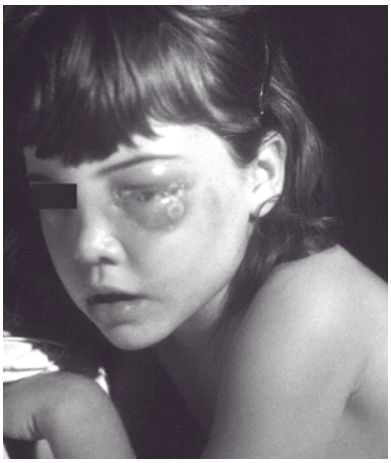
MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | February 3, 2006 / Vol. 55 / No. RR-1

Surveillance Guidelines for Smallpox Vaccine (vaccinia) Adverse Reactions



INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION
Centers for Disease Control and Prevention. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR 2006;55(No. RR-1):[inclusive page numbers].

CONTENTS

Introduction 1
Reporting Guidelines 2
Case Definition and Classification 2
- Localized Reactions 3
- Unintentional Transfer of Vaccinia Virus 3
- Diffuse Dermatologic Complications 4
- Progressive Vaccinia 6
- Rare Reactions 6
- Cardiac 7

Case Classification 10
Vaccinia Laboratory Diagnostics 11
Surveillance Results and Outcome 13
Conclusions 13
References 14
Continuing Education Activity CE-1

Disclosure of Relationship

CDC, our planners, and our content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use.

On the Cover: Child aged 5 years with inadvertent inoculation to bilateral lower eyelid; typical vaccinia lesions are visible

Surveillance Guidelines for Smallpox Vaccine (vaccinia) Adverse Reactions

Prepared by
Christine Casey, MD[1]
Claudia Vellozzi, MD[2]
Gina T. Mootrey, DO[2]
Louisa E. Chapman, MD[2]
Mary McCauley[2]
Martha H. Roper, MD[2]
Inger Damon, MD[3]
David L. Swerdlow, MD[3]
[1]*Immunization Safety Office, Office of the Chief Science Officer, Office of the Director*
[2]*National Immunization Program*
[3]*National Center for Infectious Diseases*

Summary

CDC and the U.S. Food and Drug Administration rely on state and local health departments, health-care providers, and the public to report the occurrence of adverse events after vaccination to the Vaccine Adverse Event Reporting System. With such data, trends can be accurately monitored, unusual occurrences of adverse events can be detected, and the safety of vaccination intervention activities can be evaluated.

On January 24, 2003, the U.S. Department of Health and Human Services (DHHS) implemented a preparedness program in which smallpox (vaccinia) vaccine was administered to federal, state, and local volunteers who might be first responders during a biologic terrorism event. As part of the DHHS Smallpox Preparedness and Response Program, CDC in consultation with experts, established surveillance case definitions for adverse events after smallpox vaccination. Adverse reactions after smallpox vaccination identified during the 1960s surveillance activities were classified on the basis of clinical description and included eczema vaccinatum; fetal vaccinia; generalized vaccinia; accidental autoinoculation, nonocular; ocular vaccinia; progressive vaccinia; erythema multiforme major; postvaccinial encephalitis or encephalomyelitis; and pyogenic infection of the vaccination site.

This report provides uniform criteria used for the surveillance case definition and classification for these previously recognized adverse reactions used during the DHHS Smallpox Preparedness and Response Program. Inadvertent inoculation was changed to more precisely describe this event as inadvertent autoinoculation and contact transmission, nonocular and ocular vaccinia. Pyogenic infection also was renamed superinfection of the vaccination site or regional lymph nodes. Finally, case definitions were developed for a new cardiac adverse reaction (myo/pericarditis) and for a cardiac adverse event (dilated cardiomyopathy) and are included in this report. The smallpox vaccine surveillance case definitions presented in the report can be used in future vaccination programs to ensure uniform reporting guidelines and case classification.

Introduction

Surveillance guidelines that include standardized case definitions for reporting of notifiable infectious diseases are important public health tools that contribute to the assessment of disease trends, measurement of intervention effectiveness, and detection of disease outbreaks (*1*). Comparable surveillance guidelines for the classification and reporting of adverse reactions after vaccination are nominal and have not commonly include standardized case definitions (*2,3*). The term vaccine-related "complication" is often used interchangeably with the terms "side effects" or "adverse reaction" and should be distinguished from the term "adverse event." An adverse reaction is an untoward effect that occurs after a vaccination and is extraneous to the vaccine's primary purpose of producing immunity (e.g., eczema vaccinatum). Adverse reactions have been demonstrated to be caused by the vaccination. In contrast, adverse events are untoward effects observed or reported after vaccinations, but a causal relation between the two have yet to be established. This report focuses on adverse reactions known to be caused by smallpox vaccine (with the exception of dilated cardiomyopathy that has not been shown to have a causal relation) on the basis of scientific evidence. Uniform criteria for classification of adverse reaction reports

The material in this report originated in the National Immunization Program, Anne Schuchat, MD, Director.
Corresponding preparer: Christine Casey, Immunization Safety Office, Office of the Chief of Science, 1600 Clifton Road, NE, MS E-61, Atlanta, GA 30329. Telephone: 404-639-2973; Fax: 404-639-8834; Email: ccasey@cdc.gov.

after smallpox (vaccinia) vaccination have been established. Criteria for dilated cardiomyopathy, an adverse event (not shown to have a causal relation with smallpox vaccination), also have been established. These case definitions and reporting guidelines were used by CDC and the Office of the Assistant Secretary of Defense for Health Affairs during the mandatory Department of Defense (DoD) and voluntary U.S. DHHS smallpox vaccination programs that were designed to increase national preparedness in the event of a biologic terrorism attack (*4*–*6*).

Adverse reactions caused by smallpox vaccination range from mild and self-limited to severe and life-threatening. During the recent smallpox vaccination programs, CDC, DoD, and the joint Advisory Committee on Immunization Practices (ACIP)-Armed Forces Epidemiological Board (AFEB) Smallpox Vaccine Safety Working Group (SVS WG) relied on surveillance data from the smallpox pre-eradication era to estimate frequencies of adverse reactions expected during these vaccination programs. These estimates might be limited because the targeted population during the 1960s was mostly children who had never been previously vaccinated; the recent program targeted healthy adults, some of whom had received smallpox vaccines (*6*). Furthermore, adverse reactions during the 1960s were classified and reported by providers on the basis of subjective clinical diagnosis, and standard collection or analytical tools were not applied to the clinical data (*7*–*11*). Without explicit criteria for identifying cases for public health surveillance, state health departments and individual practitioners often apply different criteria for reporting similar cases (*1*). Surveillance data for adverse reactions after smallpox vaccination must be aggressively pursued and standardized to assess accurately the frequency of adverse events after smallpox vaccination.

This report describes the case definitions used to classify reported adverse events during the DHHS smallpox vaccination program. The overall safety surveillance system and related findings are reported elsewhere (*12*).

Reporting Guidelines

These surveillance case definitions establish reporting criteria for prospective or retrospective classification of cases. Clinical, laboratory, and epidemiologic information are necessary for accurate case classification, which could not be obtained without cooperation and information exchange between treating health-care providers, state health officials, laboratorians, and CDC. Any adverse event after smallpox vaccination should be reported to state health departments and the Vaccine Adverse Events Reporting System (VAERS), particularly those events known to be adverse reactions (Table 1). Any adverse reaction that requires treatment with vaccine immune globulin (VIG) or cidofovir should be reported immediately, and adverse events that meet the regulatory criteria for "serious" (i.e., those resulting in hospitalization, permanent disability, life-threatening illness, or death) (*13*) should be reported within 48 hours; all other events should be reported within 1 week (*14*). Reports can be submitted to VAERS at http://www.vaers.hhs.gov, 877-721-0366, or P.O. Box 1100, Rockville, MD 20849-1100. Report forms and assistance with reporting are available from VAERS (800-822-7967).

Case Definition and Classification

ACIP-AFEB SVS WG was responsible for safety oversight of the DHHS and DoD smallpox preparedness programs. The majority of the case definitions for vaccinia adverse reactions were drafted by the Vaccinia Case Definition Development working group in collaboration with ACIP-AFEB SVS WG. The Vaccinia Case Definition Development working group membership included CDC and DoD medical epidemiologists, smallpox eradication experts, ophthalmologists, dermatologists, cardiologists, and infectious-disease specialists. These work groups contributed to the development of case definitions by completing literature searches, translating publications, coordinating or participating in meetings, collecting or analyzing data, investigating cases, providing subject-matter expertise, and drafting and revising case definitions. The case definition for fetal vaccinia was developed by CDC and DoD for use in the development of the National Smallpox Vaccine in Pregnancy Registry (*15*).

