NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC)
GUIDELINE SYNTHESIS

SMALLPOX VACCINATION

Guidelines

1. Center for Civilian Biodefense Strategies (CCBS). (1) Smallpox as a biological weapon: medical and public health management. (2) Smallpox as a biological weapon. (Addendum). JAMA 1999 Jun 9; 281(22): 2127-37. [51 references]; In: Henderson DA, Inglesby TV, O'Toole T, editor(s). Bioterrorism: guidelines for medical and public health management. Chicago (IL): American Medical Association; 2002. p. 99-120. [53 references]
2. Centers for Disease Control and Prevention (CDC).
    - Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. MMWR Recomm Rep 2001 Jun 22; 50(RR-10): 1-25, CE1-7. [89 references]
    - Smallpox vaccination and adverse reactions. MMWR Recomm Rep 2003 Feb 21;52(RR-04):1-28. [82 references]
    - Recommendations for using smallpox vaccine in a pre-event smallpox vaccination program. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 2003 Apr 4;52(RR-7):1-16. [52 references] **(a)**
    - Supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2003 Apr 4;52(13):282-4. [5 references] **(b)**

INTRODUCTION:

A direct comparison of the guideline recommendations for smallpox vaccination from the Center for Civilian Biodefense Strategies (CCBS) and the Centers for Disease Control and Prevention (CDC) is provided in the five tables, below. Table 1 compares objective and scope, target population, intended users and interventions and practices considered. Table 2 focuses on recommendations for smallpox vaccination and considers who should be vaccinated, when the vaccine should be administered, the method of vaccine administration, typical and non-typical responses and prevention of

contact transmission. Table 3 concerns potential complications of vaccination, recommended treatment options for those complications, and contraindications to treatment. Table 4 compares recommendations regarding groups at special risk for complications from vaccination. Table 5 contains a comparison of potential benefits and harms associated with vaccination and treatment for vaccine-related complications. Where applicable, information contained in the tables has been updated to reflect the most current guidelines from each organization. Because the focus of this Synthesis is smallpox vaccination, diagnosis and treatment of smallpox infection; infection control measures, such as quarantine and other hospital procedures; and decontamination are not considered.

Although the CCBS and CDC produced separate guidelines with different focuses, the development process appears cooperative. An individual from the CDC served on CCBSï¿½ guideline work group, and the lead author of the CCBS guideline participated in the preparation of the 2001 and February 2003 CDC recommendations.

When the CCBS and 2001 CDC guidelines were published, there were inadequate amounts of smallpox vaccine and vaccinia immune globulin (VIG) available for an effective large-scale vaccination program, even when targeting at-risk individuals, such as health care workers first responding to persons infected with smallpox. However, by the beginning of 2003, there were sufficient amounts of vaccine and VIG available to begin vaccination of smallpox public health response and health care teams. The CDC guideline recommendations included in this Synthesis reflect this updated status.

Following the content comparison tables, areas of agreement and differences between the guidelines are identified by topic.

Abbreviations:
ACIP, Advisory Committee on Immunization Practices
AIDS, Acquired immune deficiency syndrome
CCBS, Center for Civilian Biodefense Strategies
CDC, Centers for Disease Control and Prevention
DoD, US Department of Defense
FDA, US Food and Drug Administration
HICPAC, Healthcare Infection Control Practices Advisory Committee
HIV, Human immunodeficiency virus
IND, Investigational New Drug
NGC, National Guideline Clearinghouse
VIG, Vaccinia immune globulin

TABLE 1: COMPARISON OF SCOPE AND CONTENT
OBJECTIVE AND SCOPE

CCBS (1999, 2002)	• To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of smallpox as a biological weapon against a civilian population
CDC (2001-2003)	**June 2001** • To provide guidance for the use of vaccinia (smallpox) vaccine in the United States • To update the previous Advisory Committee on Immunization Practices recommendations (MMWR 1991;40; No. RR-14:1?10) and include current information regarding the nonemergency use of vaccinia vaccine among laboratory and health-care workers occupationally exposed to vaccinia virus, recombinant vaccinia viruses, and other orthopoxviruses that can infect humans • To present recommendations for the use of vaccinia vaccine if smallpox (variola) virus were used as an agent of biological terrorism or if a smallpox outbreak were to occur for another unforeseen reason **February 2003** • To provide guidance for evaluation and treatment of patients with complications from smallpox vaccination in the preoutbreak setting. • To provide information related to reporting adverse events and seeking specialized consultation and therapies for these events. **April 2003 (a)** • To supplement and update the 2001 Advisory Committee on Immunization Practices (ACIP) recommendations for vaccination of persons designated to respond or care for a suspected or confirmed case of smallpox • To clarify and expand the primary strategy for control and containment of smallpox in the event of an outbreak **April 2003 (b)** • To provide recommendations about medical screening of potential vaccinees and follow-up of persons with cardiovascular risk factors after vaccination • To supplement recommendations previously issued by the Advisory Committee on Immunization Practice

	(ACIP)
TARGET POPULATION	
CCBS (1999, 2002)	• Adults, pregnant women, children, and immunosuppressed persons exposed to or infected with smallpox as a biological weapon
CDC (2001-2003)	**June 2001** • Laboratory and health-care workers occupationally exposed to vaccinia virus, recombinant vaccinia viruses, and other orthopoxviruses that can infect humans • Individuals exposed to smallpox virus as a result of deliberate release by terrorists or for other unforeseen reasons **February 2003** • Members of smallpox public health response and health care teams • Persons who present with complications arising from smallpox vaccination **April 2003 (a)** • *Smallpox Response Teams:* Persons designated by the appropriate terrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases that might necessitate direct patient contact, as well as persons responsible for administering smallpox vaccine in the pre-event smallpox vaccination program. • *Smallpox Health Care Teams:* Acute care hospital healthcare workers expected to provide direct medical care for the first few smallpox patients requiring hospital admission, and those who would evaluate and manage patients who are examined at emergency departments with suspected smallpox. **April 2003 (b)** • Myocarditis/pericarditis related to smallpox vaccination • Cardiac ischemic events related to smallpox vaccination

INTENDED USERS	
CCBS (1999, 2002)	Allied Health Practitioners; Clinical Laboratory Personnel; Hospitals; Nurse Practitioners; Nurses; Physician Assistants; Physicians; Public Health Departments
CDC (2001-2003)	**June 2001** Allied Health Practitioners; Clinical Laboratory Personnel; Health Care Providers; Nurse Practitioners; Nurses; Physician Assistants; Physicians; Public Health Departments **February 2003** Physicians **April 2003 (a)** Allied Health Care Practitioners; Health Care Providers; Hospitals; Nurse Practitioners; Nurses; Physician Assistants; Physicians **April 2003 (b)** Allied Health Care Practitioners; Health Care Providers; Hospitals; Nurse Practitioners; Nurses; Physician Assistants; Physicians
INTERVENTIONS AND PRACTICES CONSIDERED	
CCBS (1999, 2002)	**Preexposure Interventions** *Prevention* 1. Nonemergency vaccination 2. Preexposure vaccination program **Postexposure Interventions** *Diagnosis* *Treatment* *Management during emergency* 1. Targeted smallpox vaccination • Detailed medical history including assessment for contraindications to vaccination

	• Prophylactic vaccinia immune globulin (VIG) as indicated • Use of correct vaccination technique • Prevention of contact transmission • Monitor vaccination response and revaccinate as needed • Assess for complications from vaccination • Treatment with VIG as indicated • Consultation for complications as needed 2. Infection control measures, including: • Home isolation/quarantine • Designation of separate hospitals for smallpox patients • Use of patient rooms with negative pressure and equipped with HEPA filters 3. Use of standard precautions by hospital staff 4. Proper disposal of biohazardous waste and decontamination 5. Use of high-containment laboratory facilities
CDC (2001-2003)	**Preexposure Interventions** *Prevention* **Nonemergency Vaccination** 1. Detailed medical history including assessment for contraindications to vaccination 2. Use of correct vaccination technique 3. Prevention of contact transmission 4. Monitor vaccination response and revaccinate as needed 5. Assess for complications • Treatment with vaccinia immune globulin (VIG) as indicated • Consultation for complications as needed 6. Follow-up for routine revaccination **Targeted Vaccination Program** 1. Medical history including assessment for contraindications to vaccination and screening for precautions such as underlying cardiac disease or cardiac risk factors, inflammatory eye disease, simultaneous vaccination with varicella vaccine, recent tuberculosis skin test (PPD) 2. Calf-lymph derived vaccine, Dryvax(R), containing New York City Board of Health (NYCBOH) vaccinia

strain
3. Use of correct vaccination technique
4. Patient education to prevent contact transmission
5. Interpretation of vaccination response (major or equivocal)
6. Treatment for robust takes (RTs) including rest of affected limb, use of oral nonaspirin analgesic medications, as well as oral antipruritic agents.
7. Revaccination as indicated
8. Treatment/management of adverse reactions including:
    - Diagnosis of type and severity of reaction
    - Consultation with appropriate specialists as indicated
    - Treatment:
        1. Medication, such as:
            - Vaccinia immune globulin (VIG) as first line therapy
            - Cidofovir as second line therapy (Vistide(R))
            - Topical ophthalmic antiviral drugs NOTE: VIG and cidofovir are available under Investigational New Drug protocols
        2. Infection control measures
        3. Symptom management
        4. Hospitalization and supportive care

Postexposure Interventions

Diagnosis

Treatment

Management during emergency

1. Report suspected smallpox to local/state health departments
2. Clinical consultation through Centers for Disease Control and Prevention (CDC)
3. Laboratory confirmation
4. Targeted vaccination program
5. Infection control measures, including:
    - Surveillance
    - Home isolation
    - Designation of separate hospitals for smallpox patients
    - Use of patient rooms with negative pressure and equipped with HEPA filters
    - Use of standard and contact precautions by hospital staff

	• Proper disposal of biohazardous waste and decontamination

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR SMALLPOX VACCINATION	
NONEMERGENCY VACCINE USE: WHO SHOULD BE VACCINATED	
CCBS (1999, 2002)	Smallpox vaccine is currently approved by the US Food and Drug Administration (FDA) for use only in persons in special-risk categories, including laboratory workers directly involved with smallpox or closely related orthopoxviruses.
CDC (2001)	Vaccinia vaccine is recommended for laboratory workers who directly handle: • Cultures or • Animals contaminated or infected with, nonhighly attenuated vaccinia virus, recombinant vaccinia viruses derived from nonhighly attenuated vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, vaccinia, and variola). Other health-care workers (e.g., physicians and nurses) whose contact with nonhighly attenuated vaccinia viruses is limited to contaminated materials (e.g., dressings) but who adhere to appropriate infection control measures are at lower risk for inadvertent infection than laboratory workers. However, because a theoretical risk for infection exists, vaccination can be offered to this group. Vaccination is not recommended for persons who do not directly handle nonhighly attenuated virus cultures or materials or who do not work with animals contaminated or infected with these viruses. **Revaccination Schedule** According to data regarding the persistence of neutralizing antibody after vaccination, persons working with nonhighly attenuated vaccinia viruses, recombinant viruses developed from nonhighly attenuated vaccinia viruses, or other nonvariola orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola orthopoxviruses (e.g., monkeypox), empiric

	revaccination every 3 years can be considered.
PREEXPOSURE: WHO SHOULD BE VACCINATED	
CCBS (1999, 2002)	Because of the small amounts of vaccine available, a preventive vaccination program to protect individuals such as emergency and health care personnel is not an option at this time. When additional supplies of vaccine are procured, a decision to undertake preventive vaccination of some portion of the population will have to weigh the relative risk of vaccination complications against the threat of contracting smallpox. Production of vaccine has begun with the expectation that a total of 280 million doses of vaccine would be available by late 2002. Before extensive vaccination can be undertaken, adequate supplies of vaccinia immune globulin (VIG) for use in the treatment of progressive vaccinia and severe cutaneous reactions occurring as a complication of vaccination must be available. Such supplies are now being procured for the United States.

