



## **Draft Recommendations for Use of 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)**

In June 2001, the Advisory Committee on Immunization Practices (ACIP) made recommendations for the use of smallpox (vaccinia) vaccine to protect persons working with orthopoxviruses, and to prepare for a possible bioterrorism attack and for response to an attack involving smallpox.[1] Because of the terrorist attacks in the fall of 2001, the Centers for Disease Control and Prevention (CDC) asked the ACIP to review their previous recommendations for smallpox vaccination. These supplemental recommendations update the 2001 recommendations for vaccination of persons designated to respond or care for a suspected or confirmed case of smallpox. In addition, they clarify and expand the primary strategy for control and containment of smallpox in the event of an outbreak. Recommendations for vaccination of laboratory workers who directly handle recombinant vaccinia viruses derived from non-highly attenuated vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, vaccinia, and variola) remain unchanged.[1]

The following recommendations were developed after formation of a joint Working Group of the ACIP and the National Vaccine Advisory Committee (NVAC) in April 2002, joined in September 2002 by the Healthcare Infection Control Practices Advisory Committee (HICPAC), and a series of public meetings and forums to review available data on smallpox, smallpox vaccine, smallpox control strategies, and other issues related to smallpox vaccination.

### **Smallpox Transmission and Control**

Smallpox is transmitted from an infected person. Patients are most infectious during the first 7 to 10 days following rash onset; transmission can occur during the prodromal period just prior to rash onset, when lesions in the mouth ulcerate, releasing virus into oral secretions. Infection is transmitted by large droplet nuclei, occasionally by direct contact or contact with fomites (e.g., clothes or bedding), and only rarely has airborne transmission been documented.[2] Epidemiologic studies have shown that smallpox has a lower rate of transmission than diseases such as measles, pertussis, and influenza.[2, 3] The greatest risk of infection occurs among household members and close contacts of persons with smallpox, especially those with prolonged face-to-face exposure. Isolation of cases and vaccination and close monitoring of contacts of cases at greatest risk of infection have been shown to interrupt transmission of smallpox.[4, 5] Poor infection control practices sometimes resulted in transmission in hospital [6, 7]; a review of importations into Europe during the period 1950-1971 found that more than half of the spread cases were associated with hospitals, with approximately 20% of all spread cases related to infections in healthcare workers.[6] In a review of European smallpox outbreaks, Gani and Leach found that the communicability of smallpox dropped by about one-half when hospital-based transmission was excluded. [8]

The primary strategy to control an outbreak of smallpox and interrupt disease transmission is surveillance and containment, which includes isolation of smallpox cases and vaccination of persons at risk of contracting smallpox. This strategy involves identification of infected persons through intensive surveillance, isolation of smallpox patients to prevent further transmission, vaccination of household contacts and other close contacts of infected persons (i.e., primary contacts), and vaccination of close contacts of the primary contacts (i.e., secondary contacts who would be exposed should disease develop

in the primary contacts). This strategy was instrumental in the ultimate eradication of smallpox as a naturally occurring disease even in areas that had low vaccination coverage.[4]

Depending upon the size of the smallpox outbreak and the resources that were available for rapid and thorough contact tracing, surveillance and containment activities in areas with identified smallpox cases were sometimes supplemented with vaccination of other individuals in the area where the outbreak occurred. This was done to expand the ring of immune individuals within an outbreak area and to further reduce the chance of secondary transmission from smallpox patients before they could be identified and isolated. Regardless of the geographic distribution, number of cases, or number of concurrent outbreaks, surveillance and containment activities remained the primary disease control strategy.[4]

### **Critical Considerations**

A number of factors and assumptions were used in developing these supplemental recommendations.

- **Level of disease risk and threat**

Information provided to the ACIP indicated that there is a real risk for smallpox occurring as a result of a deliberate release by terrorists, but this risk is low, and the population at risk for such an exposure cannot be determined. It was further assumed that regardless of the mode, magnitude, or duration of a bioterrorism release, the epidemiology of subsequent person-to-person transmission would be consistent with prior experience. These recommendations also assumed that in addition to vaccination, health care workers and others would be afforded some protection from infection through appropriate infection control measures, including the use of appropriate personal protective equipment.

