Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004

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The United States reinstated vaccination against smallpox among military personnel in 2002 and among selected civilian groups in January 2003. Routine smallpox vaccination had been suspended among US civilians in 1973 and among military personnel in the late 1980s. Rare adverse events causally associated with smallpox vaccination include cutaneous,1-4 ocular,1-5 and neurologic1-4,6,7 syndromes. Acute neurologic disease occurs after many vaccinations, including smallpox vaccination.5,7 Central nervous system (CNS) and peripheral nervous system complications of smallpox vaccination are rare but severe vaccine-associated adverse events. The most common CNS complication after smallpox vaccination is encephalitis (postvaccinial encephalomyelitis [PVE]).6

Other neurologic events have been associated temporally with smallpox vaccination. A recent assessment substantiates the frequency of postvaccinal headache.8 Other neurologic syndromes infrequently historically reported in temporal association with smallpox vaccination include Guillain-Barre syndrome (GBS),9 acute cranial neuropathies,10 poliomyelitis-like syndrome,11 Bell palsy,12 and transverse myelitis.10,13

Context Neurologic illness is an infrequent but severe adverse event associated with smallpox vaccination. The reinstatement of smallpox vaccination in the United States in response to possible bioterrorism renewed concerns about vaccine-related adverse neurologic events.

Objective To determine rates and describe the clinical features of neurologic events associated with smallpox vaccination.

Design and Setting We assessed reports of adverse events obtained through active case reporting and review of data reported to the Vaccine Adverse Event Reporting System among 665 000 persons vaccinated against smallpox by the Departments of Defense (n = 590 400) and Health and Human Services (n = 64 600) during the 2002-2004 US Smallpox Vaccination Program.

Main Outcome Measure Adverse neurologic events temporally associated with smallpox vaccination.

Results Between December 16, 2002, and March 11, 2004, 214 neurologic adverse events temporally associated with smallpox vaccination were reported; 111 reports involved Department of Health and Human Services and 103 involved Department of Defense vaccinees. Fifty-four percent of these events occurred within 1 week of vaccination, and 53% were among primary vaccinees. The most common neurologic adverse event was headache (95 cases), followed by nonserious limb paresthesias (n = 17) or pain (n = 13) and dizziness or vertigo (n = 13). Serious neurologic adverse events included 13 cases of suspected meningitis, 3 cases of suspected encephalitis or myelitis, 11 cases of Bell palsy, 8 seizures (including 1 death), and 3 cases of Guillain-Barré syndrome. Among these 39 events, 27 (69%) occurred in primary vaccinees and all but 2 occurred within 12 days of vaccination.

Conclusions During the 2002-2004 smallpox vaccination campaign, reported neurologic events were generally mild and self-limited, and no neurologic syndrome was identified at a rate above baseline estimates. Serious neurologic adverse events, such as postvaccinal encephalitis, Bell palsy, and Guillain-Barré syndrome, occurred in accordance with expected ranges.

See also p 2734.
Box. Case Definition: Encephalitis/Encephalomyelitis, for Use in the Smallpox Adverse Events Monitoring and Response Activity

**Case Definition for Acute Encephalitis**

A. A **confirmed case of encephalitis** is defined by demonstration of acute cerebral inflammation (± meninges) or demyelination by histopathology.

B. A **probable case of encephalitis** is defined by the acute onset of:

1. Encephalopathy (eg, depressed or altered level of consciousness, lethargy, or personality change lasting ≥24 hours)
   
   AND
   
   2. Additional clinical evidence suggestive of cerebral inflammation, including 2 or more of the following:
      
      a. Fever (temperature ≥38°C) or hypothermia (temperature ≤35°C)
      
      b. Meningismus (ie, nuchal rigidity, photophobia/phonophobia)
      
      c. CSF pleocytosis (>5 white blood cells/mm³)
      
      d. Presence of focal neurologic deficit
      
      e. Electroencephalography findings consistent with encephalitis
      
      f. Neuroimaging findings on magnetic resonance imaging (MRI) consistent with acute inflammation (± meninges) or demyelination of the nervous system
      
      g. Seizures, either new onset or exacerbation of previously controlled seizures

   AND
   
   3. No alternative (investigated) etiologies are found for presenting sign and symptoms

C. A **suspected case of encephalitis** is defined as the presence of the acute onset of:

1. Encephalopathy, as outlined for a probable case
   
   AND
   
   2. One of the criteria listed for probable encephalitis as clinical evidence suggestive of cerebral inflammation.
   
   AND
   
   3. No alternative (investigated) etiologies are found for presenting signs and symptoms

**Case Definition for Acute Myelitis**

A. A **confirmed case of myelitis** is defined by demonstration of acute spinal cord inflammation (± meninges) or demyelination by histopathology.