For all cases, exposure to vaccinia is required; vaccination, close contact with a recent vaccinee, or intrauterine exposure

TABLE 1. Adverse events after smallpox vaccination that are recommended to be reported to the Vaccine Adverse Event Reporting System and to state health departments*

Superinfection of the vaccination site or regional lymph nodes†
Inadvertent autoinoculation (nonocular)
Contact transmission (nonocular)
Ocular vaccinia
Generalized vaccinia
Eczema vaccinatum
Progressive vaccinia
Erythema multiforme major or Stevens-Johnson Syndrome§
Fetal vaccinia
Postvaccinial central nervous system disease
Myo/pericarditis
Dilated cardiomyopathy¶

* Any adverse event that is of concern to the clinician or patient should be reported.
† Previously referred to as pyogenic infection of vaccination site.
§ Clinically defined.
¶ Causal association with smallpox vaccination has not been shown.

can fulfill this criterion. Vaccinia virus can be transmitted from the vaccination site to close contacts of persons who received smallpox vaccine, and these contacts can experience the same adverse reactions as vaccinees.

Smallpox vaccine adverse events can be divided into several categories. Localized reactions include a superinfection of the vaccination site or regional lymph nodes and robust take (RT). Unintentional transfer of vaccinia virus includes transfer from the vaccination site to elsewhere on the vaccinee's body and is called inadvertent autoinoculation. When the virus is transferred from the vaccinee to a close contact, it is called contact transmission. In either case, if the virus is transferred to the eye and surrounding orbit, it is referred to as ocular vaccinia. Diffuse dermatologic complications include two groups. The first group (hypersensitivity rashes) includes nonspecific, postvaccination rash, erythema multiforme minor, and Stevens-Johnson syndrome. These lesions are not thought to contain vaccinia virus, and because these terms are defined elsewhere in the dermatologic literature, they not included in this report. The second group of diffuse dermatologic complications is thought to be caused by replicating vaccinia virus that can be recovered from the rash of generalized vaccinia (GV) (usually a benign, self-limiting condition), eczema vaccinatum (EV) (often associated with substantial morbidity), and progressive vaccinia (PV) (which is generally fatal). Rare adverse reactions include fetal vaccinia and postvaccinial central nervous system diseases such as post-vaccinial encephalitis or encephalomyelitis. Other reactions previously reported but not well described include the newly characterized cardiac adverse reaction, myo/pericarditis (M/P) or the newly described cardiac adverse event dilated cardiomyopathy (DCM), which has not been yet been demonstrated to be etiologically linked.

Localized Reactions

Superinfection of the Vaccination Site or Regional Lymph Nodes

Vaccination progression and normal local reactions are difficult to distinguish from a superinfection of the vaccination site or regional lymph nodes. Secondary infections (i.e., superinfections) of the vaccination site are uncommon (rate: 0.55 per 10,000 vacinees) (*16*) and are typically mild to moderate in clinical severity (Box 1). Persons at greatest risk are children and those who frequently manipulate and contaminate the vaccination site. Occlusive dressings might lead to maceration and increased risk for infection. Secondary streptococcal bacterial infection has been reported (*9*), but anaerobic organisms and mixed infections also might be expected.

Distinguishing superinfection of the vaccination site or regional lymph nodes can be particularly challenging because both a bacterial cellulitis and a variant of the normal major reaction or RT have similar signs and symptoms.

Robust Take

An RT is a vaccinial cellulitis and is defined as >3 inches (7.5 cm) of redness with swelling, pain, and warmth at the vaccination site. These symptoms peak on days 6–12 postvaccination and regress within the following 24–72 hours. RTs can occur in up to 16% of smallpox vaccinees (*16,17*). Suspected bacterial cellulitis after smallpox vaccination is often treated empirically with antibiotics without a period of observation, and bacterial or other cultures are rarely obtained. As clinicians have gained experience with smallpox vaccination, some have ceased treating empirically with antibiotics in favor of close observation. Clinical observations suggest that the majority of vaccinees' local symptoms resolved without intervention, leading providers to conclude that these cases were RTs (CDC, unpublished data, 2002). In contrast to an RT, superinfections refer to cellulitis caused by agents other than vaccinia.

Unintentional Transfer of Vaccinia Virus

Inadvertent Autoinoculation

Unintentional transfer of vaccinia virus includes transfer from the vaccination site (or probable site of inoculation in a person infected with vaccinia through contract transmission) to elsewhere on the vaccinee's (or contact's) body, which is called inadvertent autoinoculation (Box 2). Smallpox vaccinees or contacts can transfer vaccinia virus to their hands or fomites, which becomes a source for infection elsewhere on the body. The most common nonocular sites are the face, nose, mouth, lips, genitalia, and anus. Lesions at autoinoculation sites progress through the same stages (e.g., papular, vesicular, pustular, crusting, and scab) as the vaccination site. When autoinoculation occurs >5 days postvaccination, the developing immune response might attenuate the lesions and their progression. Persons at highest risk for inadvertent autoinoculation are children aged 1–4 years and those with disruption of the epidermis, including but not limited to abrasions and burns (*17*).

Contact Transmission

When the virus is transferred from the vaccinee to a close contact, this transmission is termed contact transmission. Persons in close contact with a recent vaccinee or associated vectors (e.g., distant lesions on a vaccinee resulting from inadvertent autoinoculation, clothing, bedding, or bandages contaminated by vaccinia) might acquire vaccinia infection. Vaccinia virus is shed from the vaccination site or from dis-

BOX 1. Surveillance case definition for superinfection of the vaccination site or regional lymph nodes after smallpox vaccination for use in smallpox vaccine adverse event monitoring and response

Superinfection of the vaccination site or regional lymph nodes is defined as a nonvaccinial superinfection (e.g., superinfection caused by bacterial, fungal, atypical, or viral organisms) that produces a local inflammatory response at the site of vaccination and can present with the same signs and symptoms as vaccinia virus replication at the vaccination site.

Case definition for superinfection of the vaccination site or regional lymph nodes

A **suspected case** of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:

- vaccination site or regional lymph nodes with three or more of the following findings:
  - — dolor (pain and/or tenderness),
  - — calor (warmth),
  - — rubor (redness), and
  - — other (regional lymphadenopathy; lymphangitic streaking; edema, induration and/or swelling; fluctuance; and blister with pus or honey-crusted plaque);

and

- temporal criterion:
  - — onset or peak symptoms occur from day of vaccination to day 5 after vaccination and/or day 13–60 after vaccination (excludes days 6–12 after vaccination);

and

- clinical course:
  - — clinical criteria persist or worsen for hours to days after vaccination; patient report is adequate.

A **confirmed case** of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:

- vaccination site or regional lymph nodes with three or more of the following findings:
  - — dolor (pain and/or tenderness),
  - — calor (warmth),
  - — rubor (redness), and
  - — other (regional lymphadenopathy; lymphangitic streaking; edema, induration and/or swelling; fluctuance; and blister with pus or honey-crusted plaque);

and

- temporal criterion:
  - — symptoms occur from day of vaccination to 60 days after vaccination (inclusive);

and

- laboratory criteria having one or more of the following findings:
  - — positive results of pathogenic culture (e.g., bacterial, fungal, atypical, or nonvaccinial viral culture),
  - — positive microscopy results (e.g., Gram stain, silver stain, acid-fast bacillus stain, or darkfield), and
  - — positive result of bioburden testing* of the vaccinia vaccine vial;

or

- radiographic findings:
  - — findings consistent with superinfection (e.g., lymphadenopathy or abscess) by magnetic resonance imaging, computed tomography scan, or ultrasound.

*Bioburden is referred to as the number of microorganisms on a contaminated object; it is also called bioload. For testing of vaccinia vaccine vial, a positive bioburden test indicates that the accepted limits of bioload have been exceeded and the vaccine is not suitable for use.

tant lesions caused by autoinoculation, GV, EV, or PV (Box 3). Viral shedding might occur until the scab detaches from the vaccination site or distant lesions; virus can survive for several days on clothing, bedding, or other fomites (*18*). Although virus exists in the scab, it is bound in the fibrinous matrix, and the scab is not thought to be highly infectious (*17*). Infection acquired through contact transmission can result in the same adverse events observed after smallpox vaccination.

Ocular Vaccinia

In the case of either contact transmission or inadvertent autoinoculation, if the virus is transferred to the eye and surrounding orbit, this transmission is referred to as ocular vaccinia. Ocular vaccinial infections result from the transfer of vaccinia from the vaccine site or other lesion containing vaccinia to or near the eye. These infections account for the majority of inadvertent inoculations (*11*) (Box 4). Infections can be clinically mild to severe and can lead to vision loss. When suspected, ocular vaccinia infections should be evaluated with a thorough eye examination, including use of a slit lamp. These cases should be managed in consultation with an ophthalmologist.

