is known to be related to this vaccine? □ Yes □ No □ Insufficient data

2.4. Event is explainable by the biological properties of the vaccine? □ Yes □ No □ Insufficient data

2.5. Vaccination-event interval compatible with the event? □ Yes □ No □ Insufficient data

2.6. The patient had similar symptoms in the past:

2.6.1. not associated with vaccination? □ Yes □ No □ Insufficient data

2.6.2. associated with other vaccinations? □ Yes □ No □ Insufficient data

2.6.3. associated with smallpox vaccination? □ Yes □ No □ Insufficient data

2.7. Concomitant / preceding drug therapy? □ Yes □ No □ Insufficient data

If yes, list: ____________________

Figure B1. Sentinel Case Pre-Review Form. CDC, Centers for Disease Control and Prevention; DoD, US Department of Defense; VAERS, Vaccine Adverse Event Reporting System.
2.8. Concomitant / preceding medical condition? □ Yes □ No □ Insufficient data
   If yes, list: ____________________________

2.9. Other vaccines received within 4 weeks prior to event onset? □ Yes □ No □ Insufficient data
   If yes, list vaccines / dates: ____________________________

2.10. Other contributing factors? □ Yes □ No □ Insufficient data
   If yes, list factors: ____________________________

3. Causal Interpretations: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

3.1. No evidence (Complete absence of clinical and epidemiological evidence) □ Yes □ No

3.2. Evidence is inadequate to accept or reject a causal association (Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive)(Cases in which medical information available is insufficient to allow adequate assessment of causal association should be placed in this category). □ Yes □ No

3.3. Evidence favors rejection of a causal relationship (Evidence does not support a causal relationship) □ Yes □ No

3.4. Evidence favors acceptance of a causal relationship (Causal evidence is strong and generally convincing but not definitive)
   □ Yes □ No
   If yes, basis for decision:
   3.4.1. Epidemiologic study demonstrating statistical significance □ Yes □ No
   3.4.2. Epidemiologic study suggesting association □ Yes □ No
   3.4.3. Pathognomonic clinical or laboratory finding □ Yes □ No
   3.4.4. Challenge – Re-challenge observations □ Yes □ No

3.5. Evidence establishes a causal relationship (Causal link is unequivocal) □ Yes □ No
   If yes, basis for decision:
   3.5.1. Epidemiologic study demonstrating statistical significance combined with additional criteria identified below □ Yes □ No
   3.5.2. Epidemiologic studies demonstrating statistical significance □ Yes □ No
   3.5.3. Pathognomonic clinical or laboratory finding □ Yes □ No

Figure B1. (Continued.)
3.5.4. Positive Challenge – Re-challenge observations □ Yes □ No

4. Evidence of biological mechanisms consistent with a proposed relationship:

Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent with or implausible in the light of current biological understandings. Further, when demonstrated epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.

4. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? □ Yes □ No

If yes, category of evidence:

4.1. Theory only (a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles) □ Yes □ No

4.2. Experimental evidence exists that the mechanism operates in animal models, in vitro systems, or humans: □ Yes □ No

4.3. Experimental evidence that the mechanism results in known disease in humans: □ Yes □ No

4.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:

□ weak □ moderate □ strong

5. Assessment of Sufficiency of Available Information:

5. Were the judgments above made on the basis of complete and sufficient clinical information? □ Yes □ No

If No, describe:

5.1. Key portions of existing medical records were unavailable □ Yes □ No

5.2. Appropriate diagnostic tests not performed, or inappropriately timed □ Yes □ No

5.3. Medical record inadequately records history of illness □ Yes □ No

5.4. Other: □ Yes □ No

Describe: ________________________________

6. Comments:

Figure B1. (Continued.)
APPENDIX C

1. Identifying information:

1.1. Case VAERS # ____________________
1.2. Date of re-review: ____/____/____ (MM / DD / YY)
1.3. Re-Reviewer Name: __________________
1.4. Date of Smallpox vaccination: ____/____/____ (MM / DD / YY)
1.5. Primary event reported: ____________________________________________
   VAERS serious? □ Yes □ No

1.6. Onset Date and Duration: □ Concur with pre-review □ Disagree
   If disagree: Onset date: ____/____/____ Duration: ____________________________
   MM / DD / YY

1.7. Current status: □ Concur with pre-review □ Disagree
   If disagree: □ Recovered to baseline □ Partially recovered □ Permanently disabled □ Dead

1.8. Do you agree with reported diagnosis? □ Concur with pre-review □ Disagree
   If disagree: □ Yes □ No □ Insufficient data to assess
   If no, your diagnosis: ____________________________________________