B. A **probable case of myelitis** is defined by the acute onset of:

1. Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and lower-motor neuron weakness, sensory level, bowel or bladder dysfunction)

   AND
   
   2. Additional evidence suggestive of spinal cord inflammation, including 2 or more of the following:
      
      a. Fever (temperature ≥38°C) or hypothermia (temperature ≤35°C)
      
      b. CSF pleocytosis (>5 white blood cells/mm³)
      
      c. Presence of focal neurologic deficit
      
      d. Electromyographic studies suggestive of central (spinal cord) dysfunction
      
      e. Neuroimaging findings on MRI demonstrating acute inflammation (± meninges) or demyelination of the spinal cord

   AND
   
   3. No alternative (investigated) etiologies are found for presenting sign and symptoms

C. A **suspected case of myelitis** is defined as presence of the acute onset of:

1. Myelopathy as outlined for a probable case

   AND
   
   2. One of the criteria listed for probable myelitis, as evidence suggestive of spinal cord inflammation

   AND
   
   3. No alternative (investigated) etiologies are found for presenting sign and symptoms

*Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as encephalomyelitis.*
suspected adverse event in DHHS vaccinees. The SVAEMRA clinicians completed case report forms, collecting information on vaccination, demographics, clinical events, and diagnostic studies, and followed up with the reporting clinician until a diagnosis was reached. A similar monitoring and consultation system was instituted by the DoD; this information was reported to VAERS and shared between the DoD and CDC.14-16 Events reported between December 16, 2002, and March 11, 2004, that were primarily neurologic, including those that met the case definition for encephalomyelitis adverse events (Box), were reviewed in detail by the lead author (J.J.S.), a board-certified neurologist and epidemiologist. Case report forms, medical records, and interviews with reporting physicians were used to ascertain vaccinee status, characterize the adverse event, and assess its association with smallpox vaccination. We reviewed all cases and conclusions with the Smallpox Vaccine Safety Working Group (SVS WG), a joint expert working group of the CDC’s Advisory Committee on Immunization Practices and the DoD’s Armed Forces Epidemiological Board.

VAERS is a passive vaccine safety surveillance system operated jointly by the CDC and the US Food and Drug Administration17 that receives reports of adverse events after administration of US-licensed vaccines. VAERS reports collect information on the nature of suspected vaccine-associated adverse events, on demographics and clinical signs and symptoms, and on vaccinee status.

All VAERS reports of neurologic events temporally associated with smallpox vaccination were received between December 16, 2002, and March 11, 2004, were reviewed. A systematic database search identified entries containing 1 or more of 199 Coding Symbol for The-saurus of Adverse Reaction Terms (COSTART) codes that suggested CNS or PNS dysfunction. The lead author (J.J.S.) reviewed VAERS reports of all identified entries to assess the clinical syndromes and the association with vaccination. Cases with minimal or no clinical detail were excluded. Demographic data on DHHS vaccinees were obtained from the Pre-Event Vaccination System and on DoD vaccinees from the Defense Eligibility Enrollment Reporting System.

We classified cases into categories according to the predominant complaint, sign, or symptom. When possible, we compared observed rates (number of reports per number of vaccinations) of neurologic syndromes among vaccinees to expected incidence rates in the general population.

Observations in this report are based on VAERS-associated surveillance and response activities, which are exempt from institutional review board review.

RESULTS

The SVAEMRA clinical team or DoD was consulted on 30 serious events (eg, resulting in hospitalization, disability, or death) temporally associated with smallpox vaccination events and features suggesting neurologic involvement. These 30 cases were actively investigated by the lead author. Twelve were neurologic, were also captured through VAERS report review, and are summarized in TABLE 1.