- **Expected severe adverse reactions to vaccination**

These supplemental recommendations assume that appropriate screening for contraindications to vaccination will be implemented and will include both the vaccinated persons as well as their household contacts. It is further assumed that recommended precautions will be taken to minimize both the risk of adverse events among vaccinees as well as the risk of transmission of vaccinia to their contacts (e.g., patients, household members) and resulting adverse events in those contacts.

- **Smallpox vaccine and vaccinia immune globulin (VIG) supply**

The supplemental recommendations assume that both will be available for use, in sufficient supply, handled and administered according to standard protocols, and that any pre-event use of smallpox vaccine would be voluntary.

### **State and local vaccination capacity and capability**

Surveillance and containment, including ring vaccination, continue to be the primary strategy for the control and containment of smallpox. In addition, state and local health departments should be able, if necessary, to expand immunization to additional groups, up to and including their entire population, in a timely manner. CDC has recently issued large-scale vaccination clinic guidelines to assist state and local health departments in developing this capacity.[9]

### **Smallpox Vaccines and VIG Availability**

The only smallpox vaccine currently licensed in the United States is Smallpox Vaccine, Dried Calf Lymph Type, Dryvax®, manufactured by Wyeth Laboratories Inc. Dryvax® is a lyophilized preparation of live vaccinia virus grown on the skin of calves. On October 25, 2002, the Food and Drug Administration (FDA) approved a labeling supplement and a manufacturing supplement to Wyeth's biologics license application for Dryvax®. The manufacturing supplement provides for a new kit that includes lyophilized vaccine in a 100 dose vial, a new supply of diluent (one prefilled diluent syringe), one transfer needle, and 100 individually wrapped bifurcated needles. With the approval of this supplement, Dryvax® can again be

distributed and used as a licensed product. Licensed lots have to meet lot release specifications, which include recent testing to demonstrate that the vaccine retains its potency. Further information regarding the supplement approval and labeling for Dryvax® can be found at <http://www.fda.gov/cber/products/smawye102502.htm>. As of December 16, 2002, two lots consisting of a total of 2.7 million doses of Dryvax® had full approval for use as a licensed product. Additional lots of Dryvax® are expected to be released by FDA under the license.

Licensed Dryvax® vaccine for civilian use will only be available through CDC. Licensed vaccine will be used for vaccinating laboratory or healthcare workers who directly handle cultures, animals, or contaminated materials containing non-highly attenuated vaccinia or recombinant vaccinia viruses, or other orthopoxviruses that infect humans.[1] Requests for smallpox vaccine for vaccinating laboratory workers involved in vaccinia or orthopoxvirus research activities should be directed to:

CDC Drug Services  
1600 Clifton Rd. MS D-09  
Atlanta, GA 30333  
Phone: 404-639-3670  
Fax: 404-639-3717

State Health Departments are developing plans for vaccination of smallpox public health and health care teams and will be responsible for making vaccine requests to CDC to support the vaccination of these teams.

The CDC National Pharmaceutical Stockpile (NPS) has developed protocols to allow for the rapid, simultaneous delivery of smallpox vaccine to every state and US territory within 12-24 hours. State and local bioterrorism response plans should provide for the rapid distribution of vaccine within their jurisdiction.

VIG is currently 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, there was enough VIG available under an IND protocol to treat more than 4,000 serious adverse events. This is enough VIG doses to treat the adverse reactions that would be expected to result from the vaccination of 40 million people based on previously observed rates of adverse reactions.[10] Production of additional supplies of VIG is in progress.

## **Surveillance**

Cases of febrile rash illnesses, for which smallpox is considered in the differential diagnosis, should be immediately reported to local and/or state health departments. Following evaluation by these health departments, if smallpox laboratory diagnostics are considered necessary, the CDC Rash Illness Evaluation Team should be consulted at 770-488-7100. As smallpox was officially certified as eradicated in 1980 and no longer occurs naturally, an initial case of smallpox must be laboratory confirmed. At this time, laboratory confirmation for smallpox is available only at CDC. Clinical consultation and a preliminary laboratory diagnosis can be completed within 8-24 hours.

