

Smallpox Vaccination in 2003: Key Information for Clinicians

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The purpose of this article is to provide clinicians with answers to some of the most important and frequently asked questions related to smallpox vaccination. Information that has direct bearing on this issue is broad in scope, complex, and multidisciplinary, and this article is offered as an attempt to distill this information into a single accessible resource. The information is organized as questions and answers and grouped in the following major sections: Purpose and Approach of the US Smallpox Vaccination Program, Description of the Current Vaccine and Vaccine Supply, Efficacy and Duration of Immunity Following Vaccination, Vaccine Administration, Vaccine Safety and Adverse Reactions, Contraindications to Smallpox Vaccination, Treatment of Vaccine-Related Complications, Liability Issues Related to Smallpox Vaccination, and The Recent Israeli Smallpox Vaccination Series.

PURPOSE AND APPROACH OF THE US SMALLPOX VACCINATION PROGRAM

Why has the President of the United States initiated a smallpox vaccination program in 2002–3? This is answered by relevant excerpts from the President's announcement of this program, from 13 December 2002:

We know, however, that the smallpox virus still exists in laboratories, and we believe that regimes hostile to the United States may possess this dangerous virus. To protect our citizens in the aftermath of September the 11th, we are evaluating old threats in a new light. Our government has no information that a smallpox attack is imminent. Yet it is prudent to prepare for the possibility

that terrorists...who kill indiscriminately would use diseases as a weapon....

Today I am directing additional steps to protect the health of our nation. I'm ordering that the military and other personnel who serve America in high-risk parts of the world receive the smallpox vaccine, men and women who could be on the front lines of a biological attack must be protected.... This particular vaccine does involve a small risk of serious health considerations....

At present, the responsible course is to make careful and thorough preparations in case a broader vaccination program should become necessary in the future. There may be some citizens, however, who insist on being vaccinated now. The public health agencies will work to accommodate them. But that is not our recommendation at this time....

We do recommend vaccinations for one other group of Americans that could be on the front lines of a biological attack. We will make the vaccine available on a voluntary basis to medical professionals and emergency personnel and response teams that would be the first on the scene in a smallpox emergency. These teams would immediately provide vaccine and treatment to Americans in a crisis and, to do this job effectively, members of these teams should be protected against the disease. [1]

What groups of persons are now being vaccinated or being offered voluntary vaccination?

The 3-phase vaccination plan is summarized in table 1. Smallpox vaccination has been mandated for a portion of the US Armed Forces, and that program has begun. Smallpox vaccination for medical and health care personnel is being administered on a voluntary basis and was initiated in late January 2003. It has been announced that vaccination will be offered to additional groups of citizens later this year, in phase II and Phase III of the planned smallpox vaccination program. Details regarding the plans of phase II and phase III are not yet available.

What is a Smallpox Response Team? The US President's smallpox vaccination plan calls for the creation of voluntary Smallpox Response Teams. These teams are intended to provide

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Table 1. Outline of the current US smallpox vaccination plan.

Group to be vaccinated	Approximate no. of persons	Status of vaccination	Time of vaccination	Program phase
Selected members of the armed forces and personnel who serve in high-risk parts of the world	500,000	Mandatory	Initiated 13 Dec 2002	I
Selected personnel from the US State Department who serve overseas	—	Voluntary	—	I
Public health response and health care teams	440,000	Voluntary	Late January 2003	I
Other medical care providers and first responders	10,000,000	Voluntary	—	II
General public	—	Not recommended at present; would be administered under oversight of a clinical trial	Possibly in late 2003 or 2004	III

NOTE. Data are from [2] and [3]. —, Information not yet determined or otherwise unavailable.

health care to patients infected with smallpox during the first 7–10 days of an outbreak and to assist in epidemiological investigation and vaccination efforts. States have been asked to form these teams according to their own planning needs, but these teams are meant to comprise health care workers and public health officials [4]. State governments have requested specific quantities of vaccine from the Centers for Disease Control and Prevention (CDC; Atlanta, GA). In turn, health care institutions are participating on a voluntary basis and, after consultation with state governments, are determining the number of volunteers to seek.