Between December 16, 2002, and March 11, 2004, approximately 665,000 civilians and military personnel received smallpox vaccine, including approximately 435,000 primary (ie, first-time) vaccinees (66%). During this period, 2,060 VAERS reports involving smallpox vaccine were received; 670 contained COSTART codes related to neurologic illness, 320 involved DHHS vaccinees (primarily civilian health care workers), and 350 involved DoD vaccinees (primarily military personnel deployed to overseas field situations). A preliminary screen excluded 456 reports unrelated to neurologic illness; the remaining 214 reports underwent detailed review; 2 misclassified cases were subsequently excluded.

The 214 neurologic VAERS reports included 111 DHHS and 103 DoD vaccinees: 105 (49%) were women, 106 (50%) were men, and sex was not identified for 3; overall, 17% of vaccinees were women.

One hundred seventy-two (80%) reports were for persons younger than 50 years; the 18- to 29-year group had the largest proportion of adverse events (66%; 31%). One hundred thirteen (53%) were reported primary vaccinees. Of reported neurologic adverse events, 54% occurred within 1 week of vaccination and 86% occurred within 30 days. A number of clinical syndromes, including dizziness or vertigo, limb weakness, syncope, and paresthesias, were poorly defined and unassociated with shortterm morbidity and will not be discussed herein.

Headache, the predominant symptom among 44% of reports (TABLE 2), was most common and often accompanied by fever, chills, and fatigue. Most headache cases had no other evidence of neurologic dysfunction and had favorable outcome. Headaches requiring hospitalization and categorized as serious have been described.18

A total of 39 serious neurologic adverse events associated with smallpox vaccination were reported to VAERS; 27 (69%) were among primary vaccinees and all but 2 occurred within 12 days of vaccination (TABLE 3).

We classified 13 cases as suspected meningitis, defined by the presence of headache and lumbar puncture performance, indicative of warranting cerebrospinal fluid (CSF) examination. Of these 13, 1 had a documented pleocytosis, and 1 was reported as having CSF “consistent with meningitis,” without further data. The remaining 11 reported normal or negative CSF or other study results (eg, head computed tomography, brain magnetic resonance imaging [MRI]). No reports of meningitis occurred more than 14 days after vaccination. Eight (62%) were primary vaccinees.

We initially classified 4 cases as suspected encephalitis or myelitis, including the 2 cases on which SVAEMRA consulted and 2 identified through VAERS review alone. One report of transverse myelitis described normal CSF and onset 61 to 120 days following vaccination and was excluded. Of the remaining 3 cases, one man had
probable encephalitis defined by altered mental status, pleocytosis, and multifocal demyelinating lesions on brain MRI 10 days after primary vaccination. Another man with suspected encephalitis developed fever, altered mental status, and pleocytosis 8 days after primary smallpox vaccination and several weeks after multiple other vaccinations; he recovered completely within 8 days. Cerebrospinal fluid polymerase chain reaction testing of both patients for vaccinia nucleic acid by the CDC’s Poxvirus Laboratory was negative. A third patient with suspected encephalitis 7 days after primary vaccination had mental “slowing” that resolved completely in 1 day;

Table 1. Case Synopses of “Serious” Suspected Neurologic Adverse Events After Smallpox Vaccination