CDC (Feb 2003, Apr 2003 [a])	In October 2002, the advisory committee on immunization practices (ACIP) recommended that enhanced terrorism preparedness should include vaccination of smallpox public health response and health care teams.
	
	• *Smallpox Response Teams:* This may include: medical team leaders, public health advisors, medical epidemiologists, disease investigators, diagnostic laboratory scientists, nurses, personnel who would administer smallpox vaccines, and security or law enforcement personnel, and other medical personnel to assist in evaluating suspected smallpox cases.
	• *Smallpox Health Care Teams:* These teams may include:
	  • Emergency room staff, including physicians and nurses caring for children and adults;
	  • Intensive care unit staff, including physicians, nurses, and in hospitals that care for infants and children, pediatricians and pediatric intensive care specialists;
	  • General medical unit staff, including nurses, internists, pediatricians, hospitalists, and family physicians in institutions where these individuals are the essential providers of primary medical care;
	  • Primary care house staff (i.e., medical, pediatric, and family physicians);
	  • Medical subspecialists, including infectious

disease specialists
- (Note: This may involve the creation of regional teams of subspecialists [e.g., local medical consultants with smallpox experience, dermatologists, ophthalmologists, pathologists, surgeons, anesthesiologists in facilities where intensivists are not trained in anesthesia] to deliver consultative services.);
- Infection control professionals;
- Respiratory therapists;
- Radiology technicians;
- Security personnel; and
- Housekeeping staff (e.g., those staff involved in maintaining the health care environment and decreasing the risk of fomite transmission)

Note: Clinical laboratory workers are not recommended for inclusion in the initial phase of pre-event smallpox vaccination.

Vaccinating Persons Administering Smallpox Vaccine in the Pre-Event Vaccination Program

Historically, vaccinators were administering smallpox vaccine as part of a disease control or eradication program, and were revaccinated frequently. No data exist regarding the risks for inadvertent inoculation of vaccinia among susceptible vaccinators, but they are assumed to have a certain level of risk. The risk might be analogous to that observed among laboratory workers handling non-highly attenuated vaccinia strains; ACIP currently recommends that these workers be vaccinated. Prior vaccination likely confers substantial protection, but local reactions can occur among revaccinees; thus, protection from clinically significant inadvertent inoculation cannot be considered absolute.

ACIP and HICPAC recommend that persons administering smallpox vaccine in the pre-event vaccination program be vaccinated to minimize the clinical effects of inadvertent inoculation, if inadvertent inoculation occurs. Ideally, vaccinators should have a confirmed vaccine take before vaccinating others, but administering vaccine to vaccinators immediately before beginning work in vaccination clinics is acceptable.

Vaccination of this group will also contribute to preparedness for smallpox response. If a smallpox release occurs, these experienced vaccinators could immediately be deployed for terrorism response.

POSTEXPOSURE: WHO SHOULD BE VACCINATED	
CCBS (1999, 2002)	**Persons who have been exposed and their household and face-to-face contacts** • As soon as the diagnosis of smallpox is made, all individuals in whom smallpox is suspected should be isolated immediately and all household and other face-to-face contacts should be vaccinated and placed under surveillance. • It is important that discretion be used in identifying contacts of patients to ensure, to the extent that is possible, that vaccination and adequate surveillance measures are focused on those at greatest risk. **Hospitals** • The working group recommends that in an outbreak setting, all hospital employees as well as patients in the hospital be vaccinated. For individuals who are immunocompromised or for whom vaccination is otherwise contraindicated, vaccinia immune globulin (VIG) should be provided, if available. • In the event of a limited outbreak, all persons isolated and those caring for them should be immediately vaccinated. Employees for whom vaccination is contraindicated should be furloughed. **Other essential personnel** The working group recommends that all essential disaster response personnel for whom vaccination is not contraindicated should be vaccinated immediately irrespective of prior vaccination status. This would include police, firefighters, transit workers, public health staff, emergency management staff; and mortuary staff who might have to handle bodies.
CDC (2001)	If an intentional release of smallpox (variola) virus does occur, vaccinia vaccine will be recommended for certain groups. Groups for whom vaccination would be indicated include: **Persons who have been exposed and their household and face-to-face contacts** • Persons who were exposed to the initial release of the virus • Persons who had face-to-face, household, or close-proximity contact (<6.5 feet or 2 meters) with a

	confirmed or suspected smallpox patient at any time from the onset of the patientï¿½s fever until all scabs have separated • Pregnant women who have had a definite exposure to smallpox virus (i.e., face-to-face, household, or close-proximity contact with a smallpox patient) and are, therefore, at high risk for contracting the disease, should also be vaccinated. Smallpox infection among pregnant women has been reported to result in a more severe infection than among nonpregnant women. Therefore, the risks to the mother and fetus from experiencing clinical smallpox substantially outweigh any potential risks regarding vaccination. In addition, vaccinia virus has not been documented to be teratogenic, and the incidence of fetal vaccinia is low. When the level of exposure risk is undetermined, the decision to vaccinate should be made after assessment by the clinician and patient of the potential risks versus the benefits of smallpox vaccination. • Children who have had a definite risk regarding exposure to smallpox (i.e., face-to-face, household, or close-proximity contact with a smallpox patient) should be vaccinated regardless of age. **Hospital/Laboratory** • Personnel involved in the direct medical or public health evaluation, care, or transportation of confirmed or suspected smallpox patients • Laboratory personnel involved in the collection or processing of clinical specimens from confirmed or suspected smallpox patients • Other persons who have an increased likelihood of contact with infectious materials from a smallpox patient (e.g., personnel responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present). • Because of increased transmission rates that have been described in previous outbreaks of smallpox involving aerosol transmission in hospital settings, potential vaccination of nondirect hospital contacts should be evaluated by public health officials. Because hospitalized patients might have other contraindications to vaccination (e.g., immunosuppression), vaccination of these nondirect hospital contacts should occur after prudent evaluation of the hospital setting with determination of the exposure potential through the less-common

	aerosol transmission route. **Other essential personnel** In a postrelease setting, vaccination might be initiated also for other groups whose unhindered function is deemed essential to the support of response activities (e.g., selected law enforcement, emergency response, or military personnel) and who are not otherwise engaged in patient care activities but who have a reasonable probability of contact with smallpox patients or infectious materials. If vaccination of these groups is initiated by public health authorities, only personnel with no contraindications to vaccination should be vaccinated before initiating activities that could lead to contact with suspected smallpox patients or infectious materials. Steps should be taken (e.g., reassignment of duties) to prevent contact of any unvaccinated personnel with infectious smallpox patients or materials.
POSTEXPOSURE: WHEN SHOULD VACCINE BE ADMINISTERED	
CCBS (1999, 2002)	Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.
CDC (2001)	Smallpox vaccine can prevent or decrease the severity of clinical disease, even when administered 3ï¿½4 days after exposure to the smallpox virus.
VACCINE ADMINISTRATION: METHOD	
CCBS (1999, 2002)	**Technique** Vaccination is normally performed using the bifurcated needle (refer to Figure 4 in the original guideline document). A sterile needle is inserted into an ampoule of reconstituted vaccine and, on withdrawal, a droplet of vaccine sufficient for vaccination is held by capillarity between the 2 tines. The needle is held at right angles to the skin; the wrist of the vaccinator rests against the arm. Fifteen perpendicular strokes of the needle are rapidly made in an area of about 5 mm in diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15 to 30 seconds. After vaccination, excess vaccine should be wiped from the site with gauze that should be discarded in a hazardous waste receptacle.

CDC (Apr 2003 [a])	**Preparation** The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle is the preferred site for smallpox vaccination. Skin preparation for vaccination is not required unless the area is grossly contaminated, in which case soap and water should be used to clean the site. If alcohol or another chemical antiseptic is used, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine virus by the antiseptic. **Technique** The multiple-puncture technique uses a pre-sterilized bifurcated needle that is inserted vertically into the vaccine vial, causing a small droplet of vaccine (approximately 0.0025 ml) to adhere between the prongs of the needle. The droplet contains the recommended dosage of vaccine, and its presence within the prongs of the bifurcated needle should be confirmed visually. Holding the bifurcated needle perpendicular to the skin, punctures are rapidly made with strokes vigorous enough to allow a trace of blood to appear after 15-20 seconds. According to the product labeling, 2-3 punctures are recommended for primary vaccination and 15 punctures for revaccination. If no trace of blood is visible after vaccination, an additional 3 insertions should be made using the same bifurcated needle without reinserting the needle into the vaccine vial. Any remaining vaccine should be wiped off the skin with dry sterile gauze and the gauze disposed of in a biohazard waste container.
VACCINATION RESPONSE	
CCBS (1999, 2002)	**Typical response** After about 3 days, a red papule appears at the vaccination site and becomes vesicular on about the fifth day (refer to Figure 5 in the original guideline document). By the seventh day, it becomes the typical Jennerian pustule—whitish, umbilicated, multilocular, containing turbid lymph and surrounded by an erythematous areola that may continue to expand for 3 more days. Regional lymphadenopathy and fever is not uncommon. As many as 70% of children have 1 or more days of temperature higher than 39°C (100°F) between days 4 and 14. The pustule gradually dries, leaving a dark crust, which normally falls off after about 3 weeks.

	Response in those with partial immunity A successful vaccination for those with partial immunity may manifest a gradient of responses. These range from what appears to be a primary take (as described herein) to an accelerated reaction in which there may be little more than a papule surrounded by erythema that reaches a peak between 3 and 7 days. A response that reaches a peak in erythema within 48 hours represents a hypersensitivity reaction and does not signify that growth of the vaccinia virus has occurred. Persons exhibiting such a reaction should be revaccinated.
CDC (Feb 2003)	Vaccination-site reactions are classified into two categories: major reactions and equivocal reactions. **Major reaction** A major reaction indicates a successful vaccine take and is characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer. **Equivocal** All other responses are equivocal reactions and are nontakes. Equivocal reactions can be caused by suboptimal vaccination technique, use of subpotent vaccine, or residual vaccinial immunity among previously vaccinated persons. Persons with equivocal reactions cannot be presumed to be immune to smallpox, and revaccination is recommended. The World Health Organization (WHO) has recommended that response to vaccination be evaluated on postvaccination day 6, 7, or 8. These are the days of peak viral replication, and the period during which take should be assessed for both first-time vaccinees and revaccinees. If the response to vaccination is evaluated too early (e.g., <6 days postvaccination), certain equivocal responses will look reactive because of dermal hypersensitivity to vaccinial proteins. These reactions are sometimes referred to as immediate reactions but are not successful takes. If the response to vaccination is evaluated too late (e.g., >8 days postvaccination), the vaccination take might be missed among persons with prior immunity to vaccinia who might experience a more rapid progression of the vaccination site. Responses among revaccinees that resolve in <6 days are sometimes referred to as

accelerated reactions and are not successful takes.