Diffuse Dermatologic Complications

Diffuse dermatologic complications include two groups. The first includes erythema multiforme minor and Stevens-Johnson syndrome, which are clinically defined elsewhere in the der-

BOX 2. Surveillance case definition for inadvertent autoinoculation (nonocular) for use in smallpox vaccine adverse event monitoring and response

Inadvertent autoinoculation occurs when a person who has received smallpox vaccine or experienced inoculation from contact might physically transfer vaccinia virus from vaccination or contact site to another part of the body through scratching or through inanimate objects such as clothing, dressings, or bedding. The most common sites of inadvertent autoinoculation, nonocular are the face, nose, mouth, lips, genitalia, and anus. Lesions at autoinoculation sites progress through the same papular, vesicular, and pustular stages as the vaccination site. When autoinoculation occurs more than 5 days postvaccination, the developing immune response might attenuate the lesions and their progression. Persons at highest risk for inadvertent autoinoculation are children aged 1–4 years and those with disruption of the epidermis, including, but not limited to, abrasions or burns.

Case definition for inadvertent autoinoculation (nonocular)

A **suspected case** of inadvertent autoinoculation is defined by the following criteria:

- affected person has been recently vaccinated and had one or more lesions at one or more sites beyond the boundaries of the dressing that was used. Lesions progress morphologically through papule, vesicle, pustule, and scab,* and
- lesions appear up to 10 days after the period beginning with initial vaccination or contact through final resolution and scarring of lesions at vaccination or contact inoculation site.

A **probable case** of inadvertent autoinoculation meets the criteria for a suspected case and

- does not meet the case definition for generalized vaccinia*, eczema vaccinatum, or progressive vaccinia, and
- other likely etiologies (e.g., bacterial or viral infection) have been excluded.

A **confirmed case** of inadvertent autoinoculation meets the criteria for a suspected or probable case of inadvertent autoinoculation and has the following laboratory evidence of vaccinia infection (on the basis of testing skin lesions distant from the vaccination site in a vaccinee):

- positive test results for vaccinia polymerase chain reaction (PCR) assay or antigen detection techniques (e.g., direct fluorescent assay or direct fluorescent antibody),

or

- demonstration of vaccinia virus by culture.

Note: Histopathologic examination showing typical orthopox cytopathic changes or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent PCR or culture.

* Generalized vaccinia should be considered if ≥20 lesions are present.

matologic literature (*19,20*), and other nonspecific postvaccination rashes with lesions that are thought to be free of vaccinia virus. For surveillance purposes, clinical diagnosis is adequate for case classification. The second group includes adverse reactions thought to be caused by replicating vaccinia virus recovered from skin lesions, which can be associated with risk for autoinoculation or contact transmission (*21*).

Generalized Vaccinia

GV is a disseminated vesicular or pustular rash and is usually benign and self-limited among immunocompetent hosts (Box 5). GV might be accompanied by fever and can produce skin lesions anywhere on the body. GV also can appear as a regional form that is characterized by extensive vesiculation around the vaccination site or as an eruption localized to a single body region (e.g., arm or leg). The skin lesions of GV are thought to contain virus spread by the hematogenous route. First-time vaccinees are at higher risk for GV than revaccinees (*22*). GV is often more severe among persons with underlying immunodeficiency who might have been inadvertently vaccinated; these patients might benefit from early intervention with VIG. GV should not be confused with multiple inadvertent inoculations that might occur in the presence of acute or chronic exfoliative, erosive, or blistering skin disease, including Darier's disease.* GV also should be differentiated from EV, which typically occurs in persons with a history of atopic dermatitis and is often associated with systemic illness.

Eczema Vaccinatum

Persons with a history of atopic dermatitis (i.e., eczema) are at highest risk for EV (Box 6). Onset of the characteristic lesions can occur concurrently or shortly after the occurrence of the reaction at the vaccination site. EV cases resulting from

* Darier's disease is a rare, dominantly inherited, keratinizing skin disorder characterized by innumerable crusts and epidermal fissures, most prominent on seborrheic areas (e.g., behind ears and on neck and sternum). The clinical manifestations, once evident, are lifelong but can wax and wane in severity.

BOX 3. Surveillance case definition for contact transmission (nonocular) for use in smallpox vaccine adverse event monitoring and response

Contact transmission of vaccinia virus occurs when virus shed from smallpox vaccination sites or from distant lesions in persons with inadvertent autoinoculation, generalized vaccinia (GV), eczema vaccinatum (EV), or progressive vaccinia (PV) is transferred to another person. Virus might be shed until the scab heals. The virus can survive for several days on clothing, bedding, or other inanimate surfaces. An unvaccinated or nonrecently vaccinated person in close contact (i.e., touching a person's lesions or vaccination site, clothing, bedding, or bandages) with a vaccinee or their inanimate objects might acquire vaccinia infection. Infection acquired through contact transmission can result in inadvertent autoinoculation from the exposure site to additional sites (including ocular vaccinia) or can result in other adverse reactions.

Case definition for contact transmission (nonocular)

A **suspected case** of contract transmission is defined as

- the development one or more lesions that progress through papule, vesicle, or pustule stages;
- history of close contact with
  - — someone who has received the vaccine <3 weeks before the exposure, or
  - — someone who has had autoinoculation GV, EV, and PV diagnosed; and
- lesions appear 3–9 days after vaccinia exposure.

A **probable case** of contact transmission meets the case definition for suspected case, and other likely etiologies (e.g., bacterial or viral infection) have been excluded.

For a **confirmed case** of contact transmission, laboratory evidence of vaccinia infection exists on the basis of testing skin lesions in a close contact of a known vaccinee. Laboratory evidence of vaccinia infection includes

- positive test results for vaccinia polymerase chain reaction (PCR) assay or antigen detection techniques (e.g., direct fluorescent antibody)

or

- demonstration of vaccinia virus by culture.

Note: Histopathologic examination showing typical orthopox cytopathic changes or electron microscopy of biopsy specimens revealing orthopox virus is strongly suggestive of infection with vaccinia and should be confirmed by subsequent PCR or culture.

secondary transmission usually appear with skin eruptions approximately 5–19 days after the suspected exposure. EV lesions follow the same dermatologic course (Jennerian progression) as the vaccination site in a vaccinee, and confluent or erosive lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are frequently systemically ill. EV tends to be most severe among first-time vaccinees, unvaccinated close contacts of vaccinees, and young children.

Early diagnosis of EV and administration of VIG is helpful to reduce associated morbidity and mortality. Two thirds of potential smallpox vaccinees failed to recall an exclusionary dermatologic condition such as atopic dermatitis (eczema) in themselves or their close contacts (*23*). Poor recall and inconsistent diagnosis of atopic dermatitis contributes to a challenging screening program to exclude persons at risk for EV (*24*). Therefore, when evaluating vaccinees or close contacts of recent vaccinees with a clinical presentation consistent with EV, despite a negative self-reported history of atopic dermatitis or Darier's disease, clinicians should consider EV and assess for treatment with VIG.

Progressive Vaccinia

PV is rare, severe, and often fatal and results when a vaccination site fails to heal and vaccinia virus replication persists. The skin surrounding the vaccination site becomes vaccinia infected, and secondary metastatic vaccinia lesions can occur (Box 7). Lesions can appear necrotic, fungated, piled-up, or well demarcated. Concomitant bacterial superinfection also can occur. PV typically occurs in persons with an underlying humoral or cellular immune deficit. Management of PV should include aggressive therapy with VIG or second line agent cidofovir, intensive monitoring, and tertiary-level supportive care (*17*).

Rare Reactions

Fetal Vaccinia

Rarely, smallpox vaccination of a pregnant woman can result in fetal vaccinia (Box 8). Transmission to the fetus can occur any time during pregnancy. The route of transmission is unknown but is presumed to be through viremia. Abortion, stillbirth, or live birth (usually premature followed by death) or birth of a surviving but pox-scarred infant can occur after the mother's exposure to vaccinia. Fetal or newborn skin lesions have been described as macular, papular, vesicular, pustular, or as scars or areas of epidermolysis (*15*).

BOX 4. Surveillance case definition for ocular vaccinia for use in smallpox vaccine adverse event monitoring and response

Ocular vaccinia is the appearance of lesions suspicious for vaccinia in or near the eye in a vaccinee (or close contact of a vaccinee) up to 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site, to include periocular* involvement, lid involvement (blepharitis†), conjunctival involvement (conjunctivitis§), and/or corneal involvement (keratitis¶).

Case definition for ocular vaccinia

A **suspected case** of ocular vaccinia is defined as the new onset of erythema or edema of the conjunctiva (conjunctivitis), eyelid (blepharitis), or periocular area or inflammation of the cornea (keratitis) in a recent vaccinee (or close contact of vaccinee) that cannot be ascribed to another ocular diagnosis

and

- Temporal criteria of
  - — onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site

    or
  - — onset during the presence of visible vaccinia lesions before scab separation.