<table>
<thead>
<tr>
<th>Patient No./Sex/Age Range, y</th>
<th>Vaccine Status</th>
<th>Symptom Onset After Vaccination</th>
<th>Method of Review†</th>
<th>Clinical Syndrome/Category Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/20-30 Primary 0 d</td>
<td>Physician interview, medical record review</td>
<td>Central facial paralysis</td>
<td>Central facial paresis, question of mild left hemiplegia; extensive neurologic evaluation failed to identify an etiology</td>
<td></td>
</tr>
<tr>
<td>2/F/30-40 Primary 10 d</td>
<td>Physician interview</td>
<td>Headache, vertigo</td>
<td>Otherwise uncomplicated headache and vertigo temporally associated with vaccination; no sequelae</td>
<td></td>
</tr>
<tr>
<td>3/F/50-60 Revaccinee 20 d</td>
<td>Medical record review</td>
<td>Transient global amnesia</td>
<td>Features consistent with transient global amnesia, including repetition of questions, confusion, complete recovery, negative imaging and CSF studies; condition has no known association with vaccination</td>
<td></td>
</tr>
<tr>
<td>4/F/30-40 Primary 7 d</td>
<td>Physician interview, medical record review</td>
<td>Paresthesias</td>
<td>Development of painful dysesthesias requiring hospitalization and pain control but no other evidence of objective neurologic dysfunction; outcome unknown</td>
<td></td>
</tr>
<tr>
<td>5/F/40-50 Revaccinee 5 d</td>
<td>Physician interview, medical record review</td>
<td>Headache</td>
<td>Patient with history of poorly controlled migraines experienced headache typical of migraines 5 d after vaccination; required brief hospitalization</td>
<td></td>
</tr>
<tr>
<td>6/M/50-60 Revaccinee 2 mo</td>
<td>Medical record review</td>
<td>Stroke</td>
<td>Occurrence of stroke 2 mo after vaccination; predisposing risk factors include hypertension and tobacco use; long interval to onset, no indication of vaccination-related event</td>
<td></td>
</tr>
<tr>
<td>7/F/40-50 Revaccinee 6 d</td>
<td>Medical record review</td>
<td>Headache</td>
<td>Headache and photophobia reported; CSF and head computed tomography normal</td>
<td></td>
</tr>
<tr>
<td>8/M/20-30 Primary 1 d</td>
<td>Physician interview, medical record review</td>
<td>Guillain-Barre syndrome</td>
<td>Service member receiving multiple other simultaneous vaccinations 14 d before and smallpox vaccine 1 d before onset of ascending flaccid paralysis</td>
<td></td>
</tr>
<tr>
<td>9/M/40-50 Primary 90 d</td>
<td>Medical record review</td>
<td>Bell palsy</td>
<td>Peripheral facial nerve palsy occurring 90 d after vaccination; complete recovery</td>
<td></td>
</tr>
<tr>
<td>10/F/50-60 Revaccinee 99 d</td>
<td>Physician interview, medical record review</td>
<td>Multiple sclerosis‡</td>
<td>Complex neurologic diagnosis with multiple neurologic complaints; extensive neurologic evaluation performed, the result of which was nondiagnostic; long interval suggests association is unlikely</td>
<td></td>
</tr>
<tr>
<td>11/M/30-40 Primary 10 d</td>
<td>Physician interview, medical record/neuroimaging review</td>
<td>PVE/ADEM</td>
<td>Vaccinee with onset of mental status changes, seizures 10 d after vaccination; lesions consistent with demyelinating disease on MRI; neurologic sequelae still present 1 y after event</td>
<td></td>
</tr>
<tr>
<td>12/M/20-30 Primary 8 d</td>
<td>Physician interview, medical record review</td>
<td>PVE</td>
<td>Service member developing unresponsiveness, pleocytosis 8 d after smallpox vaccination; other vaccinations given several weeks earlier; complete recovery</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PVE, postvaccinal encephalitis.

*Prospectively reported to the Vaccine Adverse Event Reporting System (VAERS) after being identified through consultation with the Smallpox Vaccine Adverse Events Response and Monitoring Activities and the Department of Defense.
†Review done in addition to VAERS.
‡Diagnosis in the VAERS report.
CSF white blood cell count was 6 cells/mm³ (normal <5 cells/mm³). The observed rate for encephalomyelitis with these 3 cases was 5 per million vaccinations (7/million primary vaccinations). No reports of encephalitis occurred more than 14 days after vaccination.

Bell palsy (facial weakness) was reported in 11 vaccinees. The median interval between vaccination and reported onset was 7 days (range, 3-8 days). Six (55%) were primary vaccinees. We estimate the rate of reported Bell palsy to be 1.7 per 100 000 vaccinations (0.9/100 000 primary vaccinations).