Expected Range of Vaccine Reactions

A range of expected reactions occurs after vaccination. These normal reactions do not require specific treatment and can include fatigue, headache, myalgia, regional lymphadenopathy, lymphangitis, pruritus, and edema at the vaccination site, as well as satellite lesions, which are benign, secondary vaccinial lesions proximal to the central vaccination lesions.

During the smallpox eradication era, fever after vaccination occurred frequently but was less common among adults than children. For adults, fever is more frequently noted among first-time vaccinees than revaccinees. In one vaccination series involving children, approximately 70% experienced >1 day of temperatures >100°F during the 4ï¿½14 days after primary vaccination, and 15%ï¿½20% of children experienced temperatures >102°F. After revaccination, 35% of children experienced temperatures >100°F, and 5% experienced temperatures of >102°F.

Satellite lesions occasionally occur at the perimeter of the vaccination site and should not be confused with the early discrete vesicles that might coalesce into a central pox-like lesion. Satellite lesions are a benign finding, do not require treatment, and should be cared for as vaccination sites.

Large Vaccination Reactions and Robust Takes (RTs)

Large vaccination reactions (i.e., >10 cm in diameter) at the site of inoculation occur in approximately 10% of first-time vaccinees and are expected variants of the typical evolution of the vaccination site. However, sometimes these large vaccination reactions have been reported as adverse events and misinterpreted as cellulitis, requiring antibiotic treatment.

Bacterial infection of the vaccination site is uncommon but affects children more often than adults, because children are more likely to touch and contaminate their vaccination sites. Specimens for bacterial cultures can be obtained by using swabs or aspiration. Gram stains can detect normal skin flora and are useful only when unusual pathogens are present. If empiric antibacterial therapy is administered, therapy should be adjusted after the

	bacterial pathogen and its sensitivities to various antibacterial medications are known. **Identifying RTs** Differentiating an RT from bacterial cellulitis can be difficult. RTs occur 8ï¿½10 days postvaccination, improve within 72 hours of peak of symptoms, and do not progress clinically. Fluctuant enlarged lymph nodes are not expected and warrant further evaluation and treatment. In contrast, secondary bacterial infections typically occur within 5 days of vaccination or >30 days postvaccination, and unless treated, the infection will progress. The interval of onset to peak symptoms is the key factor in diagnosing RTs. Fever is not helpful in distinguishing RTs from bacterial cellulitis because it is an expected immunologic response to vaccinia vaccination. When an RT is suspected, management includes vigilant observation, patient education, and supportive care that includes rest of the affected limb, use of oral nonaspirin analgesic medications, as well as oral antipruritic agents. Salves, creams, or ointments, including topical steroids or antibacterial medications, should not be applied to the vaccination site.
POSTVACCINATION: PREVENTING CONTACT TRANSMISSION	
CCBS (1999, 2002)	*Care of Vaccination Site* The site should be covered with a loose, nonocclusive bandage to deter the individual from touching the site and perhaps transferring virus to other parts of the body.
CDC (Apr 2003 [a])	**Preventing Contact Transmission Among Healthcare Workers** *Care of Vaccination Site* The Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommend after smallpox vaccination, healthcare personnel providing direct patient care should keep their vaccination sites covered with gauze or a similar absorbent material in combination with a semipermeable dressing to absorb exudates that develop and to provide a barrier for containment of vaccinia virus to minimize the risk of transmission. Alternatively, products combining an absorbent base with an overlying semi-permeable layer can be used to cover

	the site. Semipermeable dressings have been demonstrated to provide an effective barrier to vaccinia virus, but use of a semipermeable dressing alone is associated with maceration of the vaccination site and increased irritation and itching at the site, thereby causing touching, scratching and possible contamination of the hands. The vaccination site should be covered with gauze, a semipermeable dressing, and a layer of clothing during direct patient care until the scab separates. Dressings used to cover the site should be changed frequently (e.g., every 3-5 days or more frequently if exudates accumulate) in order to prevent buildup of exudates and consequent maceration. Hospitals should include a site-care component to their smallpox vaccination programs in which designated staff assess dressings for all vaccinated healthcare workers daily (whether involved in direct patient care or in other duties), determine if dressings need changing (e.g., when accumulation of purulent material is visible or the integrity of the dressing has been disrupted), and change the dressing if indicated. These designated staff should assess the vaccination site for local reactions and for vaccine take; reinforce education of vaccinees about the need for meticulous hand-hygiene; and record and report serious adverse events following vaccination (See Reporting and Management of Adverse Events in original guideline document). When feasible, staff responsible for dressing changes for teams should be vaccinated, but having staff change dressings is acceptable. All persons handling bandages should observe contact precautions. *Hand Hygiene* The most critical measure in preventing contact transmission is consistent hand-hygiene with antimicrobial soap and water or an approved alcohol based hand-rub (i.e., one that contains $\geq$ 60% alcohol) after any contact with the vaccination site or with materials that have come into contact with the site and before patient contact. In addition, care should be taken to prevent contact with the site or contaminated materials from the site. **Preventing Contact Transmission in Other Settings** *Care of Vaccination Site* Persons outside the patient care setting (e.g., members of public health response teams not involved in patient care, or health care workers who are not at work) can

	keep the site covered with a porous dressing (e.g., gauze); hand hygiene remains critical in preventing inadvertent inoculation. In non-patient care settings in which transmission of vaccinia is a concern because of close personal contact with children or other persons, the vaccination site should be covered with gauze or a similar absorbent material and covered with clothing. Hypoallergenic tape should be used for persons who experience tape hypersensitivity. The vaccination site should be kept dry, although normal showering or bathing can continue. A waterproof dressing may decrease the risk of autoinoculation while washing; if the site is uncovered, care should be taken to avoid touching it. After showering, if the vaccination site is wet it should be blotted dry with gauze which is then discarded; if a towel is used to dry the site it should not be used to dry the rest of the body. Alternatively, the site can be allowed to air dry before replacing the bandage. No salves, creams, or ointments should be placed on the site. Contaminated bandages and, if possible, the vaccination site scab, after it has fallen off, should be placed in sealed plastic bags before disposal in the trash to further decrease the potential for inadvertent transmission of the live virus contained in the materials. Clothing, towels, and other cloth materials that have had contact with the site can be decontaminated with routine laundering in hot water.

TABLE 3: COMPARISON OF INFORMATION ABOUT SMALLPOX VACCINE-RELATED COMPLICATIONS AND OF RECOMMENDATIONS FOR THESE COMPLICATIONS	
GENERAL INFORMATION	
CCBS (1999, 2002)	The frequency of complications associated with use of the New York Board of Health strain (the strain used throughout the United States and Canada for vaccine) is the lowest for any established vaccinia virus strain, but the risks are not inconsequential. Data on complications gathered by the Centers for Disease Control and Prevention (CDC) in 1968 are shown in Table 1 in the original guideline document. Complications occurred most frequently among primary vaccinees.
CDC (Feb 2003)	**Adverse Reactions** Adverse reactions caused by smallpox vaccination range from mild and self-limited to severe and life-threatening. Certain

	smallpox vaccine reactions are similar to those caused by other vaccines (e.g., high fever, anaphylaxis, and erythema multiforme [EM]). Other adverse reactions specific to smallpox vaccination include inadvertent inoculation, ocular vaccinia, generalized vaccinia (GV), eczema vaccinatum (EV), progressive vaccinia (PV), postvaccinial encephalopathy (PVE) and encephalomyelitis (PVEM), and fetal vaccinia. Vaccinia-specific complications can occur among vaccinees or their contacts who have been inadvertently inoculated with vaccinia.
LOCAL SKIN REACTIONS	
CCBS (1999, 2002)	The guideline does not provide information on this complication.
CDC (Feb 2003)	Local skin reactions can occur after smallpox vaccination. These include allergic reactions to bandage and tape adhesives, robust takes (RTs), and less commonly, bacterial infections of the vaccination site. Reactions to adhesives usually result in sharply demarcated lines of erythema that correspond to the placement of adhesive tape. Patients have local pruritus but no systemic symptoms and are otherwise well. Frequent bandage changes, periodically leaving the vaccination site open to air, or a change to paper tape might alleviate symptoms. Care should be used to vary the positioning of tape or bandages. This condition is self-limited and resolves when bandages are no longer needed. Topical and oral steroid treatment for this reaction should be avoided because the site contains live vaccinia virus. Salves, creams, or ointments, including topical antibacterial medications, should not be applied to the vaccination site.
MISCELLANEOUS RASHES	
CCBS (1999, 2002)	Many different rashes have been associated with vaccination. Most common are erythema multiforme and variously distributed urticarial, maculopapular, and blotchy erythematous eruptions, which normally clear without therapy.
CDC (Feb 2003)	Common nonspecific rashes associated with smallpox vaccination include fine reticular maculopapular rashes, lymphangitic streaking, generalized urticaria, and broad, flat, roseola-like erythematous macules and patches. These rashes are believed to be caused by immune response to vaccination and do not contain vaccinia. Erythematous or urticarial rashes can occur approximately 10 days (range: 4ï¿½17 days) after first-time vaccination. The vaccinee is usually afebrile, and the rash resolves spontaneously within 2ï¿½4 days. Nonspecific rashes are usually self-limited. These persons appear well and benefit from simple supportive care measures (e.g., oral anti-antihistamine agents).
ERYTHEMA MULTIFORME	