To assist medical and public health personnel in evaluating the likelihood of smallpox in patients with febrile rash illnesses, CDC has developed a rash illness assessment algorithm. Poster copies of this algorithm are available from state health departments and on the World Wide Web (<http://www.bt.cdc.gov/agent/smallpox/diagnosis>). Orders for copies of the poster can be made over the Internet at [https://www2.cdc.gov/nchstp\\_od/PIWeb/niporderform.asp](https://www2.cdc.gov/nchstp_od/PIWeb/niporderform.asp).

Surveillance activities, including notification procedures and laboratory confirmation of cases, would change if smallpox disease were confirmed in one or more patients. Additional information regarding surveillance activities following laboratory confirmation of a smallpox outbreak can be found in the [CDC Smallpox Response Plan and Guidelines](http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp) (<http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp>).

## **Pre-Release Vaccination of Selected Groups to Enhance Smallpox Response Readiness**

### ***Smallpox Response Teams***

Smallpox vaccination is recommended for persons designated by the appropriate bioterrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases that might necessitate direct patient contact. Additionally, persons responsible for administering smallpox vaccine in the pre-event smallpox vaccination program should be vaccinated (see **Vaccination of Persons Administering Smallpox Vaccine in the Pre-Event Smallpox Vaccination Program**, below).

To enhance public health preparedness and response for smallpox control, specific teams at the federal, state, and local level should be established to investigate and facilitate the diagnostic work-up of the initial suspected case(s) of smallpox and initiate control measures. These Smallpox Response Teams might include persons designated as medical team leaders, public health advisors, medical epidemiologists, disease investigators, diagnostic laboratory scientists, nurses, personnel who would administer smallpox vaccines, and security/law enforcement personnel. Such teams may also include medical personnel who would assist in the evaluation of suspected smallpox cases.

The ACIP recommends that each state and territory establish and maintain at least one Smallpox Response Team. Considerations for additional teams should take into account population and geographic considerations and should be developed in accordance with federal, state, and local bioterrorism plans.

### ***Smallpox Health Care Teams***

The ACIP and HICPAC recommend that in the first stages of the pre-event smallpox vaccination program, each acute care hospital identify a group of healthcare workers who would be vaccinated and trained to provide direct medical care for the first few smallpox patients requiring hospital admission and to evaluate and manage patients who present to the Emergency Department with suspected smallpox. This team would provide care 24 hours a day for the first several days after patients with smallpox have been identified, until additional healthcare personnel can be vaccinated. Non-vaccinated workers would be restricted from entering into the rooms of smallpox patients or (under emergency conditions) would wear personal protective equipment.

The ACIP and HICPAC recommend that Smallpox Health Care Teams include: 1) Emergency Room staff, including physicians and nurses caring for children and adults; 2) Intensive Care Unit staff, including physicians, nurses, and in hospitals that care for infants and children, pediatricians and pediatric intensive care specialists; 3) 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; 4) primary care house staff (i.e., medical, pediatric, and family physicians); 5) medical subspecialists, including infectious disease specialists;\* 6) infection control professionals; 7) respiratory therapists; 8) radiology technicians; 9) security personnel; and 10) housekeeping staff (e.g., those staff involved in maintaining the health care environment and decreasing the risk of fomite transmission). The ACIP and HICPAC anticipate that the size and composition of Smallpox Healthcare Teams will vary according to the institutions and their patient populations, but each hospital would ideally have enough vaccinated personnel from each occupational category to ensure continuity of care. When feasible, the first stage vaccination program should be comprised of previously vaccinated healthcare personnel to further decrease the potential for adverse events, as they occur less commonly in previously vaccinated individuals.

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\* 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.

Clinical laboratory workers are not recommended for inclusion in the initial phase of pre-event smallpox vaccination because the quantity of smallpox virus likely to be in clinical specimens of blood and body fluids is low. Consistent adherence to Standard Precautions and American Society for Microbiology/CDC protocols will prevent exposure to smallpox virus in clinical specimens.

### ***Vaccination Method***

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. 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.[4] 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. If no evidence of vaccine take is apparent after 7 days, the individual may be vaccinated again. Any remaining vaccine should be wiped off the skin with dry sterile gauze and the gauze disposed of in a biohazard waste container.