Eight patients had reported seizures 9 days after vaccination. Seven (88%) were primary vaccinees. Three (38%) had a history of seizures. Among the remaining 3, 1 patient’s seizure was attributed to hypoglycemia. Two had apparent new-onset seizures: neuroimaging, electroencephalography (EEG), and CSF analysis results were normal, and no recurrences were experienced 2 months after onset for one patient and 4 months for the other. The 2 remaining cases included one with apparent new-onset seizures with no EEG or MRI findings reported and another for whom seizures occurred in a clinical context of severe respiratory distress, cardiac abnormalities, and ultimately death. This case was reported in detail by a Sentinel Review process of the SVS WG and other DHHS entities, the suspected underlying etiology was a new-onset autoimmune syndrome.

GBS was reported twice in primary vaccinees and once in a revaccinee. The referring physicians attributed 2 cases to other concomitantly administered vaccinations; the interval between these vaccinations and onset was not reported. One individual for whom neurologic examination, CSF, or EMG findings were not available had GBS onset 1 day after vaccination, an interval biologically unlikely to reflect vaccine causality. Presuming all 3 temporal associations are valid and these cases were not misclassified, the maximum observed rate of GBS was 0.5 cases per 100 000 vaccinations.

Table 2. Clinical Syndrome and Incidence Among Reports of Neurologic Adverse Events Associated With Smallpox Vaccination, VAERS—United States, 2002-2004 (N = 214)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cases, No. (%)</th>
<th>Incidence per 100 000 Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (with or without other symptoms)</td>
<td>95 (44)</td>
<td>14.3</td>
</tr>
<tr>
<td>Limb paresthesias</td>
<td>17 (8)</td>
<td>2.5</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>13 (6)</td>
<td>1.9</td>
</tr>
<tr>
<td>Limb pain</td>
<td>13 (6)</td>
<td>1.9</td>
</tr>
<tr>
<td>Meningitis (with LP)</td>
<td>13 (6)</td>
<td>1.9</td>
</tr>
<tr>
<td>Bell palsy/facial weakness</td>
<td>11 (5)</td>
<td>1.7</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>11 (5)</td>
<td>1.7</td>
</tr>
<tr>
<td>Seizures</td>
<td>8 (4)</td>
<td>1.2</td>
</tr>
<tr>
<td>Mental status change</td>
<td>7 (3)</td>
<td>1.1</td>
</tr>
<tr>
<td>Syncope/pressyncope</td>
<td>5 (2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>4 (2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Encephalitis (with LP)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>4 (2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Visual changes</td>
<td>4 (2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>3 (1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Meningitis</td>
<td>12 (5)</td>
<td>2.3</td>
</tr>
<tr>
<td>Movement disorder†</td>
<td>1 (&lt;1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Demyelinating disease†</td>
<td>1 (&lt;1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Brachial neuritis</td>
<td>1 (&lt;1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (&lt;1)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: LP, lumbar puncture; VAERS, Vaccine Adverse Events Reporting System.

*Includes 1 case of transverse myelitis.
†Diagnosis in the VAERS report.

Table 3. Reports of Neurologic Adverse Events Associated With Smallpox Vaccination Reported to VAERS—United States, 2002-2004 (n = 39)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Primary Vaccinees, No. (%)</th>
<th>Interval &lt;2 d</th>
<th>Interval 2-30 d</th>
<th>Interval &gt;30 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>3 (300)</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Encephalitis/myelitis</td>
<td>3 (2)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>3 (2)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bell palsy</td>
<td>11 (55)</td>
<td>2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>9 (8)</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>39 (27)</td>
<td>5</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: VAERS, Vaccine Adverse Events Reporting System.

*Interval data unavailable for 2 cases.
occurred mainly in children younger than 2 years at 6 to 12 days after vacci- 
ination and presented as fulminant sei- 
zures, hemiplegia, and elevated intra-
cranial pressure. These patients had 
diffuse cerebral edema, lymphocytic 
meningeal infiltration, and perivascu-
lar hemorrhages. Vaccinal viremia and 
virus isolation from brain or CSF was 
sometimes detected. 36,37 Although clini-
copathologic correlates of PVE during 
the era of modern neuroimaging and 
neuroimmunology have not been pos-
sible, the demyelinating form of PVE 
probably corresponds to acute dissemi-
nated encephalomyelitis (ADEM) or 
postvaccination encephalomyelitis, 
whereas the cytotoxic form may rep- 
resent an acute neuroinvasive vac-
cinal encephalomyelitis.