CCBS (1999, 2002)	Many different rashes have been associated with vaccination. Most common are erythema multiforme and variously distributed urticarial, maculopapular, and blotchy erythematous eruptions, which normally clear without therapy.
CDC (Feb 2003)	Erythema multiforme (EM), sometimes referred to as roseola vaccinia or toxic urticaria, might appear as different types of lesions, including macules, papules, urticaria, and typical bullï¿½s-eye (targetoid or iris) lesions. Because the number of clinical descriptions of vaccinia-associated EM rashes is limited, the following details are extrapolated from common descriptions of EM occurring after herpes simplex or mycoplasma infections. The hallmark target lesion of EM associated with other infections usually appears with a central, dark papule or vesicle, surrounded by a pale zone and a halo of erythema, usually within 10 days after viral infection. The limited clinical descriptions of EM after smallpox vaccination indicate that it follows a similar course. The rash of EM might be extremely pruritic, lasting <4 weeks, and patients benefit from administration of oral antipruritics. Less commonly, hypersensitivity reactions can appear as a more serious condition, Stevens-Johnson syndrome (SJS). SJS can also arise from EM and typically includes systemic symptoms with involvement of >2 mucosal surfaces or 10% of body surface area. This condition requires hospitalization and supportive care. The role of systemic steroids for treatment of SJS is controversial; therefore, the decision to administer systemic steroids to patients with postvaccinial SJS should be made after consultation with specialists in this area (e.g., dermatologists, immunologists, or infectious disease specialists), according to the prevailing standard of care. VIG is not used to treat nonspecific rashes, EM, or SJS, because these lesions are probably a manifestation of a hypersensitivity reaction and are not believed to contain vaccinia virus.
INADVERTENT INOCULATION	
CCBS (1999, 2002)	Transmission to close contacts or autoinoculation to sites such as face, eyelid, mouth, and genitalia sometimes occurred. Most lesions healed without incident, although vaccinia immune globulin was useful in some cases of periocular implantation.
CDC (Feb 2003; Apr 2003 [a])	Inadvertent inoculation is a common but avoidable complication of smallpox vaccination. Inadvertent inoculation occurs when vaccinia virus is transferred from a vaccination site to a second location on the vaccinee or to a close contact. The most common sites involved are the face, eyelid, nose, mouth, lips, genitalia, and anus. Among immunocompetent persons, lesions follow the same course as the vaccination site. A primary prevention strategy to avoid inadvertent inoculation is to instruct vaccinees and their close contacts to avoid touching or

	scratching the vaccination site from the time of vaccination until the scab separates. In addition, vigilant handwashing with soap and warm water or hand rubs containing ≥60% alcohol, after touching an unhealed vaccination site or changing a vaccination dressing is critical. Lesions from an inadvertent inoculation contain live vaccinia virus, and the same contact precautions necessary for a vaccination site are necessary for these secondary lesions. Persons at highest risk for inadvertent inoculation are younger persons (e.g., children aged 1ï¿½4 years) and those with disruption of the epidermis. Uncomplicated inadvertent inoculation lesions are self-limited, resolving in approximately 3 weeks, and require no therapy. If extensive body surface area is involved, or severe ocular vaccinia infection (without keratitis), or severe manifestation of inoculation has occurred, treatment with VIG can speed recovery and prevent spread of disease. **April 2003 (a)** Persons with other active acute, chronic, or exfoliative conditions (e.g., burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, or psoriasis) are at higher risk for clinically severe inadvertent inoculation and should not be vaccinated until the condition resolves.
PERIOCULAR AND OCULAR IMPLANTATION	
CCBS (1999, 2002)	Vaccinia immune globulin (VIG) was useful in some cases of periocular implantation.
CDC (Feb 2003; Apr 2003 [a])	Periocular and ocular implantation (hereafter referred to as ocular vaccinial disease) accounted for the majority of reported inadvertent inoculations and were often noted within 7ï¿½10 days of vaccination among first-time vaccinees. Ocular vaccinial disease can occur in different forms, including blepharitis (inflammation of the eyelid), conjunctivitis, keratitis (inflammation of the cornea, including epithelial and stromal forms), iritis, or combinations thereof. When evaluating a patient with the new onset of a red eye or periocular vesicles, vaccinia infection should be considered and history of recent vaccinia exposure (e.g., smallpox vaccination or close contact with a vaccine recipient) should be sought. The goal of therapy of ocular disease is to prevent complications, including corneal scarring associated with keratitis, and the patient should be comanaged with an ophthalmologist. **Note:** The 2001 Advisory Committee on Immunization Practices (ACIP) recommendation states that VIG is contraindicated in a patient with vaccinial keratitis. However, in November 2002, this recommendation was reevaluated and modified by the Public Health Service. VIG should not be withheld if a comorbid condition

exists that requires administration of VIG (e.g., eczema vaccinatum [EV] or progressive vaccinia [PV]) and should be considered for severe ocular disease, except isolated keratitis. In these situations, VIG should be administered if the risk of the comorbid condition is greater than the potential risk of VIG-associated complications of keratitis.

Ocular vaccinial infections account for the majority of inadvertent inoculations. However, data upon which to base treatment recommendations are limited. To discuss treatment options for ocular vaccinia, CDC convened a meeting of ophthalmology and infectious disease consultants in November 2002. On the basis of available data and input from these clinicians, the following guidance is offered:

- Suspected ocular vaccinia infections should be managed in consultation with an ophthalmologist to ensure a thorough and accurate eye evaluation, including a slit-lamp examination, and the specialized expertise needed to manage potentially vision-threatening disease.
- Although vaccine splashes to the eye occur rarely because of the viscosity of smallpox vaccine, these occurrences should be managed by immediate eye-washing with water (avoid pressure irrigation, which can cause corneal abrasion) and a baseline evaluation by an ophthalmologist. In this situation, off-label prophylactic use of topical ophthalmic trifluridine or vidarabine has been recommended by ophthalmologists. Further treatment might not be necessary.
- Off-label use of topical ophthalmic trifluridine or vidarabine has been recommended by certain ophthalmologists and can be considered for treatment of vaccinia infection of the conjunctiva or cornea. Prophylactic therapy with these drugs might also be considered to prevent spread to the conjunctiva and cornea if vaccinia lesions are present on the eyelid, including if near the lid margin, or adjacent to the eye. The potential benefits of these drugs for prophylaxis should be balanced against the minimal but potential risk of drug toxicity and of introducing virus into the eye by frequent manipulation.
- Topical antivirals should be continued until all periocular or lid lesions have healed and the scabs have fallen off, except that topical trifluridine usually is not used for >14 days to avoid possible toxicity. When used for >14 days, trifluridine can lead to superficial punctate keratopathy, which resolves on discontinuation of the medication. Topical vidarabine might be preferable for use among children because it can be compounded into an ointment that allows less frequent dosing and stings less initially than trifluridine.
- VIG should be considered for use in severe ocular disease when keratitis is not present (e.g., severe blepharitis or blepharoconjunctivitis). Severe ocular disease is defined as marked hyperemia, edema, pustules, other focal lesions, lymphadenopathy, cellulitis, and fever. If keratitis is present with these conditions, consideration of possible VIG use must be weighed against evidence in an animal model for

	increased risk for corneal scar formation if a substantial dose is administered during multiple days. • VIG can be considered if the ocular disease is severe enough to pose a substantial risk of impaired vision as a long-term outcome (e.g., vision-threatening lid malformation). If VIG is administered specifically to treat ocular disease in the presence of keratitis, treatment usually should be limited to 1 dose, and the patient or guardian should be informed of the possible risks and benefits before its use. • Using VIG as recommended to treat other severe vaccinia disease (e.g., EV) is indicated, even in the presence of keratitis. VIG is not recommended for treating isolated keratitis. • Topical ophthalmic antibacterials should be considered for prophylaxis of bacterial infection in the presence of keratitis, including if a corneal ulcer is present or steroids are used. In severe cases of keratitis (e.g., with an ulcer and stromal haze or infiltrate) and in iritis, topical steroids should be considered after the corneal epithelium is healed to decrease immune reaction; mydriatics are also indicated. • Topical steroids should not be used without ophthalmologic consultation and should not be used acutely without topical antiviral therapy. Patients with ocular vaccinia infection, including with keratitis or iritis, should receive careful follow-up evaluation by an ophthalmologist to detect and treat possible late onset complications (e.g., scarring and immune reactions). **April 2003 (a)** Persons with inflammatory eye diseases may be at increased risk for inadvertent inoculation due to touching or rubbing of the eye. Therefore it may be prudent to defer vaccination of persons with inflammatory eye diseases requiring steroid treatment until the condition resolves and the course of therapy is complete.
GENERALIZED VACCINIA	
CCBS (1999, 2002)	A secondary eruption almost always following primary vaccination, generalized vaccinia resulted from blood-borne dissemination of virus. Lesions emerged between 6 and 9 days after vaccination and were either few in number or generalized. This complication was usually self-limited. In severe cases, vaccinia immune globulin was indicated. Refer to the section "The Role Of Vaccinia Immune Globulin (VIG) In The Management Of Vaccine-Related Complications" below for treatment recommendations.
CDC (Feb 2003)	Generalized vaccinia (GV) is characterized by a disseminated maculopapular or vesicular rash, frequently on an erythematous base, that usually occurs 6ï¿½9 days after first-time vaccination. The rash spans the spectrum of vaccinial lesions, from

	maculopapules to vesicles. Maculopapules can be mistaken for EM when they are accompanied by a substantial component of erythema. In other instances, the pearly vesicles of GV resemble the lesions of smallpox; however, GV does not follow the centrifugal distribution that is characteristic of smallpox. GV rash might be preceded by fever, but usually, patients do not appear ill. Lesions follow the same course as the vaccination site. Lesions can be present anywhere on the body, including the palms and soles and can be numerous or limited. GV can appear as a regional form that is characterized by extensive satellite vesiculation around the vaccination site, or as an eruption localized to a body part (e.g., arm or leg), with no evidence of inadvertent inoculation. A mild form of GV also exists, which appears with only a limited number of scattered lesions. The skin lesions of GV are believed to be spread by the hematogenous route and might contain vaccinia virus. Therefore, contact precautions should be used when treating these patients. Patients should be instructed to keep lesions covered and avoid physical contact with others if their lesions are too numerous to cover with bandages or clothing. The differential diagnosis of GV includes EM, EV, inadvertent inoculation at multiple sites, and uncommonly, early stages of PV or other vesicular diseases (e.g., disseminated herpes or severe chickenpox). GV is self-limited among immunocompetent hosts. These patients appear well and do not require VIG, but might benefit from simple supportive care measures (e.g., nonsteroidal anti-inflammatory agents [NSAIDs] and oral antipruritics). VIG might be beneficial in the rare case where an immunocompetent person appears systemically ill. GV is often more severe among persons with an underlying immunodeficiency, and these patients might benefit from early intervention with VIG.
ECZEMA VACCINATUM	
CCBS (1999, 2002)	A sometimes serious complication, eczema vaccinatum occurred in some vaccinees and contacts with either active or healed eczema. Vaccinial skin lesions extended to cover all or most of the area once or currently afflicted with eczema. Vaccinia immune globulin was therapeutic. Refer to the section "The Role Of Vaccinia Immune Globulin (VIG) In The Management Of Vaccine-Related Complications" below for treatment recommendations.
CDC (Feb 2003; Apr 2003 [a])	Eczema vaccinatum (EV) is a localized or generalized papular, vesicular, or pustular rash, which can occur anywhere on the body, with a predilection for areas of previous 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 lesions. EV cases resulting from secondary transmission usually appeared with skin eruptions approximately 5ï¿½19 days after the suspected exposure. EV lesions follow the same dermatological course as the vaccination site in a vaccinee, and confluent lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are systemically ill. EV tends to be more severe among first-time vaccinees or unvaccinated contacts. Atopic dermatitis, regardless of disease severity or activity, is a risk factor for experiencing EV among either vaccinees or their close contacts, but no data exist to predict the absolute risk for these persons. The majority of primary-care providers do not distinguish between eczema and atopic dermatitis when describing chronic exfoliative skin conditions, including among infants and young children. EV can be associated with systemic illness that includes fever and malaise. Management includes hemodynamic support (e.g., as for sepsis) and meticulous skin care (e.g., as for burn victims). Patients might require volume repletion and vigilant monitoring of electrolytes as a result of disruption of the dermal barrier. Patients with EV are at risk for secondary bacterial and fungal infections of the lesions, and antibacterials and antifungals are indicated as necessary. One study determined that the mortality from EV was reduced from 30%ï¿½40% to 7% after the introduction of VIG. Therefore, establishing the diagnosis early and not delaying treatment with VIG is imperative to reducing mortality. Patients are usually severely ill and can require multiple doses of VIG. Virus can be isolated from EV lesions, making these patients highly infectious. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection. **April 2003 (a)** Persons with Darier disease (keratitis follicularis) can develop eczema vaccinatum and therefore should not be vaccinated. The risk of mortality from eczema vaccinatum may be higher among contacts than among vaccines.
PROGRESSIVE VACCINIA	
CCBS (1999, 2002)	Cases of progressive vaccinia occurred both among primary vaccinees and revaccinees. It was a frequently fatal complication among those with immune deficiency disorders. The vaccinial lesion failed to heal and progressed to involve adjacent skin with necrosis of tissue, spreading to other parts of the skin, to bones, and to viscera. Vaccinia immune globulin was used for this problem. One case in a soldier with acquired immunodeficiency syndrome was successfully treated with vaccinia immune globulin