A **probable case** of ocular vaccinia is the presentation in or near the eye of lesions consistent with vaccinia infection to include formation of vesicles that progress to pustules that umbilicate and indurate in a manner similar to a normal vaccinia reaction (**Note:** see exceptions/differences to conjunctival and cornea clinical presentation footnotes § and ¶)

and

- Temporal criteria of
  - — onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site

    or
  - — onset during the presence of visible vaccinia lesions before scab separation.

A **confirmed case** of ocular vaccinia meets the criteria as a probable or suspected case of ocular vaccinia with laboratory evidence of vaccinia infection (testing lesions on or near the eye). Laboratory evidence includes

- — positive test results for vaccinia polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody)

  or
- — demonstration of vaccinia virus by culture.

* Periocular involvement (generally above the brow or below the inferior orbital rim) Papules, vesicles, or pustules not involving the ocular adnexa, lids, lid margins, or canthi.

† Blepharitis: (lid involvement): Mild — few pustules, mild edema, and no fever; Severe — pustules, edema, hyperemia, lymphadenopathy (preauricular or submandibular), cellulitis, and fever.

§ Conjunctivitis (involvement of membrane that lines inner surface of the eyelid and exposed surface of the eyeball, excluding the cornea): Conjunctiva might be inflamed (red) with serous or mucopurulent discharge if lesions involve the conjunctiva or cornea. Symptoms of ocular irritation (foreign body sensation) might be present with onset of erythema. Conjunctival lesions typically form vesicles that rapidly ulcerate and form raised "moist appearing" white lesions (rather than pustules that scab) before final resolution: Mild — mild hyperemia or edema, no membranes or focal lesions; Severe — marked hyperemia, edema, membranes, focal lesions, lymphadenopathy (preauricular and/or submandibular), and fever.

¶ Keratitis (corneal involvement): Corneal lesions might present as a grey-appearing superficial punctuate keratitis that might later coalesce to form a geographic epithelial defect resembling herpes simplex keratitis. Stromal corneal lesions might present as small subepithelial opacities resembling those observed in epidemic keratoconjunctivitis, might be associated with epithelial defect, and might progress to corneal haze/clouding: Mild — grey epitheliitis, no epithelial defect, and no stromal haze or infiltrate (cloudy cornea); Moderate — epithelial defect; Severe — ulcer, stromal haze, or infiltrate.

Postvaccinial Central Nervous System Disease

Another rare adverse reaction is postvaccinial central nervous system (CNS) disease such as postvaccinial encephalitis (PVE) or encephalomyelitis (PVEM). CNS disease after smallpox vaccination is most common among infants aged <12 months (*10*) (Box 9). Clinical symptoms reflect cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma. CNS lesions have been reported in the cerebrum, medulla, and spinal cord. Both PVE and PVEM have been described (*11,25*). No clinical criteria, radiologic findings, or laboratory tests exist that are diagnostic for PVE or PVEM. Other infectious or toxic etiologies should be considered and ruled out; the diagnosis of PVE or PVEM after smallpox vaccination is a diagnosis of exclusion.

Cardiac

Myo/pericarditis

An adverse reaction previously reported but not well described is myo/pericarditis. During 1950–1970, both myocarditis and pericarditis were reported after smallpox vaccination in Europe and Australia, where the vaccinia strains

BOX 5. Surveillance case definition for generalized vaccinia after smallpox vaccination for use in smallpox vaccine adverse event monitoring and response

Generalized vaccinia (GV) is a disseminated vesicular or pustular rash appearing anywhere on the body ≥4 days after smallpox vaccination and might be accompanied by fever. GV also can appear as a regional form that is characterized by extensive vesiculation around the vaccination site or as an eruption localized to a single body region. The skin lesions of GV are thought to contain virus spread by the hematogenous route. Primary vaccinees are at higher risk for GV than revaccinees. GV is usually self-limited among immunocompetent hosts. Vaccinia immune globulin (VIG) might be beneficial in the rare case where an immunocompetent person appears systemically ill. GV is often more severe among persons with underlying immunodeficiency, and these patients might benefit from early intervention with VIG.

Notes:

1) Systemic symptoms might be present.
2) At early onset of some cases, skin lesions might be macules or slightly elevated papules; in late cases, lesions might have developed scabs.
3) History or clinical signs of eczema/atopic dermatitis or Darier's disease or severe illness should prompt evaluation for eczema vaccinatum.
4) Presence of acute or chronic exfoliative, erosive, or blistering skin disease (e.g., acute burn and epidermolytic hyperkeratosis) should prompt consideration of multiple inadvertent inoculations.
5) A vaccinial skin eruption characterized by grouped vesicles or pustules close to or surrounding the vaccination site but do not appear to be satellite lesions (e.g., on the basis of the presence of a large number of lesions and evidence that the lesions are caused by hematogenous spread of vaccinia) might constitute a regional form of generalized vaccinia.

Case definition for generalized vaccinia

A **probable case** of generalized vaccinia occurs in persons recently vaccinated or in a close contact of a recent vaccinee and meets the following criteria:

- a vesicular or pustular eruption at one or more body areas distant from the vaccination site or inadvertent inoculation site,
- skin eruption occurring approximately 4–19 days after smallpox vaccination or contact with someone vaccinated against smallpox,
- lesions follow approximately the same morphologic progression as a primary vaccination site (i.e., papule, vesicle, pustule, scab, and scar),
- unlikely that autoinoculation accounts for skin eruption, and
- other likely etiologies have been excluded.

A **confirmed case** of generalized vaccinia can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and no laboratory evidence of vaccinia infection (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site [if identifiable]) exists in a close contact of a known vaccinee or in a patient who is not known to be a close contact.

- Laboratory evidence of vaccinia infection includes
  — demonstration of vaccinia virus by culture
  or
  — histopathologic examination shows typical orthopox cytopathic changes, and either polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

used are considered more reactogenic than the New York City Board of Health (NYCBOH) vaccine used in the United States (*26–28*). In the United States, six cases were reported before the resumption of smallpox vaccination in late 2002 (*29–34*). Findings from the DHHS and DoD smallpox programs support a causal relation between smallpox vaccination with the NYCBOH strain and myo/pericarditis (*35–38*). Myo/pericarditis refers to inflammatory disease of the myocardium, pericardium, or both. The clinical presentation of inflammatory heart disease can include pain, dyspnea, and palpitations that range from subtle to severe. Results of specific cardiac diagnostic testing are variable. The case definition (Box 10) was designed to include the spectrum of abnormalities found in inflammatory heart disease (*39*).

Dilated Cardiomyopathy

An adverse event noted in temporal association to smallpox vaccination but not demonstrated to be linked etiologically to smallpox vaccination is dilated cardiomyopathy (DCM). DCM is a known sequelae of viral myocarditis and can present

BOX 6. Surveillance case definition for eczema vaccinatum after smallpox vaccination for use in smallpox vaccine adverse event monitoring and response

Eczema vaccinatum (EV) is a localized or generalized papular, vesicular, pustular, or erosive rash syndrome that can occur anywhere on the body, with a predilection for areas currently or previously affected by atopic dermatitis lesions. Persons with a history of atopic dermatitis are at highest risk for EV. Onset of the characteristic lesions can be noted either concurrently with or shortly after the development of the local vaccinial lesion in vaccinees. EV cases resulting from secondary transmission usually appear with skin eruptions approximately 5–19 days after the suspected exposure. EV lesions follow the same dermatologic course (progression) as the vaccination site in a vaccinee, and confluent or erosive lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are frequently systemically ill. EV tends to be most severe among first-time vaccinees, young children, and unvaccinated close contacts of vaccinees. Before the availability of vaccinia immune globulin (VIG), this condition had a high mortality. Establishing the diagnosis early and treating with VIG is crucial in reducing mortality.

Notes:

1) Although a history consistent with eczema/atopic dermatitis or Darier's disease (i.e., keratosis follicularis) is included in the surveillance definition for EV, clinicians evaluating vaccinees or close contacts of recent vaccinees with a presentation consistent with EV who do not report having one of these dermatologic conditions should still consider EV as a clinical diagnosis and assess for treatment with VIG.
2) Lesions of EV are in approximately the same stage of morphologic development as each other and progress.

Case definition for eczema vaccinatum

A **probable case** of EV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- a history of or current exfoliative skin condition consistent with a diagnosis of eczema/atopic dermatitis or Darier's disease;

and

- multiple skin lesions that developed
  - — in a vaccinated person concurrently or soon after lesion at vaccination site or in a close contact of a recent vaccinee up to 3 weeks after exposure, if time of relevant exposure is known,
  - — are distant from the vaccination or likely inoculation site (i.e., are unlikely to be satellite lesions),

and

  - — are or have become vesicular/pustular sometime during their evolution (i.e., do not remain macular or papular). Erosive or ulcerative lesions might be observed;

and

- other likely etiologies have been excluded such as eczema herpeticum (which can be particularly difficult to distinguish), smallpox, chickenpox, disseminated herpes zoster, or pustular (bacterial) impetigo.