### ***Vaccination of Persons Administering Smallpox Vaccine in the Pre-Event Smallpox Vaccination Program***

Historically, vaccinators were administering smallpox vaccine as part of a disease control/eradication program, and were revaccinated frequently. There are no data on the risks of inadvertent inoculation of vaccinia among susceptible vaccinators, but they are assumed to be at some risk. The risk may be analogous to that seen in laboratory workers handling non-highly attenuated vaccinia strains; ACIP currently recommends that these workers be vaccinated.[1] Prior vaccination likely confers substantial protection, but significant local reactions can occur among revaccinees; thus, protection from inadvertent inoculation cannot be considered absolute.[11]

To minimize the clinical impact of inadvertent inoculation, should it occur, ACIP and HICPAC recommend that persons administering smallpox vaccine in the proposed pre-event smallpox vaccination program be vaccinated. It is desirable for vaccinators to have a confirmed vaccine take before vaccinating others but it is acceptable for vaccinators to be vaccinated immediately before beginning work in vaccination clinics. Vaccination of this group will also contribute to preparedness for smallpox response. Should a smallpox release occur, these experienced vaccinators could immediately be deployed for outbreak response vaccination programs.

### **Preventing contact transmission of vaccinia virus**

Following primary smallpox vaccination, vaccinia virus can be isolated from the vaccination site beginning with development of a papule (i.e., 2 to 5 days after vaccination) until the scab separates from the skin lesion (i.e., 14 to 21 days after vaccination), with maximal shedding at 4 to 14 days after vaccination. Viral shedding may be of shorter duration among re-vaccinees.[12, 13] While vaccinia virus is shed, inadvertent inoculation can occur from the vaccination site to another area of the body, most commonly the face, eyelid, nose, lips, genitalia, or anus. In addition, transmission could occur to another non-immune person, leading to self-limited infections or to more serious complications, particularly among persons with medical contraindications to vaccination. The risk of mortality from eczema vaccinatum may be higher among contacts than among vaccinees.[10, 14, 15]

Historical data suggest that primary vaccinees were the major source of vaccinia infection among contacts, presumably because they had a larger or longer duration of viral shedding than did re-vaccinees.[12, 14] Transmission generally required very close interaction and occurred most often in the home, and often involved children.[14] Nosocomial transmission of vaccinia from either patients or healthcare workers to patients has rarely been described; in most instances the source of vaccinia was a patient suffering from an adverse event after vaccination. Most of these cases involved direct person-to-person transmission, though for some, the mode of spread was not determined.[14, 16-18] These data suggest that secondary transmission of vaccinia virus occurs infrequently, especially from adults, and requires very close contact.

These historical data need to be considered with the understanding that the current situation is different in several respects. A number of factors would suggest that both the risk of transmission and the risk that a serious adverse event may result if transmission occurs may be greater today than previously. First, at the time of these earlier studies, most healthcare workers would have been previously vaccinated and therefore less likely to transmit vaccinia, and most patients would have been vaccinated and less likely to be susceptible to vaccinia. Second, it is unknown how many healthcare workers would have been vaccinated during these earlier study periods, when vaccination of healthcare workers was routinely recommended. Third, there are now increased numbers of hospitalized patients at risk of serious complications of vaccinia infection, especially those with compromised immune systems from human immunodeficiency virus [HIV] infection or acquired immunodeficiency syndrome [AIDS], chemotherapy or other immunosuppressive medications, organ transplantation, etc. There are also more patients with indwelling invasive devices requiring frequent manipulation (e.g., intravenous lines, arterial lines, dialysis, ostomies, central venous lines) on most hospital wards. On the other hand, infection control practices have improved and healthcare workers are more cognizant of infection control practices today. Additionally, new approaches to vaccination site care (i.e., semipermeable dressings) are now available which have been demonstrated to provide an effective barrier for containment of vaccinia virus.[12, 19]

After considering the data and the caveats noted above, the ACIP and HICPAC concluded that good infection control practices should essentially eliminate the risk of vaccinated healthcare workers transmitting vaccinia to patients, and that placing healthcare workers on administrative leave could create staffing shortages that would be a risk to patients.[20, 21]

Consequently, following smallpox vaccination, the ACIP and HICPAC recommend that 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.[12, 19] 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 [19], 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.