	and ribavirin. Refer to the section "The Role Of Vaccinia Immune Globulin (VIG) In The Management Of Vaccine-Related Complications" below for treatment recommendations.
CDC (Feb 2003)	Progressive vaccinia (PV) (also referred to as vaccinia necrosum, vaccinia gangrenosa, prolonged vaccinia, and disseminated vaccinia), is a rare, severe, and often lethal complication that occurs among persons with immunodeficiencies. This diagnosis should be suspected if the initial vaccination lesion continues to progress without apparent healing >15 days after smallpox vaccination. Anecdotal experience suggests that, despite treatment with VIG, persons with cell-mediated immune deficits have a poorer prognosis than those with humoral deficits. PV is characterized by painless progressive necrosis at the vaccination site with or without metastases to distant sites (e.g., skin, bones, and other viscera). The vaccination lesion does not heal, presumably secondary to an immune derangement, and progresses to an ulcerative lesion, often with central necrosis. Initially, limited or no inflammation appears at the site, and histopathology can reveal absence of inflammatory cells in the dermis. During the weeks that follow, patients might experience bacterial infection and signs of inflammation. With PV, vaccinia virus continues to spread locally and can metastasize to distant sites through viremia. Live vaccinia virus can be isolated from the skin lesions of these patients. Infection-control precautions, which include contact isolation, are required to avoid vaccinial infection of other persons and to limit risk for secondary infections. The differential diagnosis of PV includes severe bacterial infection, severe chickenpox, other necrotic conditions (e.g., gangrene), and disseminated herpes simplex infections. Persons at highest risk for PV include those with congenital or acquired immunodeficiencies, HIV/AIDS, cancer, and those on immunosuppressive therapies for organ transplantation or autoimmune disease. The degree and type of immunocompromise probably correlates with the risk for PV, although the protective level of cellular count or humoral immunity is unknown. Before the introduction of VIG and early antiviral medications, PV was universally fatal; but after VIG was used for PV treatment, the survival rate improved. Surgical debridement was used infrequently with variable success to treat the primary progressive necrotic lesions of PV. Management of PV should include aggressive therapy with VIG, intensive monitoring, and tertiary-level supportive care. Despite advances in medical care, PV probably will continue to be associated with a high mortality rate.
POSTVACCINIAL CENTRAL NERVOUS SYSTEM DISEASE	

CCBS (1999, 2002)	Postvaccinial encephalitis occurred at a rate of 1 case per 300,000 vaccinations and was observed only in primary vaccinees; one fourth of these cases were fatal and several had permanent neurological residua. Between 8 and 15 days after vaccination, encephalitis symptoms developed. Recovery was either complete or associated with residual paralysis and other central nervous system symptoms and, sometimes, death. There was no treatment.
CDC (Feb 2003)	Postvaccinial central nervous system disease after smallpox vaccination is most common among infants aged <12 months and is a diagnosis of exclusion. Clinical symptoms reflect cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma. Central nervous system (CNS) lesions occur in the cerebrum, medulla, and spinal cord. Lumbar puncture can reveal an increased opening cerebral spinal fluid (CSF) pressure, and examination of CSF might indicate monocytosis, lymphocytosis, and elevated CSF protein. Both postvaccinial encephalopathy (PVE) and postvaccinial encephalomyelitis (PVEM) have been described. PVE typically affects infants aged <2 years and reflects cerebral damage as a result of vascular changes. Acute onset of symptoms occurs 6ï¿½10 days postvaccination and can include seizures, hemiplegia, aphasia, and transient amnesia. Associated histopathological changes include generalized cerebral edema, mild lymphocytic menigineal infiltration, widespread ganglion degenerative changes, and occasionally, perivascular hemorrhages. Patients can be left with cerebral impairment and hemiplegia. PVEM (or encephalitis) affects persons aged ≥2 years and includes abrupt onset of fever, vomiting, headache, malaise, and anorexia approximately 11ï¿½15 days after vaccination. Symptoms can progress to loss of consciousness, amnesia, confusion, disorientation, restlessness, delirium, drowsiness, seizures, and coma with incontinence or urinary retention, obstinate constipation, and sometimes menigismus. CSF, although under increased pressure, reveals normal chemistries and cell count. Histopathological features include perivenous demyelination and microglial proliferation in demyelinated areas with lymphocytic infiltration but limited cerebral edema. These pathological features are similar to what is observed in other postinfectious encephalitides. The strain of vaccinia virus used in smallpox vaccines might influence the frequency of PVE and PVEM. Reports based on European data indicate generally higher rates of PVE among persons vaccinated with non-NYCBOH strains. In the United States, where the principal strain used was the NYCBOH, the occurrence of PVE or PVEM was rare among first-time vaccinees. No clinical criteria, radiographic findings, or laboratory tests are

	specific for the diagnosis of PVE. PVE/PVEM are diagnoses of exclusion, and other infectious or toxic etiologies should be considered before making these diagnoses. No study has indicated that VIG can be an effective therapy for PVE or PVEM, and therefore, VIG is not recommended for treatment of PVE or PVEM. No specific therapy exists for PVE or PVEM; however, supportive care, anticonvulsants, and intensive care might be required. Because the clinical symptoms of PVE or PVEM are not believed to be a result of replicating vaccinia virus, the role of antivirals is unclear.
FETAL VACCINIA	
CCBS (1999, 2002)	The guideline does not address this complication.
CDC (Feb 2003)	Fetal vaccinia, resulting from vaccinial transmission from mother to fetus, is a rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception; <50 cases have been reported in the literature. Fetal vaccinia is manifested by skin lesions and organ involvement, and often results in fetal or neonatal death. The skin lesions in the newborn infant are similar to those of GV or PV and can be confluent and extensive. The number of affected pregnancies maintained until term is limited. Affected pregnancies have been reported among women vaccinated in all three trimesters, among first-time vaccinees as well as in those being revaccinated, and among nonvaccinated contacts of vaccinees. Because fetal vaccinia is so rare, the frequency of, and risks for, fetal vaccinia cannot be reliably determined. Whether virus infects the fetus through blood or by direct contact with infected amniotic fluid is unknown. No known reliable intrauterine diagnostic test is available to confirm fetal infection. Apart from the characteristic pattern of fetal vaccinia, smallpox vaccination of pregnant women has not been clearly associated with prematurity, low birth weight, and fetal loss. In addition, smallpox vaccine has not been demonstrated to cause congenital malformations. VIG might be considered for a viable infant born with lesions, although no data exist for determining the appropriate dosage or estimating efficacy. No indication exists for routine, prophylactic use of VIG for an unintentionally vaccinated pregnant woman; however, VIG should not be withheld if a pregnant woman experiences a condition where VIG is needed (e.g., EV).
OTHER VACCINE-SPECIFIC COMPLICATIONS/CONCERNS	

CCBS (1999, 2002)	The guideline does not address this topic.
CDC (Feb 2003; Apr 2003 [a]; Apr 2003 [b])	Less frequently reported adverse events temporally associated with smallpox vaccination include myocarditis, pericarditis (see April 2003 [b] below), precipitation of erythema nodosum leprosum or neuritis among leprosy patients, and osteomyelitis (sometimes confirmed by recovery of vaccinia virus). Reported skin changes at the vaccination scar have included malignant tumors (e.g., melanoma, discoid lupus, and localized myxedema as a symptom of Graves disease). Reported neurologic complications after smallpox vaccination include transverse myelitis, seizures, paralysis, polyneuritis, and brachial neuritis. Whether these conditions are caused by smallpox vaccination or represent coincidental occurrences after vaccination is unclear. Temporal association alone does not prove causation. **April 2003 (a)** **Vaccination and Blood Donation** The US Food and Drug Administration (FDA) has recommended that vaccinees be deferred from donating blood for 21 days or until the scab has separated. Contacts of vaccinees, who have inadvertently contracted vaccinia, also should be deferred from donating blood for 14 days after complete resolution of their complication. FDA guidance can be found at http://www.fda.gov/cber/gdlns/smpoxdefquar.htm. If a substantial number of persons are vaccinated within a short time period, the resulting donor deferrals could impact blood availability. Blood supply shortages can be very serious. Blood and platelet donors can help sustain blood supplies by donating immediately before being vaccinated and donating again once they are eligible. Because the donor deferral period needs to be documented carefully, all vaccinees should save the written record of their vaccination. Saving this record also will help to determine vaccination status and donor eligibility in the event of a smallpox outbreak. **Simultaneous Administration of Smallpox Vaccine with other Vaccines** Simultaneously administering the most widely used live and inactivated vaccines has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine. The immune response to one live-virus vaccine might be impaired if administered within 30 days of

another live-virus vaccine, if not administered simultaneously. To minimize the potential risk for interference, parenterally administered live vaccines not administered on the same day should be administered ≥4 weeks apart whenever possible. If parenterally administered live vaccines are separated by <4 weeks, the vaccine administered second should not be counted as a valid dose and should be repeated. The repeat dose should be administered ≥4 weeks after the last, invalid dose.

Smallpox vaccine can be administered at the same time as certain other vaccines, with levels of safety and efficacy comparable to those observed when the vaccines are given separately. Vaccines that have been documented to be effective when given simultaneously with smallpox vaccine include oral polio vaccine, bacille of Calmette and Guï¿½rin (BCG) vaccine, yellow fever vaccine, measles vaccine, and diphtheria and tetanus toxoids and whole cell pertussis vaccine. However, no data exist regarding simultaneous administration of smallpox vaccine with other vaccines now routinely administered to children and adults in the United States.