A **confirmed case** of EV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and laboratory evidence of vaccinia infection exists (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site, if identifiable) in a close contact of a known vaccinee or in a patient who is not known to be a close contact.

- Laboratory evidence of vaccinia infection includes
  - — demonstration of vaccinia virus by culture

or

  - — polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia, histopathologic examination showing typical orthopox cytopathic changes, and electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

weeks to months after acute infection (*40*). Although DCM has not been reported in association with vaccinia vaccination, three DCM cases with symptom onset after smallpox vaccination were identified among DHHS vaccinees (*12,41,42*). The causal relation between smallpox vaccination and these cases of DCM is unclear. However, because vaccinia might induce myo/pericarditis and DCM is a rare but recognized outcome of viral myocarditis, an etiologic association between the occurrence of DCM after smallpox vaccination is biologically plausible. The case definition for DCM should be used for surveillance in the context of smallpox preparedness programs (Box 11).

BOX 7. Surveillance case definition for progressive vaccinia for use in smallpox vaccine adverse event monitoring and response

Progressive vaccinia (PV) refers to continued vaccinia virus replication with progressive infection of skin surrounding the vaccination site or inadvertent inoculation site and sometimes the occurrence of secondary metastatic lesions in a person with underlying immune deficit (humoral or cellular). The condition is rare, severe, and often lethal. The description of the vaccination site lesion is usually that of a necrotic lesion; however, this is not the only presentation described with PV. Lesions can appear "clean," fungated, piled-up, well-demarcated, or have bacterial superinfection.

Case definition for progressive vaccinia

A **suspected case** of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- have a known or suspected depressed or defective immune system (suspicion might arise as result of clinical suspicion of PV);

and

- have a vaccination site lesion or inadvertent inoculation site with one of the following criteria:
  - — no or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion,
  - — progressive expansion at or after 15 days of vaccination, or
  - — Failure to heal or failure of lesion to regress at or after 15 days of vaccination;

and

- other likely etiologies (e.g., bacterial superinfection) have been excluded.

A **probable case** of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- a known or suspected depressed or defective immune system

and

- a vaccination site lesion or inadvertent inoculation site with one of the following criteria:
  - — no or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion,
  - — progressive expansion at or after 21 days of vaccination, or
  - — failure to heal or failure of lesion to regress at or after 21 days of vaccination;

and

- other likely etiologies (e.g., bacterial superinfection) have been excluded.

A **confirmed case** of PV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a suspected case and laboratory evidence of vaccinia infection (on the basis of testing skin lesions at least 15 days after vaccination or likely time of inoculation in a close contact of a recent vaccinee or in persons with no known contact with a vaccinee) exist

Laboratory evidence of vaccinia infection include

- demonstration of vaccinia virus by culture

or

- histopathologic examination showing typical orthopox cytopathic changes, and either polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

Case Classification

Case definitions are designed to identify the entities under surveillance, not to define the certainty of an etiologic relation between the entities under surveillance and vaccinia exposure. Thus, cases are classified as suspected if they have compatible clinical features but either further investigation is required or investigation of the case did not provide enough supporting evidence for the diagnosis. Cases are classified as probable if they have compatible clinical features and information is supportive of, but not definitive for, the diagnosis. Cases are classified as confirmed if pathognomonic findings or other evidence definitely supporting the diagnosis is documented. In certain instances, confirmation is made on the basis of verification of the presence of vaccinia or of orthopox virus DNA by culture or polymerase chain reaction (PCR) detection. Confirmation also might be determined on the basis of other evidence in instances in which vaccinia presence is not a pathognomonic feature of the entity under surveillance (e.g., myocarditis or pericarditis, both of which are believed to be an immune-mediated response to vaccination rather than mediated through vaccinia viral infection).

Classification of certain smallpox adverse vaccine reactions can be confounded by lack of information or the absence of pathognomonic findings. This is illustrated by the limited un-

BOX 8. Surveillance case definition for fetal vaccinia for use in smallpox vaccine adverse event monitoring and response

Fetal vaccinia is a rare but serious complication resulting from vaccinia infection in utero that can occur in any trimester of pregnancy. It has been characterized by the presence of multiple skin lesions, including macules, papules, vesicles, pustules, scars, ulcers, areas of maceration, and epidermolysis (blisters or bullae). When fetal vaccinia occurs, the outcome is usually fetal death, stillbirth, or premature birth of a neonate that dies shortly after birth. Survival of babies with apparent in utero infection such as scarring has also been described. Vaccinia infection in products of conception occurs rarely.

Case definition for fetal vaccinia

A **suspected case** of fetal vaccinia is the presence of any skin lesion in a fetus or newborn exposed to vaccinia virus in utero and no other attributable cause.

A **probable case** of fetal vaccinia is the presence of multiple skin lesions that might include macules, papules, vesicles, pustules, scars, ulcers, areas of maceration, or epidermolysis (blisters/bullae) in a fetus or newborn exposed to vaccinia in utero and no other attributable cause.

A **confirmed case** of fetal vaccinia meets the criteria for a probable case and has laboratory evidence for vaccinial infection:

Laboratory criteria for diagnosis includes

- positive test results for vaccinia virus by polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody), or
- demonstration of vaccinia virus by culture.

Vaccinia infection: Fetus, newborn, or product of conception with laboratory evidence of infection and without any clinical symptoms or signs.

derstanding of the vaccinia virus' pathogenesis and the relevance of vaccinia testing in conditions such as postvaccinial CNS diseases and fetal vaccinia. No large-scale study examining the cerebral spinal fluid (CSF) of smallpox vaccinees exists; therefore, the significance of the presence or absence of vaccinia neutralizing antibodies or vaccinia virus recovered from the CSF of a vaccinee with CNS findings is not fully understood. Testing for the presence or absence of vaccinia virus cannot confirm or refute a smallpox vaccine-associated etiology for these conditions. Conversely, the inability to recover vaccinia virus from burnt-out lesions from an infant exposed to vaccinia in utero and born with skin lesions compatible with fetal vaccinia does not mean that intrauterine infection did not occur. To address these limitations, the suspected category for these adverse reactions allows a clinically compatible case with indeterminate or no testing to remain under consideration.

Vaccinia Laboratory Diagnostics

The smallpox vaccine is made from live vaccinia virus, a species of the Orthopoxvirus genus, and protects against smallpox disease. It does not contain the related Orthopoxvirus variola, which is the causative agent of smallpox disease (*25*). When evaluating a reported adverse event after smallpox vaccination, standard laboratory testing should be conducted to rule out other infections, including viral infections (e.g., herpes zoster, varicella, enteroviruses, and herpes simplex). During an outbreak of other orthopoxviruses (e.g., monkeypox and smallpox), specific testing also should be completed for these viruses.

Laboratory testing for vaccinia is still largely a research tool assisting the evaluation, diagnosis, and treatment of adverse reactions after smallpox vaccination. Testing is available through the Laboratory Response Network (LRN) (*43*), which can be accessed through state and local health departments with confirmatory testing at CDC. Diagnostic techniques that can aid in the detection of vaccinia include electron microscopy (EM), viral culture, and PCR (*17*). Although these tests can identify orthopoxviruses, only certain PCR tests or biologic characterization of viral growth on chick chorioallantoic membrane specifically identifies the presence of vaccinia virus. Positive results for EM, PCR, and viral culture should be interpreted with caution. EM or culture results compatible with orthopox virus and presumed to be vaccinia might be another zoonotic orthopox virus or, in the worst case scenario, variola itself. Experience with vaccinia diagnostics is limited. Molecular contamination resulting in false-positive PCR results can occur. Therefore, use of appropriate controls is essential. PCR techniques, which test for orthopoxvirus nucleic acid presence, at LRN have undergone multicenter validation studies, and these data along with clinical experience with these assays is being compiled to enable the U.S. Food and Drug Administration to review the test reagents and assay for wider diagnostic use (*17*). Serologic testing of single serum samples for vaccinia is of limited value because it cannot discern existing immunity from recent infection. Testing of paired acute and convalescent sera antibody titers is rarely available during initial assessment of a suspected vaccinia adverse event (*17*).