How are health care institutions identifying volunteers for this program? Individual health care organizations have been asked to identify volunteers in their institutions who could care for patients with smallpox during the first 7–10 days after a biological attack with smallpox virus. Such volunteers and the members of their households should have no contraindications to vaccination (see the section Contraindications to Smallpox Vaccination, below). The Advisory Committee on Immunization Practices (ACIP) of the CDC has recommended that health care institutions have teams that include the following groups of persons [5]:

1. Emergency department staff, including both physicians and nurses.
2. Intensive care unit staff, including physicians, and nurses. In hospitals that care for infants and children, this encompasses pediatricians, pediatric intensivists, and pediatric emergency department physicians and nurses.
3. General medical unit staff, including internists, pediatricians, obstetricians, and family physicians in institutions where these individuals are the essential providers of primary medical care.
4. Primary-care house staff (i.e., selected medical, pediatric, obstetric, and family physicians).
5. Medical subspecialists, including infectious diseases spe-

cialists. This may also involve the creation of regional teams of subspecialists (e.g., local medical consultants with smallpox experience, dermatologists, ophthalmologists, pathologists, surgeons, and anesthesiologists in facilities where intensivists are not trained in anesthesia) to deliver consultative services.

6. Infection-control professionals.
7. Respiratory therapists.
8. Radiology technicians.
9. Security personnel.

10. Housekeeping staff (e.g., those staff involved in maintaining the health care environment and decreasing the risk of fomite transmission).

Some health care organizations have indicated that they will only vaccinate persons who have been previously vaccinated, because of the lower incidence of side effects in that population. This would exclude most persons aged <33 years, a group that includes a large number of interns, residents, and nurses.

Why have some hospitals decided not to participate in the US smallpox vaccination program? A number of hospitals have declined participation. Leaders of those institutions have said that they do not believe that the threat of smallpox attack, as currently articulated, justifies the risks that vaccination would pose to their staff or their patients. Other concerns include liability and workers' compensation issues. A recent survey suggested that at least 80 of the 5000 hospitals in the United States have declined participation. The Emergency Infections Network of the Infectious Diseases Society of America asked participants, "Is your primary hospital currently planning to vaccinate a group of HCWs [health care workers] when the vaccine is released?" Responses from 301 participants indicated that 241 (80%) planned to participate, 23 (8%) planned not to participate, and 37 (12%) were undecided (L. Strausbaugh, personal communication).

Why not designate "smallpox hospitals," as was done in some cities in the early 1900s? In June 2002, the ACIP sug-

gested that states designate hospitals that have isolation facilities as smallpox hospitals, in the event of an outbreak. There was historic precedent for this, including the Boston epidemic of 1901–1903, in which all patients were hospitalized at 2 publicly administered smallpox hospitals [6]. However, it was later decided by the ACIP that this was not feasible, because patients would most likely to go to hospitals where they are accustomed to receiving care. In addition, it was judged likely that few health care organizations would choose to become one of the few dedicated smallpox hospitals.

DESCRIPTION OF THE CURRENT VACCINE AND VACCINE SUPPLY

What was the origin of the early smallpox vaccine? The original smallpox vaccine used by Edward Jenner in 1796 was an inoculum of cowpox, an orthopox virus that causes a pustular rash on the skin of cattle. Eventually, smallpox vaccinations were performed with vaccinia virus, another orthopox-virus. It is unclear when vaccinia supplanted cowpox as the commonly used vaccine virus. The global eradication effort in the 1960s and 1970s led to the development of a stable, freeze-dried formulation of vaccinia virus. The product, which was produced by Wyeth Pharmaceuticals in the United States, was called DryVax.

What is the vaccine currently licensed by the US Food and Drug Administration (FDA)? The strain of smallpox virus used to produce DryVax was provided by the New York City Board of Health (NYCBH) in the 1970s for a mass production program. It is grown in the skin of calves. DryVax is freeze-dried and packaged in 100-dose vials that are reconstituted with 50% glycerin and 0.25% phenol. After reconstitution, DryVax has a potency that averages 1.6×10^7 pfu/mL [7]. Approximately 14.8 million doses of DryVax exist.

Where is the vaccine stored and how does one acquire it? The CDC controls the repository of smallpox vaccine. The CDC is in the process of distributing vaccine to state health departments in sufficient quantity to vaccinate the ~440,000 health care personnel and public health officials identified in phase I of the smallpox vaccination plan (table 1). In the event of a smallpox attack, vaccine would be distributed to the locations where it is needed by way of the National Pharmaceutical Stockpile (NPS). The NPS is a supply of prepacked essential medical equipment and pharmaceuticals that is stored in undisclosed locations around the country in environmentally controlled and secured warehouses, ready for rapid deployment [8].