Varicella vaccine virus lesions could be confused with vaccinia lesions if the vaccines were administered simultaneously. In uncontrolled trials of persons ≥13 years of age, approximately 1,600 vaccinees who received one dose and 955 who received two doses of varicella vaccine were monitored for 42 days for adverse events. After the first and second doses, a nonlocalized rash consisting of a median number of five lesions developed in 5.5% and 0.9% of vaccinees, respectively, and occurred at a peak of 7-21 days and 0-23 days postvaccination, respectively.

Smallpox vaccine may be administered simultaneously with any inactivated vaccine, (e.g., influenza vaccine) to encourage appropriate receipt of all indicated vaccines (e.g., among such populations as health care workers). With the exception of varicella vaccine, smallpox vaccine may be administered simultaneously with other live virus vaccines. To avoid confusion in ascertaining which vaccine may have caused post-vaccination skin lesions or other adverse events, and facilitate managing such events, varicella vaccine and smallpox vaccine should only be administered ≥4 weeks apart.

Timing of Tuberculosis Screening and Smallpox Vaccination

Suppression of tuberculin skin test (purified protein derivative [PPD]) reactivity has been demonstrated following administration of smallpox vaccine, as has been observed following administration of other parenteral live virus vaccines. Healthcare workers scheduled to receive an annual PPD skin test should not receive the skin test for one month after smallpox vaccination to prevent possible false negative reactions.

	April 2003 (b) **Cardiac Adverse Events and Smallpox Vaccination** On March 28, 2003, CDC reported cases of cardiac adverse events among persons vaccinated recently with smallpox vaccine. ACIP recommends that persons be excluded from the pre-event smallpox vaccination program who have known underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking). ACIP supported including these risk factors in prevaccination education materials so that potential vaccinees can evaluate their risk status, if they have concerns, with their personal physician before reporting for vaccination; at the vaccination clinic, verbal screening for known risk factors is recommended. In response to these recommendations, prevaccination screening forms and other materials have been revised; these materials have been provided to state health departments and are available at http://www.bt.cdc.gov/agent/smallpox. ACIP did not recommend special medical follow-up for persons with cardiovascular risk factors who have been vaccinated. Persons with risk factors or known atherosclerotic coronary artery disease should be cared for by their physicians in accordance with standard guidelines for treatment and control of these conditions, such as those issued by the National Cholesterol Education Program Expert Panel and other expert groups.
THE ROLE OF VACCINIA IMMUNE GLOBULIN (VIG) IN THE MANAGEMENT OF VACCINE-RELATED COMPLICATIONS	
CCBS (1999, 2002)	**Prophylaxis** If persons with contraindications have been in close contact with a smallpox patient or the individual is at risk for occupational reasons, vaccinia immune globulin (VIG), if available, may be given simultaneously with vaccination to prevent complications (refer to the original guideline document for dosing recommendation). This does not alter vaccine efficacy. If VIG is not available, vaccine administration may still be warranted, given the far higher risk of an adverse outcome from smallpox infection than from vaccination. The working group recommends that in an outbreak setting, all hospital employees as well as patients in the hospital be vaccinated. For individuals who are immunocompromised or for whom vaccination is otherwise contraindicated, VIG should be provided, if available.

	Vaccinia Immune Globulin (VIG) Therapy for Complications Vaccinia immune globulin (VIG) is valuable in treating patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and periocular infections resulting from inadvertent inoculation. (Refer to original guideline document for dosage and administration instructions.) Because the availability of VIG is so limited, its use should be reserved for the most serious cases. **Consultation** Consultative assistance in the diagnosis and management of patients with complications can be obtained through state health departments.
CDC (2001-2003)	**June 2001** **Consultation Regarding Complications of Vaccinia Vaccine** Centers for Disease Control and Prevention can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia vaccination. Vaccinia immune globulin (VIG) is available when indicated. Physicians should telephone Centers for Disease Control and Prevention at (404) 639-3670 during Mondaysï¿½Fridays, except holidays, or (404) 639-3311 during evenings, weekends, and holidays. Health-care workers are requested to report complications of vaccinia vaccination to the Vaccine Adverse Event Reporting System at (800) 822-7967, or to their state or local health department. **February 2003** **Prophylaxis** Historically, VIG was administered prophylactically to persons at increased risk for vaccine-related adverse events who required vaccination or who were inadvertently vaccinated. However, VIG administration is not without risk, and the efficacy of VIG as a prophylactic against vaccinial infection has not been studied in a controlled setting. (Refer to Table 5 for potential harms of VIG.) Until VIG is evaluated for such use, it is not recommended for prophylaxis when persons with contraindications to smallpox vaccination are inadvertently exposed to vaccinia and are otherwise well. Such persons should have careful clinical follow-up to ensure prompt diagnosis and treatment of an adverse event, if one occurs. Furthermore, in the absence of circulating smallpox virus, VIG is not recommended for concomitant use with smallpox vaccination among persons with contraindications. As recommended by the advisory committee on immunization practices (ACIP), careful screening criteria should be used to

	exclude persons with contraindications from preoutbreak smallpox vaccination programs. **Treatment** VIG is a sterile solution of the immunoglobulin fraction of plasma, containing antibodies to vaccinia virus from persons who were vaccinated with smallpox vaccine. VIG has demonstrated efficacy in the treatment of smallpox vaccine adverse reactions that are secondary to continued vaccinia virus replication after vaccination. Such adverse reactions include eczema vaccinatum (EV), progressive vaccinia (PV), or vaccinia necrosum, and severe cases of generalized vaccinia (GV). VIG has no proven effectiveness for postvaccinial central nervous system disease. VIG is recommended for treating EV and PV. Because the majority of cases of GV are self-limited, VIG is recommended for treating GV only if the patient is seriously ill or has serious underlying disease that is a risk factor for a complication of vaccination (e.g., such immunocompromised conditions as HIV/AIDS). VIG can also be useful in treating ocular vaccinia that results from inadvertent implantation. When ocular vaccinia with keratitis is present, consideration of VIG should include the possible increased risk for corneal scarring.
CDC (Apr 2003 [a])	**April 2003 (a)** **Availability** Vaccinia immune globulin (VIG) is available from CDC only under Investigational New Drug (IND) protocols (i.e., protocols for products that are not yet licensed). As of January 31, 2003, enough VIG was available under an IND protocol to treat more than 4,000 serious adverse events, which is enough VIG doses to treat the expected number of adverse reactions resulting from vaccination of 40 million persons, on the basis of previously observed rates of adverse reactions.
OTHER TREATMENT OPTIONS FOR VACCINE-RELATED COMPLICATIONS	
CCBS (1999, 2002)	The guideline does not address this topic. Note: The use of cidofovir as a treatment for smallpox infection rather than as a treatment for vaccine-related complications is discussed but not recommended.
CDC (Feb 2003; Apr 2003 [a])	**Cidofovir** Cidofovir, a nucleotide analogue of cytosine, has demonstrated antiviral activity against certain orthopoxviruses in cell-based in

	vitro and animal model studies. Its effectiveness in the treatment of vaccinia-related complications among humans is unknown. Cidofovir has been demonstrated to be nephrotoxic among humans and carcinogenic among animals, even at low doses. It is administered with probenecid and hydration. Cidofovir is approved by the United States Food and Drug Administration (FDA) for treating cytomegalovirus (CMV) retinitis among patients with acquired-immune deficiency syndrome (AIDS). Its use for treating smallpox vaccination complications is recommended only under Investigational New Drug (IND) protocols from CDC and the U.S. Department of Defense (DoD). (Refer to the original guideline document for more information on the IND protocol.) Cidofovir will be released for civilian use by CDC and for military use by the Department of Defense (DoD), if 1) a patient fails to respond to VIG treatment; 2) a patient is near death; or 3) all inventories of VIG have been exhausted. This proposed use of cidofovir is investigational and has not been studied among humans; therefore, the benefit of cidofovir therapy for vaccinia-related complications is uncertain. Insufficient information exists to determine the appropriate dosing and accompanying hydration and dosing of probenecid if antiviral therapy is needed to treat smallpox vaccine-related adverse events among the pediatric age group. Dosages for these patients should be determined in consultation with specialists at CDC and the DoD. Additional information regarding dosing and administration of cidofovir is included in the Investigatorï¿½s Brochure that accompanies the release of this product to the clinician when cidofovir is used under the IND protocol. **Topical Ophthalmic Antiviral Drugs** Refer to Table 3, above, "Periocular and Ocular Implantation" regarding the use of topical ophthalmic antiviral drugs for ocular vaccinial infections. **April 2003 (a)** Individuals with progressive vaccinia, eczema vaccinatum, and severe generalized vaccinia or inadvertent inoculation might benefit from therapy with VIG or cidofovir, although the latter has not been approved by FDA for this indication. Suspected cases of these illnesses or other clinically significant adverse events after smallpox vaccination should be reported immediately to state health departments. VIG and cidofovir are available from CDC for treatment of adverse events among smallpox vaccine recipients and their contacts under Investigational New Drug protocols.

TABLE 4: COMPARISON OF RECOMMENDATIONS REGARDING GROUPS AT SPECIAL RISK FOR COMPLICATIONS FROM SMALLPOX VACCINATION	
ECZEMA, ATOPIC DERMATITIS	
CCBS (1999, 2002)	*Vaccinees:* Persons with eczema are ordinarily considered at special risk of smallpox vaccine complications.
CDC (2001-2003)	**June 2001** *Vaccinees and Household Contacts:* Persons with a history or presence of eczema or other skin conditions (e.g., atopic dermatitis, burns, impetigo, or varicella zoster) or their household contacts should not be vaccinated for routine nonemergency indications. **April 2003 (a)** *Vaccinees and Household Contacts:* • Atopic dermatitis, irrespective of disease severity or activity, is a risk factor for developing eczema vaccinatum after smallpox vaccination in either vaccinees or their close contacts, but no data exist to predict the absolute risk for this population. • Because the majority of primary care providers do not distinguish between eczema and atopic dermatitis, particularly when describing chronic exfoliative skin conditions in infants, the Advisory Committee on Immunization Practices (ACIP) recommends that smallpox vaccine should not be administered to persons with a history of eczema or atopic dermatitis, irrespective of disease severity or activity.
ACUTE, CHRONIC OR EXFOLIATIVE SKIN CONDITIONS	
CCBS (1999, 2002)	*Vaccinees:* Persons with significant exfoliative skin conditions are ordinarily considered at special risk of smallpox vaccine complications.
CDC (Apr 2003 [a])	*Vaccinees and Household Contacts:* • Persons with active acute, chronic, or exfoliative conditions (e.g., burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, or psoriasis) are at higher risk for clinically