BOX 9. Surveillance case definition for postvaccinial central nervous system disease after smallpox vaccination for use in smallpox vaccine adverse event monitoring and response

Postvaccinial central nervous system disease is an inflammation of the parenchyma of the central nervous system after smallpox vaccination. When the inflammation occurs in the brain it is called "encephalitis," and when it occurs in the spinal cord it is called "myelitis." Confirmation of diagnosis is made only on the basis of the demonstration of central nervous system (CNS) inflammation by histopathology or neuroimaging, but might be suggested by clinical features.*

Case definition for encephalitis

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

- encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours)
- clinical evidence suggestive of cerebral inflammation to include one of the following:
  - — fever (temperature >100°F [>38°C]) or hypothermia (temperature <95°F [<35°C]),
  - — meningismus (i.e., nuchal rigidity and photo/phonophobia),
  - — cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells/mm^3),
  - — presence of focal neurologic deficit,
  - — electroencephalography findings consistent with encephalitis,
  - — neuroimaging findings on magnetic resonance imaging consistent with acute inflammation (with or without meninges) or demyelination of the nervous system, or
  - — seizures (either new onset or exacerbation of previously controlled seizures);

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

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

- encephalopathy as outlined for a suspected case,

and

- two or more of the criterion listed for suspected encephalitis as clinical evidence suggestive of cerebral inflammation,

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

A **confirmed case** of encephalitis is defined as

- demonstration of acute cerebral inflammation (with or without meninges) or demyelination by histopathology

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

Case definition for acute myelitis

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

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

and

- additional evidence suggestive of spinal cord inflammation, to include one of the following:
  - — fever (temperature >100°F [>38°C]) or hypothermia (temperature <95°F [<35°C]),
  - — CSF pleocytosis (>5 white blood cells/mm^3),
  - — presence of focal neurologic deficit,
  - — electromyographic (EMG) studies suggestive of central (spinal cord) dysfunction, or
  - — neuroimaging findings on MRI demonstrating acute inflammation (with or without meninges) or demyelination of the spinal cord,

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

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

- myelopathy as outlined for a suspected case,

and

- two or more of the criterion listed for suspected myelitis as evidence suggestive of spinal cord inflammation,

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

A **confirmed case** of myelitis is defined by

- demonstration of acute spinal cord inflammation (with or without meninges) or demyelination by histopathology,

and

- no alternative (investigated) etiologies are found for presenting sign and symptoms.

Note: Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as encephalomyelitis.

* Some cases of postvaccinial encephalomyelitis might be caused by direct infection of the CNS by vaccinia virus, resulting in acute cytotoxic neuronal damage and inflammation. However, laboratory evidence of virus replication is lacking in the majority of cases and might be attributable to immunopathological mechanisms instead. In the majority of cases, histopathologic findings similar to other "postinfectious" encephalitides are found, suggestive of an inflammatory demyelinating condition (acute disseminated encephalitis/encephalomyelitis [ADEM]). The distinction between these two pathologic mechanisms might be difficult to make clinically in the early stages of illness. A diagnosis of ADEM might be favored by a longer interval of onset after vaccination; magnetic resonance imaging findings of multifocal areas of increased signal on T2, fluid attenuation inversion recovery, and diffusion weighted imaging sequences, suggestive of acute demyelination; and an absence of CSF pleocytosis.

BOX 10. Surveillance case definition for myo/pericarditis for use in smallpox vaccine adverse event monitoring and response

Myo/pericarditis

Myo/pericarditis is defined as a spectrum of disease caused by inflammation of the myocardium and/or pericardium. Patients might have symptoms and signs consistent with myocarditis, pericarditis, or both. For the purpose of surveillance reporting, patients with myocarditis or pericarditis will be reported as having myo/pericarditis. These categories are intended for surveillance purposes and not for use in individual diagnosis or treatment decisions.

Case definition for acute myocarditis

A **suspected case** of acute myocarditis is defined by the following criteria and the absence of evidence of any other likely cause of symptoms or findings below:

- presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a patient with either one of the following:
  - — electrocardiogram (ECG) abnormalities beyond normal variants, not documented previously, including
    - – ST-segment or T-wave abnormalities,
    - – paroxysmal or sustained atrial or ventricular arrhythmias,
    - – AV nodal conduction delays or intraventricular conduction defects, or
    - – continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy

    or
  - — Evidence of focal or diffuse depressed left-ventricular (LV) function of indeterminate age identified by an imaging study (e.g., echocardiography or radionuclide ventriculography).

A **probable case** of acute myocarditis, in addition to the above symptoms and in the absence of evidence of any other likely cause of symptoms, has one of the following:

- elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred);
- evidence of focal or diffuse depressed LV function identified by an imaging study (e.g., echocardiography or radionuclide ventriculography) that is documented to be of new onset or of increased degree of severity (in the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow-up studies, these findings resolve, improve, or worsen); or
- abnormal result of cardiac radionuclide imaging (e.g., cardiac MRI with gadolinium or gallium-67 imaging) indicating myocardial inflammation.

A case of acute myocarditis is confirmed if histopathologic evidence of myocardial inflammation is found at endomyocardial biopsy or autopsy.

Case definition for acute pericarditis

A suspected case of acute pericarditis is defined by the presence of

- typical chest pain (i.e., pain made worse by lying down and relieved by sitting up and/or leaning forward) and
- no evidence of any other likely cause of such chest pain.

A **probable case** of acute pericarditis is a suspected case of pericarditis, or a case in a person with pleuritic or other chest pain not characteristic of any other disease, that, in addition, has one or more of the following:

- pericardial rub, an auscultatory sign with one to three components per beat,
- ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions that are not previously documented, or
- echocardiogram indicating the presence of an abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or a large posterior pericardial effusion alone).

Note: A case of acute pericarditis is confirmed if histopathologic evidence of pericardial inflammation is evident from pericardial tissue obtained at surgery or autopsy.

Surveillance Results and Outcome

The voluntary DHHS civilian smallpox preparedness and response program established adverse event case monitoring capacity and response within CDC and state and local health departments. Data collected were derived from the standardized case definitions and enabled rapid classification, reporting, and the ability to compare adverse reaction surveillance data from various sources. Accurate classification of vaccinia adverse reactions is necessary for appropriate use of VIG and cidofovir for the treatment of select vaccinia reactions.

Conclusions

Surveillance case definitions rely on a constellation of clinical, laboratory, and epidemiologic criteria for classification. They are not intended to replace clinical judgment and should not be used to direct individual patient care, assess causality, or determine disability compensation or reimbursement for medical care. The definitions have been developed specifically for the surveillance of adverse events during the voluntary DHHS civilian smallpox preparedness and response program and might not apply to vaccinees in other settings (e.g., clini-

BOX 11. Surveillance case definition for dilated cardiomyopathy for use in smallpox vaccine adverse event monitoring and response

Dilated cardiomyopathy (DCM) is defined by the World Health Organization as a disease of the heart muscle characterized by dilatation and impaired contraction of the left ventricle or both ventricles. It might be idiopathic, familial/genetic, viral, and/or immune, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. Histology is nonspecific. Presentation is usually with heart failure, which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and can occur at any stage. Despite full cardiac workup, the etiology of DCM often cannot be determined. Because other viruses are known to cause DCM, the occurrence of DCM after smallpox vaccination is plausible, although not previously described. Because histologic findings of DCM are often nonspecific, endomyocardial biopsy is not likely to confirm an etiologic role for vaccinia but might rule out other known etiologies of DCM (e.g., sarcoidosis and amyloidosis). The following case definition describes the structural and functional cardiac criteria and clinical conditions required to define a case of DCM for use in the smallpox adverse events monitoring and response activity.

Case definition for dilated cardiomyopathy after smallpox vaccination

Smallpox vacinees are defined as having DCM if they meet all of the following criteria:

- cardiac muscle dysfunction exists, characterized by ventricular dilatation (e.g., left ventricular end-diastolic dimension >55 mm) and impaired contraction of one or both ventricles (e.g., left ventricular ejection fraction $\leq$0.45);
- no evidence of DCM or congestive heart failure before vaccination, either by history (e.g., dyspnea on exertion and fatigue) or by cardiac evaluation, including chest radiography or echocardiography if available; and
- no other cardiac or noncardiac disease can account for the symptoms or abnormalities present. If another cardiac disease coexists, it is not sufficient to cause the degree of myocardial dysfunction present (e.g., ischemic or valvular heart disease or long-standing hypertension). No other etiology of DCM can be determined, such as alcohol or cocaine use, hypertension, morbid obesity, or other causes.

cal trials). These surveillance case definitions might not apply to the international community, which administers non-NYCBOH vaccinia strains and faces different considerations in health-care use and surveillance systems. These case definitions are a component of a dynamic surveillance process. As knowledge and experience increase, they might be modified or improved. Ongoing input from health-care providers and health departments are important for the successful implementation and use of these case definitions.