Are new smallpox vaccines being developed? In addition to DryVax, there is also a supply of a second vaccine produced years ago by Aventis Pasteur; this vaccine is also in the NPS and would be available for use as an investigational new drug in the event of an emergency. There are 85 million doses of

this Aventis vaccine available. It could be diluted 1:5, if necessary. Four other vaccines are under study; they are as follows.

Acam1000 vaccine. In 2000, Acambis (Cambridge, UK) was contracted to produce 54 million doses of vaccine from the NYCBH strain by means of a modernized vaccine development process in which vaccinia is grown in MRC-5 cell culture [9]. The ACAM1000 vaccine is in development, but phase I clinical trials that enrolled 100 individuals have been completed and yielded a 100% “take” rate (i.e., the proportion of patients who demonstrated a major reaction to the vaccine, or a “take,” which is defined as the presence of a papule, vesicle, ulcer, or crusted lesion, surrounded by erythema and induration, on days 6–8 after vaccination [10]). Phase II trials are under way.

Acam2000 vaccine. After 11 September 2001, it was decided that the stockpiles of smallpox vaccine needed to be rapidly augmented. The US government contracted with Acambis-Baxter to produce 155 million doses of vaccine employing the same process developed for Acam1000 but using a Vero cell culture system. Bulk production has been completed, and a considerable amount of vaccine has been delivered to the NPS. Delivery of all 155 million doses is expected by April 2003. Phase I trials have been completed, and phase II trials were initiated in January 2003.

Modified vaccinia Ankara (MVA) vaccine. This vaccine was attenuated by high passage in chick embryo fibroblasts, and it shows reduced replication capacity in mammalian cells. It is administered by needle and syringe. In contrast to DryVax, which induces a skin lesion that permits measurement of the strength of the reaction (the “take”) and, thus, the effectiveness of the vaccine, MVA does not produce a skin lesion. The serologic response to MVA in humans will be compared to that noted for DryVax, and the ability of MVA to protect monkeys exposed to monkeypox virus will be evaluated. Because of its inability to replicate, MVA is expected to be safer than DryVax. Studies in mice show that MVA elicits a cell response comparable to that achieved with replication competent vaccinia in immunocompromised individuals [11]. MVA is undergoing phase I studies at the National Institute for Allergy and Infectious Diseases (National Institutes of Health), and a contract program has been initiated for its industrial development and acquisition [12].

Japanese strain LC16m8 vaccine. This vaccine is an attenuated, temperature-sensitive vaccine strain produced by repeated passage of Lister strain vaccinia in rabbit kidney cells. It was initially developed in Japan in the 1970s, and vaccination of 50,000 well-studied Japanese children resulted in less-severe reactions than those observed with other vaccines. Currently, it is licensed by Vaxgen from Kaketsuken. Vaxgen is planning to initiate phase I trials in the spring of 2003 [13].

How large is the smallpox vaccine supply in the United States? The existing DryVax supply consists of 14.8 million

doses. There are 85 million doses of the Aventis product. Both of these vaccines could be diluted 1:5, if necessary [7, 14, 15]. When the Acam1000 and Acam2000 production is complete, there will be an additional 209 million doses of vaccine available [9].

EFFICACY AND DURATION OF IMMUNITY FOLLOWING VACCINATION

When administered prior to exposure to smallpox virus, vaccinia vaccine has historically had an efficacy in the range of 90.7%–96.7% [16]. Vaccination within the first few days (perhaps as late as 4 days) after exposure to smallpox virus may prevent or significantly ameliorate subsequent illness [16].

Are individuals who have been previously vaccinated protected against smallpox? In the United States, routine vaccination ceased in 1972. With relatively few exceptions, since global eradication was declared by the World Health Organization in 1980, the only US citizens who have undergone vaccination have been some military personnel in the 1980s and personnel in experimental laboratories who were at risk of exposure to non–highly attenuated orthopoxviruses. Neutralizing antibodies and evidence of cell-mediated immunity (CMI) may persist for ≥ 30 years after primary (first-time) vaccination, but it is not known what serologic markers correlate with protection against infection. Prior to smallpox eradication, immunity to smallpox in countries where it was endemic resulted from the combined effects of vaccination and exposure to variola virus that led only to subclinical disease (variola sine eruptione). Data from countries where smallpox virus was introduced after a prolonged absence does show that having been vaccinated many years before is at least partially protective against a fatal outcome. Among patients who were infected with smallpox after it had been imported into Europe, ~52% of those who had never been vaccinated died, whereas only 11.1% of those vaccinated >20 years previously died [17]. Best estimates are that an increased level of protection against smallpox persists for at least 3 years after primary vaccination and that substantial but waning immunity may persist for ≥ 10 years [18].