The most critical measure in preventing contact transmission is consistent hand-hygiene with antimicrobial soap and water or an approved alcohol based hand-rub after any contact with the vaccination site or with materials that have come into contact with the site and before patient contact.[22] In addition, care should be taken to prevent contact with the site or contaminated materials from the site.

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 (i.e., when accumulation of purulent material is visible), 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**). When feasible, staff responsible for dressing changes for teams should be vaccinated, but it is acceptable for unvaccinated staff to change dressings; all persons handling bandages should observe contact precautions.

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 important to prevent inadvertent inoculation. In non-patient care settings in which transmission of vaccinia is a concern due to close personal contact with children or other persons (e.g., care for young children), 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; or the site may 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.[23, 24]

### **Administrative Leave for Vaccinated Health Care Workers**

Administrative leave is not required routinely for newly vaccinated healthcare personnel unless they: 1) are physically unable to work due to systemic signs and symptoms of illness; 2) have extensive skin lesions which cannot be adequately covered, or if they 3) are unable to adhere to the recommended infection control precautions. The very close contact required for transmission of vaccinia to household contacts is unlikely to occur in the healthcare setting.

### **Vaccination and Blood Donation**

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 would 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 many 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 just prior to being vaccinated and donating again once they are eligible. Since the donor deferral period needs to be documented carefully, it is suggested that all vaccinees 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.

## **Contraindications for Use of Smallpox Vaccine in the Pre-event Smallpox Vaccination Program**

In the pre-event vaccination program, smallpox vaccination is contraindicated for persons with a history or presence of eczema or atopic dermatitis; that have other acute, chronic, or exfoliative skin conditions; that have conditions associated with immunosuppression; who are pregnant or breast-feeding; are aged <1 year; or who have a serious allergy to any component of the vaccine (Table 1). 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.

Atopic dermatitis, irrespective of disease severity or activity, is a risk factor for developing eczema vaccinatum following smallpox vaccination in either vaccinees or their close contacts [10, 25-29], 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 [30, 31], 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.

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 significant inadvertent inoculation and should not be vaccinated until the condition resolves. Additionally, persons with Darier's disease can develop eczema vaccinatum and therefore should not be vaccinated [28, 32].

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.,  $\geq 2$  mg/kg body weight or 20 mg/day of prednisone for  $\geq 2$  weeks]). Individuals 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 last 3 months should not be vaccinated.[33] Persons with immunosuppression also include hematopoietic stem cell transplant recipients who are <24 months posttransplant, and hematopoietic stem cell transplant recipients who are  $\geq 24$  months posttransplant, but have graft-versus-host disease or disease relapse. It is also reported that some patients with severe clinical manifestations of some autoimmune diseases (e.g., systemic lupus erythematosus) may have some degree of immunocompromise as a component of the disease.[34] While there are no data to indicate that an individual is at risk from live virus vaccines due to severe autoimmune disease in the absence of immunosuppressive therapy, individuals with immunodeficiency as a clinical component of their autoimmune disease should not receive smallpox vaccine during the pre-event vaccination program.

According to the product labeling, smallpox vaccine is not recommended for use in breast-feeding women (Wyeth Laboratories, package insert <http://www.fda.gov/cber/products/smawye102502.htm>); it is not known whether vaccine virus or antibodies are excreted in human milk. ACIP does not recommend smallpox vaccination of children and adolescents <18 years of age in the current pre-event vaccination program, and smallpox vaccine is contraindicated for infants <1 year of age.

Pre-event vaccination is also contraindicated among persons with household contacts: that have a history or presence of eczema or atopic dermatitis, irrespective of disease severity or activity; that have other acute, chronic, or exfoliative skin conditions; that have conditions associated with immunosuppression (see above); or who are pregnant. For purposes of screening for contraindications for pre-event vaccination, "household contacts" should be considered to include persons with prolonged intimate contact with the potential vaccinee, including the potential for direct contact with the vaccination site, e.g., sexual contacts.



The presence of an adolescent or child (including an infant) in the household is not a contraindication to vaccination of adult members of the household; data suggest that the risk of serious complications from transmission from an adult to a child is extremely small. Nonetheless, the ACIP recognizes that some programs may defer vaccination of household contacts of infants <1 year of age because of data suggesting a higher risk of adverse events among primary vaccinees in this age group, compared with that among older children.[27] The presence of a breast-feeding woman or a person with a vaccine component allergy in the household is also not a contraindication to vaccination of other household members (Table 1).