References

1. CDC. Case definitions for infectious conditions under public health surveillance. MMWR 1997;46(No. RR-10).
2. Iskander JK, Miller ER, Pless RP, Chen RT. Vaccine safety post-marketing surveillance: the Vaccine Adverse Event Reporting System. Atlanta, GA: US Department of Health and Human Services, CDC, National Immunization Program; 2002. Available at http://www.cdc.gov/nip/vacsafe/VAERS/CME-post-mktg-surv.pdf.
3. CDC. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. In: Surveillance Summaries, January 24, 2003. MMWR 2003;52(No. SS-1).
4. US Department of Health and Human Services. Declaration regarding administration of smallpox countermeasures. Federal Register 2003;68:4212–3.
5. Grabenstein JD, Winkenwerder W. US military smallpox vaccination program experience. JAMA 2003;289:3278–82.
6. CDC. Update: adverse reactions following civilian smallpox vaccination—United States, 2003. MMWR 2003;52:475–7.
7. Lane JM, Millar JD, Neff JM. Smallpox and smallpox vaccination policy. Annu Rev Med 1971;22:251–72.
8. Neff JM, Levine RH, Lane JM, et al. Complications of smallpox vaccination—United States 1963. II: results obtained by four statewide surveys. Pediatrics 1967;39:916–23.
9. Neff JM, Lane JM, Pert JH, Moore R, Millar JD, Henderson DA. Complications of smallpox vaccination. I: national survey in the United States, 1963. N Engl J Med 1967;276:125–32.
10. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis 1970;122:303–9.
11. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination: national surveillance in the United States, 1968. N Engl J Med 1969;281:1201–7.
12. Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States, January–October 2003. JAMA 2005;294:2734–43.
13. Postmarking reporting of adverse experiences, 21 CFR Part 600.80. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdoes/cfefr/CFRSearc.cfm?FR=600.80.
14. CDC. Smallpox (vaccinia) vaccine and adverse event reporting. Available at http://www.bt.cdc.gov/agent/smallpox/vaccination/ae-reporting.asp.
15. CDC. Women with smallpox vaccine exposure during pregnancy reported to the National Smallpox Vaccine in Pregnancy Registry—United States, 2003. MMWR 2003;52:386–8.
16. Vellozzi C, Averhoff F, Lane JM, et al. Superinfection following smallpox vaccination (vaccinia), United States: surveillance January 2003 through January 2004. Clin Infect Dis 2004; 39:1660–6.

17. CDC. Smallpox vaccination and adverse reactions: guidance for clinicians. MMWR 2003;52(No. RR-4).
18. Sepkowitz KA. Current concepts: how contagious is vaccinia? N Engl J Med 2003;348.
19. Habif TP. Clinical Dermatology. 3rd ed. Mosby-Year Book, Inc.; 1996.
20. Hurwitz S. Clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence. 2nd ed. Philadelphia, PA: W.B. Saunders; 1993.
21. Neff JM, Lane JM, Fulginiti VA, Henderson DA. Contact vaccinia-transmission of vaccinia from smallpox vaccination. JAMA 2002;288:1901–5.
22. Vellozzi C, Lane JM, Averhoff F, et al. Generalized Vaccinia, progressive vaccinia and eczema vaccinatum are rare following smallpox (Vaccinia) vaccination: United States surveillance, 2003. Clin Infect Dis 2005;41:689–97.
23. Naleway AL, Belongia EA, Greenlee RT, Kieke Jr BA, Chen RT, Shay DK. Eczematous skin disease and recall of past diagnoses: implications for smallpox vaccination. Ann Intern Med 2003;139:1–7.
24. Belongia EA, Naleway A, Kieke B, et al. Validation of a screening instrument to identify persons for exclusion from smallpox vaccination. Clin Infect Dis 2005;40:620–3.
25. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva, Switzerland: World Health Organization; 1988.
26. Feery BJ. Adverse reactions after smallpox vaccination. Med J Aust 1977;2:180–3.
27. Marennikova SS. Evaluation of vaccine strains by their behavior in vaccinated animals and possible implications of the revealed features for smallpox vaccination practice. Presented at the International Symposium on Smallpox Vaccine, Bilthoven, The Netherlands, October 11–13, 1972.
28. Karjalainen J, Heikkila J, Markku S, et al. Etiology of mild acute infectious myocarditis. Acta Med Scand 1983;213:65-73.
29. CDC. Update: adverse reactions following smallpox vaccination—United States, 2003. MMWR 2003;52:278–82.
30. Dolgopol VB, Greenberg M, Aronoff R. Encephalitis following smallpox vaccination. AMA Arch of Neuro Psych.1955;73:216–23.
31. Phillips M, Rabinowitz M, Higgins JR, Boran KJ, Reed T, Virmani R. Sudden cardiac death in Air Force recruits; a 20-year review. JAMA 1986;256:2696–9.
32. McNalley MC, Qamar Y. Cardiac complications of progressive generalized vaccinia. Report of a case. Dis Chest 1966;49:333–5.
33. Cangemi VF. Acute pericarditis after smallpox vaccination. N Engl J Med 1958;258:1257–9.
34. Mead J. Serum transaminase and electrocardiographic findings after smallpox vaccination: case report. J Am Geriat Soc 1966;14:754–65.
35. CDC. Update: adverse reactions following civilian smallpox vaccination—United States, 2003. MMWR 2003;52:313–5.
36. Chen RT, Lane JM. Myocarditis: the unexpected return of smallpox vaccine adverse events [Commentary]. Lancet 2003;362:1345–6.
37. Halsell JS, Riddle JR, Atwood JE, et al. Myopericardits following smallpox vaccination among vaccinia-naïve US military personnel. JAMA 2003;289:3283–9.
38. Arness MK, Eckart RE, Love SS, et al. Myopericarditis following smallpox vaccination. Am J Epidemiol 2004;160:642–51.
39. CDC. Update: Cardiac-related events during the civilian smallpox vaccination program—United States, 2003. MMWR 2003; 52:492–496.
40. Dec GW, Fuster V. Medical progress: idiopathic DCM. N Engl J Med 1994;331:1564–75.
41. CDC. Record of the meeting of the Advisory Committee on Immunization Practices, October 27–28, 2004. Available at http://www.cdc.gov/nip/acip/minuties.htm.
42. CDC. Update: cardiac and other adverse events following civilian smallpox vaccination—United States, 2003. MMWR 2003;52:639–42.
43. CDC. Biological and chemical terrorism: strategic plan for preparedness and response. MMWR 2000;49(No. RR-4).

The Vaccinia Case Definition Development Working Group

Francisco Averhoff, MD, Karen Broder, MD, Christine Casey, MD, Inger Damon, MD, Michael Deming, MD, Daniel B. Fishbein, MD, Susan Goldstein, MD, La Mar Hasbrouck, MD, James D Heffelfinger, MD, Barbara Herwaldt, MD, Kristen Kenyan, Katrin Kohl, MD, Andrew Kroger, MD, Herschel W. Lawson, MD, Sheryl Lyss, MD, Anne C. Moore, MD, Gina T. Mootrey, DO, Juliette Morgan, MD, Joe Mulinare, MD, Linda Neff, PhD, Monica E. Parise MD, Russell Regnery PhD, Martha H. Roper, MD, Scott Santibanez, MD, Richard A. Schieber, MD, James Sejvar, MD, Jane F. Seward, MBBS, David L. Swerdlow, MD, Bruce C. Tierney, MD, Thomas J. Török, MD, Claudia Vellozzi, MD, Charles R. Vitek, MD, CDC; J Edwin Atwood, MD, R. Dana Bradshaw, MD, Limone C. Collins, MD, Laurie L. Duran, Robert E. Eckart, MD, Renata J. Engler, MD, Jeffrey S. Halsell, MD, Mylene T. Huynh, MD, Robert J. Labutta, MD, Felisa S. Lewis, MD, Scott A. Norton, MD, Margaret Ryan, MD, US Department of Defense; Vincent A. Fulginiti, MD, Health Science Center, University of Arizona; J. Michael Lane, MD (retired), Smallpox Eradication Program, Communicable Disease Center; Laurence S. Sperling, MD, Section of Preventive Cardiology, Emory University School of Medicine, Atlanta, Georgia.

Advisory Committee on Immunization Practices-Armed Forces Epidemiological Board Smallpox Vaccine Safety Working Group

Chairs: John F. Modlin, MD, Dartmouth Medical School; John Neff, MD, University of Washington, Seattle; Guthrie Birkhead, MD, New York State Department of Health

Members: Fernando A. Guerra, MD, San Antonio Metropolitan Health District, Texas; Pierce Gardner, MD, New York State University–Stony Brook; Gregory Poland, MD, Mayo Clinic; W. Dana Flanders, MD, Emory University, Rollins School of Public Health, Atlanta, Georgia; Gregory C. Gray, MD, University of Iowa College of Public Health, Iowa City; Robert Shope, MD, University of Texas at Galveston (deceased); Rose Marie Robertson, MD, American Heart Association; Clyde Yancy, MD, University of Texas Southwestern, Dallas; Toby Maurer, MD, Tim Berger, MD, University of California–San Francisco; Kent A. Sepkowitz, MD, Memorial Sloan Kettering; Jane Siegel, MD, University of Texas Southwestern, Dallas.