2. Questions regarding the primary event reported:

2.1. Frequency of occurrence of adverse event? □ Concur with pre-review □ Disagree
   If disagree: □ Rare □ Intermediate □ Common

2.2. Similar events known to occur with other disease? □ Concur with pre-review □ Disagree
   If disagree: □ Yes □ No □ Insufficient data

2.3. Event is known to be related to this vaccine? □ Concur with pre-review □ Disagree
   If disagree: □ Yes □ No □ Insufficient data

2.4. Event is explainable by the biological properties of the vaccine? □ Concur with pre-review □ Disagree
   If disagree: □ Yes □ No □ Insufficient data

2.5. Vaccination-event interval compatible with the event? □ Concur with pre-review □ Disagree
   If disagree: □ Yes □ No □ Insufficient data

Figure C1. Sentinel Case Re-Review Form. VAERS, Vaccine Adverse Event Reporting System.
2.6. The patient had similar symptoms in the past: □ Concur with pre-review □ Disagree

   If disagree:
   2.6.1. not associated with vaccination? □ Yes □ No □ Insufficient data
   2.6.2. associated with other vaccinations? □ Yes □ No □ Insufficient data
   2.6.3. associated with smallpox vaccination? □ Yes □ No □ Insufficient data

2.7. Concomitant / preceding drug therapy? □ Concur with pre-review □ Disagree

   If disagree:
   □ Yes □ No □ Insufficient data

   If yes, list: ________________________________

2.8. Concomitant / preceding medical condition? □ Concur with pre-review □ Disagree

   If disagree:
   □ Yes □ No □ Insufficient data

   If yes, list: ________________________________

2.9. Other vaccines received within 4 weeks prior to event onset? □ Concur with pre-review □ Disagree

   If disagree:
   □ Yes □ No □ Insufficient data

   If yes, list vaccines / dates: ________________________________

2.10. Other contributing factors? □ Concur with pre-review □ Disagree

   If disagree:
   □ Yes □ No □ Insufficient data

   If yes, list factors: ________________________________

3. Causal Interpretations: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

□ Concur with pre-review □ Disagree with pre-review

   If disagree:

3.1. No evidence (Complete absence of clinical and epidemiological evidence) □ Yes □ No

3.2. Evidence is inadequate to accept or reject a causal association (Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive)(Cases in which medical information available is insufficient to allow adequate assessment of causal association should be placed in this category). □ Yes □ No

3.3. Evidence favors rejection of a causal relationship (Evidence does not support a causal relationship) □ Yes □ No

---

**Figure C1.** (Continued.)
3.4. Evidence favors acceptance of a causal relationship \textit{(Causal evidence is strong and generally convincing but not definitive)} \quad \square \text{Yes} \quad \square \text{No}

If yes, basis for decision:

3.4.1. Epidemiologic study demonstrating statistical significance \quad \square \text{Yes} \quad \square \text{No}

3.4.2. Epidemiologic study suggesting association \quad \square \text{Yes} \quad \square \text{No}

3.4.3. Pathognomonic clinical or laboratory finding \quad \square \text{Yes} \quad \square \text{No}

3.4.4. Challenge – Re-challenge observations \quad \square \text{Yes} \quad \square \text{No}

3.5. Evidence establishes a causal relationship \textit{(Causal link is unequivocal)} \quad \square \text{Yes} \quad \square \text{No}

If yes, basis for decision:

3.5.1. Epidemiologic study demonstrating statistical significance

combined with additional criteria identified below \quad \square \text{Yes} \quad \square \text{No}

3.5.2. Epidemiologic studies demonstrating statistical association \quad \square \text{Yes} \quad \square \text{No}

3.5.3. Pathognomonic clinical or laboratory finding \quad \square \text{Yes} \quad \square \text{No}

3.5.4. Positive Challenge – Re-challenge observations \quad \square \text{Yes} \quad \square \text{No}

\textbf{4. Evidence of biological mechanisms consistent with a proposed relationship:}

\textit{Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent with or implausible in the light of current biological understandings. Further, when demonstrated epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.}

\square \text{Concur with pre-review} \quad \square \text{Disagree with pre-review} \quad \text{If disagree:}

4. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? \quad \square \text{Yes} \quad \square \text{No}

If yes, category of evidence:

4.1. Theory only \textit{(a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles)} \quad \square \text{Yes} \quad \square \text{No}

4.2. Experimental evidence exists that the mechanism operates in animal

\textbf{Figure C1.} (Continued.)
models, in vitro systems, or humans: □ Yes □ No
4.3. Experimental evidence that the mechanism results in known disease in humans: □ Yes □ No
4.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:
□ weak □ moderate □ strong