VACCINE ADMINISTRATION

How is the smallpox vaccine administered? Multiple cutaneous punctures are made with a bifurcated needle to introduce an inoculum of vaccinia into the dermis. The person who administers the vaccine (the vaccinator) should have been vaccinated previously. The vaccinator can be vaccinated and begin administering vaccine immediately, but, in nonemergency conditions, it would be safer for the vaccinator to have proven take before beginning vaccinations.

The following are step-by-step instructions for administration of the vaccine, as recommended by the CDC [5].

1. The CDC recommends no skin preparation. Skin preparation with alcohol or acetone is not recommended—it will diminish the viable viral inoculum and lead to decreased vaccination take rates.

2. Dip the bifurcated needle into the vaccine vial. A small amount of vaccine will be retained by the bifurcated needle by capillary action.

3. Rapidly make 15 epidermal punctures on the deltoid area with the bifurcated needle. Each puncture should be of sufficient depth that a trace of blood appears at the vaccination site after 15–30 s, and the punctures should be contained within a 5-mm diameter. Note that the package insert recommends 3 punctures for primary vaccinations. When the bifurcated needle was introduced for use in the 1960s, the package insert called for 3 punctures for primary vaccinations and 15 for revaccinations. The validity of this recommendation was never substantiated by special studies. World Health Organization staff who conceived and tested the multiple-puncture technique found that, with 15 rapidly performed punctures, take rates were consistently close to 100%. With 3 punctures, frequent failures were observed. There were no apparent differences with respect to the frequency of reactions, whether 3 or 15 punctures were made. Note that recent studies of the vaccine preparations have used 15 punctures. The package insert recommendation for 3 punctures, unfortunately, does not reflect 12 years of experience with millions of vaccinations.

4. Use sterile gauze to absorb blood, discharge, and excess vaccine from the vaccination site.

5. Discard any used materials in a sealed plastic biohazard waste container.

6. Cover the lesion with sterile gauze or a similar absorbent material to absorb the exudate that develops. Gauze should be covered with a semioclusive cover, such as Opsite (Smith and Nephew)

7. The CDC recommends a “site care component” for the smallpox vaccination protocol, which specifies that dressings of vaccination sites should be inspected daily to evaluate local reactions, to determine whether there is a take, to change the gauze dressing, and to reinforce the importance of strict hand hygiene. All contaminated materials (i.e., gauze dressings, gowns, gloves, and instruments) should be treated as biohazards.

What instructions should be given to the vaccine recipient? The vaccinee must understand that there is viable vaccinia virus in the lesion from the moment the papule forms (which occurs on days 2–5 after vaccination) until the scab dislodges (on days 14–21) [19]. For revaccination, this time period is accelerated. Thus, the vaccination site should be cov-

ered (as described in the previous subsection, “How is the smallpox vaccine administered?”), because vaccinia may be transmitted to an unvaccinated individual after close contact (termed “contact vaccinia”) or to other body parts of the vaccinee (termed “accidental vaccinia”) after the accidental contamination of the vaccinee’s hands by touching the site of the recent vaccination. Accidental autoinoculation may lead to serious complications, such as keratitis. The vaccinee should be instructed not to touch, rub, or scratch the site, even though pruritis is typically experienced. Showering is acceptable, but the dressing should be replaced afterward to keep the site dry. Prolonged exposure to water should be avoided. The vaccinee should avoid contact with persons who have contraindications to vaccination until the scab spontaneously separates. Strict hand hygiene should be maintained after vaccine administration and changes of the dressing, to prevent transmission of vaccinia.