We identified 3 persons with prob-
able or suspected encephalitis after 
smallpox vaccination, with cerebral 
inflammation evidenced by altered men-
tal status and pleocytosis. One patient 
had a longer interval between vaccina-
tion and illness onset and MRI findings 
suggestive of ADEM, and the other 2 had 
features more consistent with acute vi-
ral encephalitis, including a shorter in-
terval between vaccination and onset and 
rapid recovery. Our estimated report-
ning rate of probable or suspected PVE 
cases of 5 cases per million vaccinees is 
consistent with previous assessments 
conducted in the United States. Wide 
availability of neuroimaging and CSF ex-
amination allow distinction between 
mild neurologic symptoms and true ce-
rebral inflammation, reducing misclas-
sification of encephalitis. None of the 
persons in this study with suspected en-
cephalitis died, perhaps because of im-
proved supportive neurocritical care.

Aseptic meningitis was reported in 
13 patients. However, only 2 demon-
strated pleocytosis, suggesting that 
aseptic meningitis may have been over-
diagnosed in earlier studies.

Bell palsy and GBS have been re-
ported after infections and immuniza-
tions. Most population-based assess-
ments have not found higher-than-
expected rates of these phenomena after 
vaccination, but a statistically signifi-
cant association has been made for Bell 
palsy after intranasal influenza vac-
cine and hepatitis B vaccination 38,39 
and for GBS after rabies vaccination and 
some formulations of influenza vac-
cine. 40,41 However, specific antecedent 
events are not usually evident. The 
expected rate of Bell palsy among the 
general population ranges between 15 
and 40 cases per 100 000 per year. 42,43 The 
11 cases of Bell palsy yields a rate of 1.7 
per 100 000 vaccinations, about or 
lower than the expected incidence. Pub-
lished estimates of GBS among the gen-
eral population range from 0.4 to 4.0 
cases per 100 000 per year. 44 The 3 cases 
of suspected GBS (estimated report-
ning rate of 0.5/100 000 vaccinations) is 
much lower than that observed within 
the general population. Further, 1 case 
of GBS was reported 1 day after vacci-
nation, which suggests it was misclas-
sified because a biological link with 
vaccination would be implausible.

Our estimations of the occurrences 
of GBS, Bell palsy, and PVE per number 
of vaccinations are ratios of reported events 
compared with the number of vaccina-
tions. They are not expressed relative to 
units of time and are not directly com-
parable to the published population-
based incidence rates. Although not sta-
tistically valid, comparison of these ratios 
with known background rates may be 
a useful indicator of adverse-events 
trends associated with vaccinations.
45,46 Overall, 69% of the serious 
neurologic adverse events, including all 
3 cases of encephalitis, occurred among 
primary vaccinees, which is consistent 
with historical data describing more ad-
verse events among primary vaccinees 
than among revaccinees.

Our assessment has limitations. Like 
all passive surveillance systems, VAERS 
reports are subject to underreporting, as-
certainty bias and differential report-
ing, and variability in report quality and 
completeness. 40 We did not attempt to 
obtain additional information from 
medical record reviews beyond the 12 
cases prospectively identified through 
clinical consultation. Some military per-
sonnel receive multiple vaccinations, 
making it difficult to associate any one 
with the presumed adverse event. Data 
on intercurrent infections in cases of sus-
pected meningitis and encephalitis were 
not available.

Our findings identified many milder 
neurologic adverse events temporally 
but not necessarily causally associated 
with smallpox vaccination. They 
suggest that such events are generally 
self-limited, nonserious, and not associ-
ated with severe morbidity or mortality 
when screening defers persons with 
high-risk conditions.

Smallpox vaccine is given to healthy 
people, which creates a low tolerance 
for associated risk. Risks associated with 
vaccines are best identified through 
population-based assessments. 47,48 New, 
possibly less reactogenic smallpox vac-
cines are currently under develop-
ment. Continued monitoring for neu-
rologic events is needed to assess 
the safety of smallpox vaccines and to bet-
ter characterize the spectrum of neu-
rologic illness associated with them.