It should be emphasized that these conditions are contraindications in the pre-event vaccination program. No absolute contraindications exist regarding vaccination of a person with a high-risk exposure to smallpox; persons at greatest risk for experiencing serious vaccination complications are also at greatest risk of death if they become infected with the smallpox virus. If a relative contraindication to vaccination exists in the setting of a bioterrorism threat or exposure, the risk for experiencing serious vaccination complications must be weighed against the risk for experiencing a potentially fatal smallpox infection.[1]

### ***Precautions for Smallpox Vaccination***

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.

### ***Screening for Atopic Dermatitis as a Contraindication for Vaccination***

To assist providers in identifying persons that should defer smallpox vaccination, the ACIP suggests two screening questions (Figure 1). While sensitive, this approach to screening may preclude vaccination of many individuals who could otherwise be safely vaccinated. For persons in whom the dermatological risk factor or diagnosis is uncertain, some organizations, such as the military or CDC, may elect to develop more precise screening tools. These secondary screening tools should weigh the individual's risk of developing an adverse event with the requirement of occupational readiness through safe smallpox vaccination.

### ***Screening for Pregnancy as a Contraindication for Vaccination***

Fetal vaccinia is a very rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception. Infection, which may spread to the fetus if viremia occurs after vaccination, is manifested by typical skin lesions, organ involvement, and fetal or early neonatal death.[35] Among 20 pregnancies affected between 1932-72 that were reported in one case series, 18 occurred when the pregnant woman was vaccinated and 2 occurred in pregnant contacts; 13 occurred among primary vaccinees and 3 in those being revaccinated; 7 occurred during the first trimester and 13 in the second trimester; only one of 20 pregnancies was maintained until term, and of 21 affected births, 3 infants survived.[35] A cohort study of pregnant women vaccinated during a mass campaign in Sweden in 1963 showed a higher than expected rate of fetal loss [36]; pathology was not done to evaluate causation, however, and vaccinees may have been at higher risk for adverse outcomes of pregnancy. Smallpox vaccination of pregnant women has not been associated with an increased risk of congenital malformations.[37]

Because of the small 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 and not 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 thinks she could 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 access 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.[38]

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. Vaccination during pregnancy should not ordinarily be a reason to terminate pregnancy. To expand understanding of the risk of fetal vaccinia and to document whether other adverse pregnancy outcomes may be associated with vaccination, a prospective pregnancy registry should be maintained and any adverse pregnancy outcomes among pregnant women who were inadvertently vaccinated (if any) should be carefully investigated.

### ***Screening for HIV Infection as a Contraindication for Vaccination***

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, there are few data on the risk of vaccination among HIV infected persons. A single case report has been published of a U.S. military recruit who developed disseminated vaccinia following smallpox vaccination and was successfully treated with VIG but later died of complications of AIDS.[39] Although the exact number of HIV-infected persons who were vaccinated in the military program is unclear, 732 recruits who were in the service between 1981-85 when vaccinations were administered tested HIV-positive during the period 1985-88, for an estimated frequency of serious adverse events among HIV-positive persons of 1/732, or 0.137% (95% CI 0.084%-0.22%); if only half were HIV-positive at the time of vaccination, the frequency increases to 1/366, or 0.273% (95% CI 0.17%-0.44%) (Birx, Walter Reed Army Institute of Medicine, personal communication, September 2002). Since it is likely that the immunologic status of the HIV-infected person is the key to the risk from vaccination and the immunologic status of the recruits at the time of vaccination is not known, these estimated rates may not apply to other groups of HIV-infected persons today.

There are 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.[40] Estimates of the number of infected health care workers range from about 21,000 to 48,000 (unpublished data, Division of Health Care Quality Promotion, CDC); 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. Among US adults between 18-49 years old, 85% report being sexually active, and of these 11% reported having multiple sex partners in the preceding 12 months. In addition, 4.2% reported high-risk behaviors such as use of intravenous drugs, treatment for a sexually transmitted disease, or anal sex without a condom, or having a positive HIV test.[41] Substantial numbers of HIV infected persons, however, 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 vaccinia complications among persons

with HIV infection or other immunosuppressive conditions; persons who think they may have one of these conditions should not be vaccinated.