What is the expected (typical) reaction after primary smallpox vaccination? The local reaction after primary vaccination typically begins as a papule that occurs at the vaccination site 3–4 days after vaccination. Subsequently, a vesicle with surrounding erythema develops, and by days 8–9, a pustule is well formed. The size of the pustule depends on the size of the area of inoculation; it is usually 7–12 mm in diameter, but larger reactions occur. This pustule crusts over and forms a scab, which spontaneously detaches, usually on days 17–21 after vaccination [7, 20]. The presence of a papule, vesicle, ulcer, or crusted lesion, surrounded by erythema and induration, when the lesion is examined at days 6–8, is considered to be a major reaction (a take) [10]. The evolution of the normal local reaction or take with primary vaccination is shown in table 2. A major reaction indicates that virus growth has taken place and implies that there is immunity to smallpox, with antibody and cytotoxic T cell response [7]. All other reactions are deemed “equivocal.” Since equivocal reactions are not guaranteed to indicate immunity, it is recommended that persons who have equivocal reactions be revaccinated. The take rate for primary vaccination depends largely on the quality of the vaccine and whether proper vaccination technique was used. In a recent trial that compared administration of diluted and undiluted DryVax vaccine to 680 previously unvaccinated, healthy adult volunteers aged 18–32 years, the take rate was 97.1%–99.1%, which demonstrated that DryVax maintains efficacy at dilutions as high as 1:10 [7]. Phase I clinical trials using the Acam1000 and Acam2000 vaccine have resulted in 99%–100% take rates.

Common local reactions are to be expected in up to 6.6% of patients who receive primary vaccination (hereafter, “primary vaccinees”); they are less frequent among patients who are revaccinated. These reactions include satellite lesions, lymphangitis in regional axillary nodes, lymphadenopathy, local edema, and intense circumferential erythema (often confused

Table 2. The evolution of the normal local reaction to primary smallpox vaccination.

Day(s) after vaccination	Event and/or lesion
0	Vaccination
3–4	Papule
5–6	Vesicle with or without erythema
8–9	Pustule
≥12	Crust forms and becomes a scab
17–21	Scab detaches and leaves a scar

NOTE. Data are from [19].

with bacterial cellulitis). Common systemic symptoms include headache, nausea, fever, chills, malaise, and myalgia. At least 1 of these symptoms is noted in most vaccine recipients. The onset of systemic symptoms typically peaks on days 8–10 after vaccination, and the symptoms generally resolve in 1–3 days [7]. Fever with a temperature of $\geq 38.8^{\circ}\text{C}$ is noted in 10%–15% of vaccine recipients; fever with a temperature of $>38.9^{\circ}\text{C}$ or fever after day 16 are seen in $\sim 1\%$ of vaccine recipients [7].

What if there is no vaccination take? A “take” is defined as presence of a papule, vesicle, ulcer, or crusted lesion, surrounded by an area of induration, on days 6–8 after primary vaccination or revaccination [10]. More than 95% of primary vaccinees who experience this reaction will have a serologic response [21]. “Equivocal reaction” is the term for other reactions that do not meet these criteria because of suboptimal vaccination, suboptimal vaccine, or prior immunity; such a reaction should be interpreted as a “nontake” and implies inadequate immune response and the need for revaccination, which can be done at the time that a reaction interpreted as being a nontake.

What is the expected (typical) reaction after smallpox revaccination? Response after revaccination is variable and is influenced by the immune status of the host. In some vaccinees, the typical primary reaction, with an unambiguous pustule, will develop ~ 1 week after vaccination. Individuals with some residual immunity exhibit fewer systemic symptoms, and a pustule may develop somewhat earlier than in primary vaccinees. In other subjects who have substantial residual immunity, erythema only (without a pustule) develops in 24–48 h and is considered a hypersensitivity reaction. Because it is not possible to distinguish a hypersensitivity reaction from failed vaccination, this is termed an “equivocal reaction.” Revaccination should be strongly considered for persons who exhibit an equivocal reaction [22].

VACCINE SAFETY AND ADVERSE REACTIONS

What type of reactions commonly follow smallpox vaccination? Compared with other currently available vaccines in

the United States, the smallpox vaccine has a higher rate of local reactions (95%), systemic reactions (20%–40%), and serious or life-threatening reactions (15–50 reactions per million persons vaccinated). The CDC recently published an extensive review of adverse events associated with smallpox vaccinations, which includes guidance for their management [10].

Mild local reactions. Nearly all vaccinees develop a local reaction characterized by a pustule and erythema with pain and/or pruritis. The absence of a local reaction implies that the vaccination did not “take,” and vaccination should be repeated. The take rate and extent of the reaction is reduced among persons who are revaccinated, depending to some extent on the duration between vaccinations. Persons with full immunity can be expected have a minimal take or no take. Satellite lesions consist of 1–10 small pustules within a few centimeters of the primary lesion. These progress through the stages of healing in parallel with the primary lesion. All vaccine recipients who have a take develop a ring of erythema around the pustule. In recent studies, the erythema averaged 5 cm in diameter [7]. However, 10% of recipients developed large local reactions, or “robust primaries.”