	significant inadvertent inoculation and should not be vaccinated until the condition resolves. • Persons with Darier disease (keratosis follicularis) can develop eczema vaccinatum and therefore should not be vaccinated.
IMMUNOSUPPRESSION	
CCBS (1999, 2002)	*Vaccinees:* • Smallpox vaccination is contraindicated for persons with hereditary immune deficiency disorders • Patients with leukemia, lymphoma, or generalized malignancy who are receiving therapy with alkylating agents, antimetabolites, radiation or large doses of corticosteroids are considered at special risk of smallpox vaccine complications.
CDC (Apr 2003 [a])	*Vaccinees and Household Contacts:* • Replication of vaccinia virus can be enhanced among persons with cellular or humoral immunodeficiencies and among those with immunosuppression (e.g., including HIV/AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplantation, or therapy with alkylating agents, antimetabolites, radiation, or high-dose corticosteroids [i.e., ≥2 mg/kg body weight or 20 mg/day of prednisone for ≥2 weeks]). • Persons who are taking or have taken high dose corticosteroids should not be vaccinated within one month of completing corticosteroid therapy, and persons treated with other immunosuppressive drugs within the previous 3 months should not be vaccinated. • Persons with immunosuppression also include hematopoietic stem cell transplant recipients who are <24 months posttransplant, and hematopoietic stem cell transplant recipients who are ≥24 months posttransplant, but have graft-versus-host disease or disease relapse. • Patients with severe clinical manifestations of some autoimmune diseases (e.g., systemic lupus erythematosis) may have some degree of immunocompromise as a component of the disease. • Although no data exist to indicate that a person is at risk from live-virus vaccines because of severe autoimmune disease in the absence of immunosuppressive therapy, persons with immunodeficiency as a clinical component of their autoimmune disease should not receive smallpox vaccine during the pre-event vaccination program.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)/ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)	
CCBS (1999, 2002)	*Vaccinees:* Persons with HIV infection are considered at special risk of smallpox vaccine complications.
CDC (Apr 2003 [a])	*Vaccinees and Household Contacts:* Persons with HIV infection and AIDS may have an increased risk of severe adverse reactions with live virus vaccines. Because the HIV epidemic began after the cessation of routine smallpox vaccination, data are limited regarding the risk from vaccination among HIV-infected persons. An estimated 850,000 to 950,000 HIV-infected persons in the United States (prevalence, 0.3%), and of these, an estimated 180,000 to 280,000 are unaware that they are infected. Estimates of the number of HIV-infected health care workers range from about 21,000 to 48,000, and the proportion of these infected health care workers who remain undiagnosed is unknown. Risk assessment screening followed by counseling and testing is useful in identifying many persons with HIV infection. However, substantial numbers of HIV-infected persons may not recognize or acknowledge their risk during risk assessment screening. Smallpox vaccine should not be administered to persons with HIV infection or AIDS as part of a pre-event program because of their increased risk of progressive vaccinia (vaccinia necrosum). Before vaccination, potential vaccinees should be educated about the risk of severe vaccinial complications among persons with HIV infection or other immunosuppressive conditions; persons who think they may have one of these conditions should not be vaccinated. ACIP does not recommend mandatory HIV testing prior to smallpox vaccination, but recommends that HIV testing should be readily available to all persons considering smallpox vaccination. HIV testing is recommended for persons who have any history of a risk factor for HIV infection and who are not sure of their HIV infection status. Because known risk factors cannot be identified for some persons with HIV infection, anyone who is concerned that they could have HIV infection also should be tested. HIV testing should be available in a confidential or anonymous setting, as allowed by local laws and regulations, with results communicated to the potential vaccinee before the planned date of vaccination. Persons with a positive test result should be advised not to be vaccinated. Information about local testing options should be provided to all potential

	vaccinees, including sites where testing is performed at no cost. The recently licensed rapid HIV test may facilitate availability of HIV testing to potential vaccinees.
PREGNANCY	
CCBS (1999, 2002)	*Vaccinees:* Pregnant women are ordinarily considered at special risk of smallpox vaccine complications.
CDC (Apr 2003 [a])	*Vaccinees and Household Contacts:* Because of the limited risk but severe consequences of fetal infection, smallpox vaccine should not be administered in a pre-event setting to pregnant women or to women who are trying to become pregnant. Before vaccination, women of childbearing age should be asked if they are pregnant or intend to become pregnant in the next 4 weeks; women who respond positively should not be vaccinated. To further reduce the risk of inadvertently vaccinating a woman who is pregnant, at the time of pre-screening women of childbearing age should be educated regarding what is known about fetal vaccinia. Women should be counseled to avoid becoming pregnant until at least four weeks after vaccination, and abstinence or highly effective contraceptive measures should be recommended to reduce the risk of pregnancy before or within four weeks after vaccination. Any woman who believes she might be pregnant or who wants additional assurance that she is not pregnant should perform a urine pregnancy test with a first-morning void urine on the day scheduled for vaccination. Such tests could be made available at the pre-screening and vaccination sites to avoid cost or other barriers to testing. However, women should be informed that a negative urine pregnancy test cannot exclude a very early pregnancy and therefore they and their healthcare providers should not base a decision about their pregnancy status solely upon a urine pregnancy test result. If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after smallpox vaccination, she should be counseled regarding the basis of concern for the fetus. Smallpox vaccination during pregnancy should not ordinarily be a reason to terminate pregnancy. To expand understanding of the risk for fetal vaccinia and to document whether other adverse pregnancy outcomes might be associated with vaccination, CDC has established a pregnancy registry to prospectively follow the outcome of such pregnancies and facilitate the investigation of any adverse pregnancy outcome among pregnant women who were inadvertently vaccinated. Pre-event vaccination is also contraindicated among persons with household contacts who are pregnant.

BREASTFEEDING WOMEN	
CCBS (1999, 2002)	The guideline does not address this topic.
CDC (Apr 2003 [a])	*Vaccinees:* According to the product labeling, smallpox vaccine is not recommended for use in breast-feeding women; whether vaccine virus or antibodies are excreted in human milk is unknown.
INFANTS AND CHILDREN	
CCBS (1999, 2002)	The guideline does not address this topic.
CDC (Apr 2003 [a])	*Vaccinees:* ACIP does not recommend smallpox vaccination of children and adolescents <18 years of age in the pre-event vaccination program, and smallpox vaccine is contraindicated for infants <1 year of age.
VACCINE COMPONENT ALLERGY	
CCBS (1999, 2002)	The guideline does not address this topic.
CDC (2001-2003)	**June 2001** *Vaccinees:* Vaccinia vaccine should not be administered for routine nonemergency indications to persons with allergies to vaccine components. The currently available vaccinia vaccine (i.e., Dryvax®) contains trace amounts of polymyxin B sulfate, streptomycin sulfate, chlorotetracycline hydrochloride, and neomycin sulfate. Persons who experience anaphylactic reactions (i.e., hives, swelling of the mouth and throat, difficulty breathing, hypotension, and shock) to any of these antibiotics should not be vaccinated. **April 2003 (a)** *Vaccinees:* Smallpox vaccination is contraindicated for persons with allergies to vaccine components. According to the package insert, the vaccine may contain trace amounts of polymyxin B, streptomycin, tetracycline, and neomycin, and the diluent

	contains glycerin and phenol.

TABLE 5: BENEFITS AND HARMS	
BENEFITS	
CCBS (1999, 2002)	Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.
CDC (2001-2003)	**June 2001** • Administration of vaccinia vaccine within the first days after initial exposure to smallpox virus can reduce symptoms or prevent smallpox disease. • Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other orthopoxviruses (e.g., monkeypox, cowpox, and variola viruses). Although the efficacy of vaccinia vaccine has never been measured precisely during controlled trials, epidemiologic studies demonstrate that an increased level of protection against smallpox persists for ≤5 years after primary vaccination and substantial but waning immunity can persist for ≥10 years. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. **February 2003** • Stringent medical screening of potential vaccinees for risk factors for adverse events, coupled with improved infection control measures to prevent vaccinia transmission, will probably decrease preventable complications of vaccination • Appropriate diagnosis, treatment, and management of adverse reactions to smallpox vaccination **April 2003 (a)** • Effective control and containment of smallpox in event of an outbreak • Appropriate pre-release vaccination of selected groups to enhance smallpox response readiness • Appropriate infection control practices to reduce contact transmission in the healthcare setting

	April 2003 (b) • Improved screening for cardiac disease and risk factors among potential vaccinees • Decreased cardiac-related morbidity and mortality in vaccinees
HARMS	
CCBS (1999, 2002)	*Please refer to Table 3 above, for potential harms of smallpox vaccination.* The guideline does not address potential harms of treatment for vaccine-related complications.
CDC (Feb 2003)	*Please refer to Table 3 above, for potential harms of smallpox vaccination.* **Potential Harms of Treatment for Vaccine-Related Complications** ***Vaccinia Immune Globulin (VIG)*** *Side Effects:* • VIG administration has been associated with mild, moderate, and severe adverse reactions. Mild adverse reactions include local pain and tenderness, swelling, and erythema at the injection site after intramuscular (IM) administration of immunoglobulins and can persist from hours to 1ï¿½2 days after administration. • Moderate adverse reactions include joint pain, diarrhea, dizziness, hyperkinesis, drowsiness, pruritis, rash, perspiration, and vasodilation. Back and abdominal pain, nausea, and vomiting can occur within the first 10 minutes of injection. Chills, fever, headache, myalgia, and fatigue can begin at the end of infusion and continue for hours. More severe reactions of this type might require pretreatment with corticosteroids or acetaminophen, if another dose of VIG is required. • Serious adverse events associated with administration of intravenous (IV) VIG are expected to be similar to those observed with other intravenous immune globulin (IVIG) products, and can include hypotension, anaphylaxis and anaphylactoid systemic reactions, renal dysfunction, and aseptic meningitis syndrome (AMS). When AMS occurs, it usually begins from within hours to 2 days after treatment and can occur more frequently in association with high dosage (2 g/kg body weight) therapy. It is characterized by severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and

vomiting. Discontinuation of IVIG treatment has resulted in remission of AMS within days without sequelae.

- Anaphylaxis and anaphylactoid systemic reactions have been reported after IM or IV injection of human immunoglobulin preparations. The symptoms of classic anaphylactic reactions include flushing, facial swelling, dyspnea, cyanosis, anxiety, nausea, vomiting, malaise, hypotension, loss of consciousness, and in certain cases, death. Symptoms appear from within seconds to hours after infusion. The treatment of such reactions is immediate discontinuation of immune globulin and administration of epinephrine, oxygen, antihistamines, IV steroids, and cardiorespiratory support.
- When proteins prepared from human blood or plasma are administered, the potential for transmission of infectious agents cannot be totally excluded. This also applies to infectious agents that might not have been discovered or characterized when the current preparations of VIG were formulated. To reduce the risk of transmitting infectious agents, stringent controls are applied in the selection of blood and plasma donors, and prescribed standards are used at plasma-collection centers, testing laboratories, and fractionation facilities.

Potential Risks and Contraindications:

- Contraindications to VIG administration include an acute allergic reaction to thimerosal (for VIGIM) or a history of a severe reaction after administration of human immunoglobulin preparations. Persons with selective immunoglobulin A (IgA) deficiency might have antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.
- Whether VIG can cause fetal harm when administered to a pregnant woman or if it affects reproductive capacity is unknown. VIG should be administered to a pregnant woman only if clearly needed.
- Similarly, whether VIG is excreted in breast milk is unknown; therefore, caution should be exercised when VIG is administered to a nursing woman.
- VIG is made from human plasma; therefore, a possible risk of transmission of viruses and a theoretical risk of transmission-adventitious agents that can cause Creutzfeldt-Jacob disease exist.