Author Contributions: Dr Sejvar had full access to all 
of the data in the study and takes responsibility for the 
integrity of the data and the accuracy of the data 
analysis.
Study concept and design: Sejvar, Chapman, 
Grabenstein, Iskander.
Acquisition of data: Sejvar, Labutta, Chapman, 
Grabenstein, Iskander, Lane.
Analysis and interpretation of data: Sejvar, Labutta, 
Chapman, Grabenstein, Iskander, Lane.
Drafting of the manuscript: Sejvar, Chapman, 
Grabenstein, Lane.
Critical revision of the manuscript for important in-
tellectual content: Sejvar, Labutta, Chapman, 
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SMALLPOX VACCINATION AND NEUROLOGIC EVENTS

als; state, territorial, county, city, and local health department professionals; and the civilian response team and monitoring activity volunteers. We thank Claudia Chesley, BA, for review and editing of the manuscript.

REFERENCES:

That approach leaves several critical issues unresolved. First, federal policy actively discourages high-quality research by making access to marijuana by researchers exceedingly difficult. Even when access to marijuana is finally granted, there is substantial variability in the purity and content of the product. Second, researchers need to test the assumption noted by Das that THC is the active ingredient responsible for the perceived beneficial effects. Although that assumption is reasonable, there remains the possibility that marijuana, not THC in isolation, achieves the desirable effects. Third, researchers should test the most efficient delivery system. There may be some added value in smoking that needs to be evaluated.

If research concludes that THC is the beneficial ingredient and that delivery by tablet is safest and most effective, then there is justification for approval of that method only. A synthetic THC oral medication (dronabinol) is already available for prescription with US Food and Drug Administration-approved indications for anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Regulation of the use of marijuana for medical purposes is feasible and socially desirable, but it will require a different way of thinking about the problem. It requires viewing marijuana as a potential medication subject to carefully controlled research, rather than as a drug of strict prohibition.

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blood pressure regulation and provides the basis for targeting research to the stimulation of endogenous nitric oxide synthesis as a novel blood pressure–lowering principle.

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CORRECTIONS

Incorrect Data: In the Original Contribution entitled “Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial” published in the November 15, 2006, issue of JAMA (2006;296[19]:2319-2328), a P value was incorrectly reported. On page 2323 in the “Efficacy End Points” subsection, the section of the first sentence that read “or 146 (71%) of 207 receiving tamsulosin (P=.03 vs placebo)” should have read “P=.064 vs placebo.”

Incorrect Title: In the Perspectives on Care at the Close of Life: Coda entitled “Lateral Sclerosis: ‘Prepare for the Worst and Hope for the Best’” published in the September 12, 2007, issue of JAMA (2007;298[10]:1208-1208), the title should have read “Amyotrophic Lateral Sclerosis: ‘Prepare for the Worst and Hope for the Best.’”

Incorrect Data: In the Original Contribution entitled “Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004” published in the December 7, 2006, issue of JAMA (2006;296[21]:2744-2750) the abstract misstated the subgroups of civilian and military vaccinates. The 665,000 persons vaccinated against smallpox were compiled from the experience of the Departments of Defense (n=625,400) and Health and Human Services (n=39,400). The erroneously reported subtotal values (Department of Defense n=590,400 and Department of Health and Human Services n=64,600) appeared only in the abstract, were not used in the analyses, and did not influence the information reported in the body of the article. On page 2748, at the top of the second column, the reporting rate of Bell palsy among primary vaccinates was also misstated. The correct rate is 1.4/100,000, not 0.9/100,000. The overall rate described was correctly stated (1.7/100,000 vaccinations). The number of seizures reported in Table 3 was also misstated, although they are correctly stated elsewhere in the article. Overall 8 seizures were reported, of which 7 (85%) were among primary vaccinates. Five of these occurred in the interval of 2-30 days, and thus 29 adverse events occurred in that interval in Table 3. The error in reported seizure cases was carried over to the total number of serious neurologic events reported elsewhere in the article. The correct value is 38 (not 39), with 26 (not 27) among primary vaccinates, and a proportion among primary vaccinates of 68% (not 69%). On page 2748, in the first sentence of the first paragraph in column 2, the word “median” is missing. That sentence should read, “Eight patients had reported seizures a median of 9 days after vaccination.” We consider none of these errors to affect the discussion points or the conclusions of this article, nor to affect the validity of the conclusions reached in our study.