Ex-Officio Representatives: DoD: James R. Riddle, DVM, Roger L. Gibson, PhD, U.S. Air Force, Office of Health Affairs; John D. Grabenstein, PhD, U.S. Army, Military Vaccine Agency, Office of the Army Surgeon General, U.S. Department of Defense. Karen Goldenthal, MD, Ann McMahon, MD, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration; Vito M. Caserta, MD, Carol Konchan, MD, Health Resources and Services Administration; Linda Quick, MD, Louisa Chapman, MD, National Immunization Program, CDC.

Consultants: Michael D. Blum, MD, Leslie A. Killion, MD, Wyeth Research.

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | February 3, 2006 / Vol. 55 / No. RR-1

Continuing Education Activity Sponsored by CDC

Surveillance Guidelines for Smallpox Vaccine (vaccinia) Adverse Reactions

EXPIRATION — February 3, 2009

You must complete and return the response form electronically or by mail by **February 3, 2009**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 1.75 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 1.9 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 55, RR-1), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **February 3, 2009**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 55, RR-1), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **February 3, 2009**, to
   Fax: 770-488-8555
   Mail: MMWR CE Credit
   Division of Scientific Communications
   Coordinating Center for Health Information and Service, MS K-95
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.75 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training. CDC will award 0.15 continuing education units to participants who successfully complete this activity.

Continuing Nursing Education (CNE). This activity for 1.9 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This *MMWR* provides surveillance guidelines for adverse reactions after smallpox vaccination. The case definitions and classifications were developed by CDC, in conjunction with staff of the Department of Defense, the Advisory Committee on Immunization Practices-Armed Forces Epidemiological Board Smallpox Vaccine Safety Working Group, and smallpox subject-matter experts. The goal of this report is to provide the case definitions used to classify reported adverse events after smallpox vaccination during the 2003 Department of Health and Human Services (DHHS) smallpox vaccination program. Upon completion of this educational activity, the reader should be able to 1) identify the known adverse reactions to smallpox vaccination and be familiar with their case definitions, 2) recognize the importance of reporting adverse events after smallpox vaccination, 3) describe those adverse reactions after smallpox vaccination that require laboratory confirmatory testing for vaccinia, and 4) describe when and how to report all adverse events after vaccination.

To receive continuing education credit, please answer all of the following questions.

1. Which of the following can fulfill the criteria for exposure to vaccinia?
- A. Smallpox vaccination.
- B. Close contact with a recent smallpox vaccinee.
- C. Intrauterine exposure.
- D. A and B are correct.
- E. All of the above.

2. Normal vaccination reactions are often confused with…
- A. superinfection of the vaccination site.
- B. generalized vaccinia.
- C. eczema vaccinatum.
- D. none of the above.

3. Contact transmission can occur as a result of which of the following?
- A. generalized vaccinia.
- B. progressive vaccinia.
- C. eczema vaccinatum.
- D. All of the above.

4. When evaluating a reported adverse event after smallpox vaccination, standard laboratory testing should include…
- A. herpes zoster virus.
- B. enteroviruses.
- C. herpes simplex virus.
- D. other orthopox viruses during specific outbreaks.
- E. all of the above.

5. Eczema vaccinatum and progressive vaccinia are adverse reactions after smallpox vaccination and…
- A. thought to be associated with replicating vaccinia virus recovered from skin lesions.
- B. are benign and self-limited.
- C. usually require vaccinia immune globulin (VIG).
- D. often can be prevented by screening persons before smallpox vaccination.
- E. A, C, and D.

6. Reports to the Vaccine Adverse Event Reporting System can be submitted…
- A. by fax.
- B. mail.
- C. on line.
- D. all of the above.

7. Surveillance case definitions for adverse events after smallpox vaccination during the DHHS smallpox preparedness and response program can…
- A. enable classification and reporting of adverse events after smallpox vaccination.
- B. direct patient care.
- C. assess causality.
- D. determine disability compensation.
- E. A and C.

8. All of the following are adverse reactions after smallpox vaccination except…
- A. superinfection.
- B. contact transmission.
- C. ocular vaccinia.
- D. generalized vaccinia.
- E. dilated cardiomyopathy.
- F. myo/pericarditis.

9. Ocular vaccinia accounts for the majority of inadvertent inoculations.
- A. True.
- B. False.

10. Without standardized case definitions, health-care providers often apply different criteria for reporting similar cases.
- A. True.
- B. False.

11. Which best describes your professional activities?
- A. Physician.
- B. Nurse.
- C. Health educator.
- D. Office staff.
- E. Other.

12. I plan to use these recommendations as the basis for …*(Indicate all that apply.)*
- A. health education materials.
- B. insurance reimbursement policies.
- C. local practice guidelines.
- D. public policy.
- E. other.

13. Overall, the length of the journal report was…
- A. much too long.
- B. a little too long.
- C. just right.
- D. a little too short.
- E. much too short.

14. After reading this report, I am confident I can identify the known adverse reactions to smallpox vaccination, and I am familiar with their case definitions.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I recognize the importance of reporting adverse events after smallpox vaccination.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe those adverse reactions after smallpox vaccination that require laboratory confirmatory testing for vaccinia.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe when and how to report adverse reactions to vaccination.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. The learning outcomes (objectives) were relevant to the goals of this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. The boxes and table (instructional strategies) used in this report helped me learn the material.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. The content was appropriate given the stated objectives of the report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

MMWR Response Form for Continuing Education Credit
February 3, 2006/Vol. 55/No. RR-1
Surveillance Guidelines for Smallpox Vaccine (vaccinia) Adverse Reactions

To receive continuing education credit, you must
1. provide your contact information (**please print or type**);
2. indicate your choice of CME, CME for nonphysicians, CEU, or CNE credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by **February 3, 2009**.

Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Check One
☐ CME Credit
☐ CME for nonphysicians Credit
☐ CEU Credit
☐ CNE Credit

Last Name (**print or type**) First Name

Street Address or P.O. Box

Apartment or Suite

City State ZIP Code

Phone Number Fax Number

E-Mail Address

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A [ ]B [ ]C [ ]D [ ]E	15. [ ]A [ ]B [ ]C [ ]D [ ]E		
2. [ ]A [ ]B [ ]C [ ]D	16. [ ]A [ ]B [ ]C [ ]D [ ]E		
3. [ ]A [ ]B [ ]C [ ]D	17. [ ]A [ ]B [ ]C [ ]D [ ]E		
4. [ ]A [ ]B [ ]C [ ]D [ ]E	18. [ ]A [ ]B [ ]C [ ]D [ ]E		
5. [ ]A [ ]B [ ]C [ ]D [ ]E	19. [ ]A [ ]B [ ]C [ ]D [ ]E		
6. [ ]A [ ]B [ ]C [ ]D	20. [ ]A [ ]B [ ]C [ ]D [ ]E		
7. [ ]A [ ]B [ ]C [ ]D [ ]E	21. [ ]A [ ]B [ ]C [ ]D [ ]E		
8. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F	22. [ ]A [ ]B [ ]C [ ]D [ ]E		
9. [ ]A [ ]B	23. [ ]A [ ]B [ ]C [ ]D [ ]E		
10. [ ]A [ ]B	24. [ ]A [ ]B [ ]C [ ]D [ ]E		
11. [ ]A [ ]B [ ]C [ ]D [ ]E	25. [ ]A [ ]B [ ]C [ ]D [ ]E		
12. [ ]A [ ]B [ ]C [ ]D [ ]E	26. [ ]A [ ]B		
13. [ ]A [ ]B [ ]C [ ]D [ ]E	27. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F		
14. [ ]A [ ]B [ ]C [ ]D [ ]E			

Signature ***Date I Completed Exam***

21. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree

22. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

23. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

25. The *MMWR* format was conducive to learning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

26. Do you feel this course was commercially biased? *(Indicate yes or no; if yes, please explain in the space provided.)*
A. Yes.
B. No.

27. How did you learn about the continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. E; 2. A; 3. D; 4. E; 5. E; 6. D; 7. A; 8. E; 9. A; 10. A.

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format and on a paid subscription basis for paper copy. To receive an electronic copy each week, send an e-mail message to *listserv@listserv.cdc.gov*. The body content should read *SUBscribe mmwr-toc*. Electronic copy also is available from CDC's World-Wide Web server at *http://www.cdc.gov/mmwr* or from CDC's file transfer protocol server at *ftp://ftp.cdc.gov/pub/publications/mmwr*. To subscribe for paper copy, contact Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Address inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop K-95, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone 888-232-3228.

All *MMWR* references are available on the Internet at http://www.cdc.gov/mmwr. Use the search function to find specific articles.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

☆U.S. Government Printing Office: 2006-523-056/40018 Region IV ISSN: 1057-5987