Cidofovir

Side Effects/Potential Harms:

- The major complication of cidofovir therapy is renal toxicity, which is sometimes irreversible, results in renal failure, and requires dialysis to prevent death. To reduce the renal toxicity of cidofovir, it must be administered with careful IV

	hydration and with probenecid, a renal tubular blocking agent. • Cidofovir has also been associated with neutropenia, proteinuria, decreased intraocular pressure/ocular hypotony, anterior uveitis/iritis, and metabolic acidosis. Cidofovir related carcinogenicity, teratogenicity, and hypospermia have been reported in animal studies. • Probenecid (taken with cidofovir) has been associated with headache, anorexia, nausea, vomiting, urinary frequency, hypersensitivity reactions, anemia, hemolytic anemia, nephritic syndrome, hepatic necrosis, gout, uric acid stones, and renal colic. Probenecid should be used with caution among children, pregnant women and persons with sulfa drug allergy (see manufacturerï¿½s package insert).

GUIDELINE CONTENT COMPARISON

The Center for Civilian Biodefense Strategies (CCBS) and the Centers for Disease Control and Prevention (CDC) present recommendations for smallpox vaccination and provide explicit reasoning behind their judgments. The original scope and focus of the guidelines differs significantly.

The CCBS guideline, released in 1999 and updated in 2002, focuses on the use of smallpox as a biological weapon. Therefore, the guideline provides recommendations for the management of smallpox in a postrelease situation (i.e., during an outbreak after release of smallpox as a bioweapon) and includes detailed discussion of diagnosis, postexposure therapy, infection control, hospital procedure and decontamination.

In contrast, although the 2001 CDC guideline addresses smallpox prevention in nonemergency, prerelease (i.e., before release of smallpox as a bioweapon) and postrelease situations, the interventions target nonemergency vaccination. The guideline provides recommendations as a response to a deliberate release, but this is not its main focus. The subsequent February 2003, April 2003 (a), and April 2003 (b) CDC guidelines address smallpox vaccination in the context of a national initiative for "enhanced terrorism preparedness."

Availability of smallpox vaccine and vaccinia immune globulin (VIG) were important considerations to both groups when developing their guidelines. The 1999 CCBS and 2001 CDC guidelines were published when there were inadequate amounts of vaccine and VIG for an effective large-scale vaccination program, even when targeting at-risk individuals, such as health care workers first responding to persons infected with smallpox. Both organizations

developed additional information and recommendations as the supply of vaccine and VIG increased. In addition, the CDC expanded recommendations as part of its response to the U.S. Presidentï¿½s plan (announced in December 2002) to protect Americans against the threat of smallpox attack by hostile groups or governments.

CCBSï¿½ additional information and recommendations surrounding the issue of increased vaccine and VIG supply were published in 2002. Their additional information was added into the original 1999 recommendations (NGC has analyzed the content differences between the two documents and has labeled these additional recommendations as an addendum). The CDC issued a clinical guidance document on January 24, 2003 providing vaccination recommendations for health care professionals and emergency response personnel who are candidates for the national selected vaccination program (a program developed in response to the U.S. Presidentï¿½s initiative). This CDC guideline also presents expanded information on vaccine-related complications and their treatment, including options available under Investigational New Drug (IND) protocols. The CDCï¿½s draft recommendations, issued February 10, 2003 and also targeted toward smallpox response teams, provide additional information on contraindications to smallpox vaccination and an update on the availability of vaccine and VIG. The CDCï¿½s supplemental recommendations issued April 4, 2003 (b), responded directly to reports of cardiac-related events following vaccination and provided screening recommendations to address these concerns.

Areas of Agreement

CCBS and CDC agree in many aspects of smallpox vaccination.

Non-Emergency and Prerelease Vaccination

Both organizations agree that the smallpox vaccination is not intended for administration to the general population, noting that since the risk of exposure is low, the benefits of vaccination do not outweigh the risks of vaccine complications. Rather, in a non-emergency situation, the vaccine should be available only to designated personnel, such as laboratory workers in contact with orthopoxviruses. The 2001 CDC guideline expands the categories of professionals who might be offered the vaccine and under what circumstances. This guideline also provides a schedule for routine revaccination. For a prerelease vaccination program, the February 2003 CDC guideline defines the target population as smallpox public health response and health care teams. The April 2003 (a) CDC guideline provides additional information on the makeup of these teams, including a listing of allied healthcare professionals who might be candidates for vaccination.

Postexposure Vaccination

In the event of exposure, both the CCBS and CDC guidelines provide recommendations regarding who should be vaccinated and when. There is general agreement that three main groups should be targeted for vaccination: 1) persons exposed and their household and face-to-face contacts; 2) hospital/laboratory staff who provide care; and 3) essential personnel such as emergency services, military and law enforcement. Both groups recommend vaccination within 4 days of exposure.

Vaccine Administration, Response, and Care of the Vaccination Site

The CCBS and CDC recommend a similar technique for administration and provide information on clinical presentation following vaccination, including common side effects such as fever as well as indications for revaccination in cases of an equivocal response to primary vaccination. The guidelines discuss the risk of contact transmission from persons who have recently been immunized and recommend covering the vaccination site. Providing additional detail, the CDC offers recommendations regarding the type of bandage and care for the site and emphasizes thorough hand washing with antimicrobial soap or the use of an approved alcohol-based hand rub to prevent transmission.

Areas of Differences

Postexposure Vaccination

Both the CCBS and 2001 CDC guidelines make recommendations for vaccination in a hospital setting. For major outbreaks, the CCBS explicitly recommends vaccination for all hospital employees and patients, with VIG also given for selected patients and employees. In contrast, the CDC recommends selected vaccination of those with ï¿½increased likelihood of contactï¿½ with smallpox patients or infectious materials and recommends ï¿½prudent evaluationï¿½ of the hospital setting before widescale vaccination of hospitalized patients who might have contraindications to vaccination (e.g., immunocompromised).

Vaccine-Related Complications

The CCBS and CDC guidelines list the same six complications of smallpox vaccine and provide similar information regarding clinical presentation and treatment. However, with publication of the February 2003 guideline, the CDC provides updated information on vaccine-related adverse reactions, ranging from common to life-threatening, including information on fetal vaccinia and less frequently reported adverse events, such as myocarditis and seizures. Ocular vaccinial infections are considered by both organizations, but the CDC recommends ophthalmology consult and off-label uses of topical ophthalmic antiviral drugs, whereas these interventions are not discussed in the CCBS guideline.

In addition, the CDC April 2003 (a) guideline provides new information on vaccine-related precautions including inflammatory eye disease, blood donation, simultaneous vaccination, and tuberculin skin testing. The April 2003 (b) CDC recommendations provide specific precautions for persons with cardiac history or cardiac risk factors.

Treatment for Complications

The use of vaccinia immune globulin (VIG) and cidofovir as treatment for vaccine-related complications under IND protocols is a major difference between the earlier (1999/2002, and 2001) and more recent (2003) guidelines.

Vaccinia Immune Globulin (VIG)

At the time the 1999 CCBS and 2001 CDC guidelines were written, vaccinia immune globulin (VIG) was the most recognized treatment for vaccine complications. Both guidelines recommended its use for treatment of eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and severe ocular viral implantation. VIG was also recommended as prophylaxis when vaccinating persons with contraindications. Because the VIG supply was limited, both groups recommended its use only for the most serious cases.

Noting that the supply of VIG had increased to meet demand, the 2002 CCBS addendum continues to recommend use of VIG for vaccine-related complications and as prophylaxis for contraindications. However, with release of the 2003 guideline, the CDC changed three of its recommendations regarding VIG. First, the April (a) 2003 guideline no longer recommends prophylactic use of VIG, suggesting instead rigorous screening criteria to exclude persons with contraindications. Second, the guideline recommends consideration of VIG for vaccinial keratitis only in the presence of specific comorbid conditions. In the 2001 guideline, the CDC recommended against the use of VIG for vaccinial keratitis; the presence of comorbid conditions was not discussed. Finally, when a recommendation is made for VIG, the CDC states that it will be available under an IND protocol. Following an IND protocol was not mentioned in the 2001 CDC or the CCBS guidelines even though VIG was recommended in each.

In addition, the CDC provides a list of possible side effects and contraindications to VIG use. The 2002 CCBS addendum does not address VIG side effects and contraindications.

The following table provides a comparison of each guidelineï¿½s recommendations regarding the use of VIG for specific vaccine-related indications.

Comparison of Recommendations for Using Vaccinia Immune Globulin (VIG)

VIG Indication	CCBS 1999, 2002	CDC 2001 - 2003*
Prophylactic use	Recommended	Not recommended
Local skin reactions	Indication not addressed	No intervention recommended
Miscellaneous rashes	No intervention recommended	Not recommended
Erythema Multiforme	No Intervention recommended	Not recommended
Inadvertent Inoculation	Not generally recommended but can be considered for periocular implantation	Recommended in select circumstances
Periocular & Ocular Implantation	Considered useful in some cases	Considered for severe ocular disease (except isolated keratitis)
Vaccinial Keratitis	Indication not addressed	Considered in presence of comorbid condition that requires VIG
Generalized Vaccinia	Recommended for severe form	Recommended for severe form
Eczema Vaccinatum	Recommended	Recommended
Progressive Vaccinia	Recommended	Recommended
Postvaccinial Central Nervous System Disease	No intervention recommended	Not Recommended
Fetal Vaccinia	Indication not addressed	Considered for a viable infant

*When recommended, the April 2003 (a) CDC guideline clearly states that VIG will be available under Investigational New Drug (IND) protocols from CDC and the U.S. Department of Defense (DoD).

Antiviral Drugs

Use of antiviral drugs, notably cidofovir, for treatment of vaccine-related complications represents another area of difference between the guidelines. Citing a lack of evidence, the 1999 CCBS guideline and 2002 addendum discussed, but did not recommend, cidofovir

use in the context of treatment for smallpox infection. Its potential use as a treatment for vaccine-related complications was not considered. Because the evidence was lacking, the CDC recommends use of cidofovir for smallpox vaccine-related complications under an IND protocol. The February 2003 guideline lists cidofoviri¿½s side-effects and potential harms, and provides details regarding the protocol, including information about how clinicians can obtain cidofovir.

Contraindications to Vaccination/Groups at Special Risk

The CCBS guideline provides a basic list of five groups most at risk for complications. The CDC expands the list to include infants and children, women who are breastfeeding and patients with allergies to vaccine components. The CDC also divides the contraindications into 2 categories: 1) contraindications that apply to vaccination candidates *and* their close contacts and 2) contraindications that apply only to vaccination candidates. Both CCBS and CDC recommend "prudent evaluation" of the potential risks versus the benefits of vaccination; however, the CDC provides much more information on each contraindication, most notably for persons with HIV/AIDS and pregnant women.

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