5. Assessment of Sufficiency of Available Information:
□ Concur with pre-review □ Disagree with pre-review □ If disagree:
5. Were the judgments above made on the basis of complete and sufficient clinical information? □ Yes □ No
If No, describe:
5.1. Key portions of existing medical records were unavailable □ Yes □ No
5.2. Appropriate diagnostic tests not performed, or inappropriately timed □ Yes □ No
5.3. Medical record inadequately records history of illness □ Yes □ No
5.4. Other: □ Yes □ No
Describe: ____________________________________________________________

6. Comments:

7. Recommendations:

Figure C1. (Continued.)
APPENDIX D

1. Identifying information:

1. Date of Cluster Assessment: ___/___/___ (MM/DD/YY)

2. Cluster Assessment Reviewer Name: ________________________________

3. Sentinel Case Cluster Identification #: □□□ 3.1. identifying feature of cluster: ____________
   3.2. number of cases in cluster □□□

4. Do these cases appear to be presentations of a common syndrome?
   □ No   □ Yes   □ Only the indicated cases appear to belong to a common syndrome

5. VAERS numbers of cases in cluster: Checked cases belong to common syndrome:
   Case VAERS # □□□□□□□  □
   Case VAERS # □□□□□□□  □
   Case VAERS # □□□□□□□  □
   Case VAERS # □□□□□□□  □
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   Case VAERS # □□□□□□□  □
   Case VAERS # □□□□□□□  □

   If a cluster is identified, proceed to questions 6 & 7. Otherwise, skip to question 8.

Figure D1. Sentinel Case Review for Signal Clarification Cluster Assessment Form. VAERS, Vaccine Adverse Event Reporting System.
6. Causal Interpretations with regard to possible association between the perceived syndrome and vaccine: Beginning from a position of neutrality, does the weight of available clinical and epidemiologic evidence allow you to shift to one of the following positions?

6.1. No evidence (Complete absence of clinical and epidemiological evidence) □ Yes □ No

6.2. Evidence is inadequate to accept or reject a causal association (Evidence is not reasonably convincing either in support of or against causality; evidence is sparse, conflicting, of weak quality, or just suggestive) (Cases in which information available is insufficient to allow adequate assessment of causal association should be placed in this category). □ Yes □ No

6.3. Evidence favors rejection of a causal relationship (Evidence does not support a causal relationship) □ Yes □ No

6.4. Evidence favors acceptance of a causal relationship (Causal evidence is strong and generally convincing but not definitive) □ Yes □ No

   If yes, basis for decision:

   6.4.1. Epidemiologic study demonstrating statistical significance □ Yes □ No

   6.4.2. Epidemiologic study suggesting association □ Yes □ No

   6.4.3. Pathognomonic clinical or laboratory finding □ Yes □ No

   6.4.4. Challenge – Re-challenge observations □ Yes □ No

6.5. Evidence establishes a causal relationship (Causal link is unequivocal) □ Yes □ No

   If yes, basis for decision:

   6.5.1. Epidemiologic study demonstrating statistical significance combined with additional criteria identified below □ Yes □ No

   6.5.2. Epidemiologic studies demonstrating statistical significance □ Yes □ No

   6.5.3. Pathognomonic clinical or laboratory finding □ Yes □ No

   6.5.4. Positive Challenge – Re-challenge observations □ Yes □ No

7. Evidence of biological mechanisms consistent with a proposed relationship:

Evidence regarding biological mechanisms can never prove causality. However, such evidence can assist in assessing whether associations demonstrated by epidemiological analysis are consistent

Figure D1. (Continued.)
with or implausible in the light of current biological understandings. Further, when demonstrated epidemiological associations are absent, identification of sound biological mechanisms may influence the development of research agendas.

7. Are biological mechanisms identifiable that might be consistent with a relationship between the vaccine exposure and the adverse clinical outcome? □ Yes □ No

   If yes, category of evidence:

   7.1. Theory only (a reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles) □ Yes □ No

   7.2. Experimental evidence exists that the mechanism operates in animal models, in vitro systems, or humans: □ Yes □ No

   7.3. Experimental evidence that the mechanism results in known disease in humans: □ Yes □ No

   7.4. Summary judgment of body of evidence supporting presence of identifiable biological mechanisms that could be operational:

       □ weak □ moderate □ strong

8. Assessment of Sufficiency of Available Information:

8. Were the judgments above made on the basis of complete and sufficient clinical information? □ Yes □ No

   If No, describe:

   8.1. Key portions of existing medical records were unavailable □ Yes □ No

   8.2. Appropriate diagnostic tests not performed, or inappropriately timed □ Yes □ No

   8.3. Medical record inadequately records history of illness □ Yes □ No

   8.4. Other: □ Yes □ No

       Describe: ____________________________________________

9. Comments:

10. Recommendations:

Figure D1. (Continued.)
References