The 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, where permitted by law, anonymous setting with results communicated to the potential vaccinee before the planned date of vaccination. Persons with a positive test result should be told not to present to the vaccination site for immunization. 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.[42]

### **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.[43-46] 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.[47, 48] To minimize the potential risk for interference, parenterally administered live vaccines not administered on the same day should be administered  $\geq 4$  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  $\geq 4$  weeks after the last, invalid dose.[33]

It has been shown that smallpox vaccine can be administered at the same time as a number of other antigens, usually at a different site, 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, Bacillus of Calmette and Guérin (BCG) vaccine, yellow fever vaccine, measles vaccine, and diphtheria and tetanus toxoids and whole cell pertussis vaccine.[49] However, there are no data on simultaneous administration of smallpox vaccine with other vaccines now routinely administered to children and adults in the United States.

It is possible that varicella vaccine virus lesions could be confused with vaccinia lesions if the vaccines were given simultaneously. In uncontrolled trials of persons  $\geq 13$  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 (Merck and Company, Inc., package insert). 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.[50]

Smallpox vaccine may be administered simultaneously with any inactivated vaccine, such as influenza vaccine, to encourage appropriate receipt of all indicated vaccines, e.g., in populations such 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  $\geq 4$  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 [51], as has been observed following administration of other parenteral live virus vaccines [33]. Healthcare workers due 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.

### **Reporting and Management of Adverse Events**

Individuals with progressive vaccinia, eczema vaccinatum, and severe generalized vaccinia or inadvertent inoculation may 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 following 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. Recommendations on treatment of adverse events have recently been published.[52]

Additionally, clinically significant adverse events following smallpox vaccination should be reported to the Vaccine Adverse Event Reporting System. Reports may be made via the Internet through a secure web-based system at <https://secure.vaers.org/VaersDataEntryintro.htm>. Printable VAERS forms are located online at [http://www.vaers.org/pdf/vaers\\_form.pdf](http://www.vaers.org/pdf/vaers_form.pdf) or postage-paid forms may be obtained by calling 1-800-822-7967. Submission of VAERS reports via the Internet is encouraged to expedite processing and data entry. Completed forms can be faxed toll-free to 1-877-721-0366 or mailed to P.O. Box 1100, Rockville, MD 20894-1100. Further information on VAERS reporting can be obtained by calling 1-822-7967 or via email at [info@vaers.org](mailto:info@vaers.org).

### **Future Directions**

The ACIP will review these recommendations periodically, or more urgently if necessary. These reviews will include new information or developments related to smallpox disease, smallpox vaccines (including licensure of additional smallpox vaccines), risk of smallpox attack, smallpox vaccine adverse events, and the experience gained in the implementation of the current recommendations. Revised recommendations will be developed as needed.

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**Table 1.** Contraindications for use of smallpox vaccine in pre-event smallpox vaccination among vaccinees and their household contacts

	Vaccinees	Household contacts*
History or presence of eczema or atopic dermatitis	x	x
Other acute, chronic, or exfoliative skin conditions†	x	x
Immunosuppression**	x	x
Pregnancy	x	x
Breast-feeding	x	
Aged <1 year††	x	
Vaccine component allergy	x	

\* For purposes of screening for contraindications, "household contacts" should be considered to include persons with prolonged intimate contact with the potential vaccinee, including the potential for direct contact with the vaccination site, e.g., sexual contacts.

† Conditions include burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis, or psoriasis. Persons with these conditions should not be vaccinated until the dermatologic condition resolves.

\*\* Conditions include human immunodeficiency virus, acquired immunodeficiency syndrome, leukemia, lymphoma, generalized malignancy, solid organ transplantation, cellular or humoral immunodeficiencies, or therapy with alkylating agents, antimetabolites, radiation, or high-dose corticosteroids.

†† Vaccination of infants <1 year of age is contraindicated. Additionally, ACIP does not recommend vaccination of children and adolescents <18 years in the pre-event smallpox vaccination program.

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**Figure 1.** Screening for eczema and atopic dermatitis among potential recipients of smallpox vaccine.