Rash. Generalized rash was commonly observed, especially in children. Most rashes were nonspecific macular-papular rashes or benign generalized vaccinia. “Generalized vaccinia” is a term used to describe small macules, papules, or occasional vesicles that develop in a small proportion of vaccine recipients [10]. Generalized vaccinia was described in all age groups during the 1960s but may have been more common in young children. These children usually did not appear to be ill, and the lesions resolved without scarring. Some patients with generalized vaccinia were more seriously ill, and, in selected instances, therapy with vaccinia immune globulin (VIG) may be justified, especially if these lesions are noted in an immunocompromised vaccine recipient or an immunosuppressed contact. More-serious rash illnesses occurred less frequently (see discussions of other forms of skin reactions, below).

What is a “robust take”? This is a local reaction that is ≥ 10 cm in diameter. This reaction is noted in 2%–16% of primary vaccinees [10]. A robust take may be very pruritic or painful, and it is often confused with bacterial cellulitis, which is quite rare [23]. Most robust takes improve within 24–72 h, with or without antibiotic therapy. Clues to bacterial infection are as follows: onset before day 5 or later than day 30 after vaccination, association with adenopathy, and failure to improve spontaneously within 72 h. Fever is not a distinguishing feature [10].

Mild systemic reactions. Approximately 20%–40% of primary vaccinees will have systemic symptoms: fever, chills, headache, myalgias, and/or fatigue. In the largest recent primary vaccination trial in the United States, 30% of participants

missed school or work because of vaccine-related symptoms [7].

How should local and systemic reactions be managed? Pruritis and pain at the injection site are common. First-generation antihistamines are commonly prescribed for treatment of pruritis; they do not work well for focal pruritic lesions but may help the patient to sleep. For pain, nonaspirin analgesics, such as acetaminophen or nonsteroidal anti-inflammatory agents, are recommended. Topical administration of agents such as steroids and antibiotics is not useful. Reactions to the tape used for dressings are managed with frequent bandage changes and switch to paper tape. Systemic reactions that manifest as fever, chills, myalgias, malaise, and headaches are best managed with nonsteroidal anti-inflammatory agents.

Reactions external to the vaccination site. The reported rate of these complications is highly variable and is dependent on the type of study conducted, the age of the recipients, the vaccine status of the hosts, and the integrity of the hosts’ immune systems (table 3). The most commonly quoted publications on adverse reactions are 2 reviews conducted in 1968: a US national survey (table 4) [24] and a 10-state US survey [25]. Compared with the national survey, the state survey found a 10-fold higher rate of serious reactions (64 vs. 890 reactions per million persons vaccinated), most probably for the reasons articulated below (see “Why do the rates of serious reactions vary substantially in different reports and case series?” below). Most of the data in the national survey are for minimal adverse event rates, and the data in the 10-state survey reflect active surveillance for complications. Therefore, a range is often reported. Of the reactions included, 3 are regarded as serious: progressive vaccinia, postvaccinial encephalitis, and eczema vaccinatum. An analysis of 67 vaccination-associated deaths from 1959 through 1966 and in 1968 found that 36 deaths (54%) resulted from postvaccinial encephalitis, 19 (28%) resulted from progressive vaccinia (in patients with severe immunodeficiency) and 12 (18%) resulted from eczema vaccinatum [10]. These studies were conducted in an era when screening and testing may have been less sophisticated than they are in current practice. It should also be noted that today’s population is likely more vulnerable because it is immunologically naive to vaccinia and because of the increased prevalence of atopic dermatitis and immunosuppression.

Compared with primary vaccination, what is the complication rate associated with revaccination? Data from the 10-state study of 5.6 million vaccine recipients found that the incidence of serious reactions was 10-fold less among persons who were revaccinated than among primary vaccinees [25]. This reduction applied to all categories of reactions except progressive vaccinia (table 5).

Why do the rates of serious reactions vary substantially in

Table 3. Summary of data and recommendation regarding vaccine reactions among primary smallpox vaccinees.

Reaction	Frequency in 1968, cases/million vaccinees	Pathogenesis	Clinical observations	Diagnostic findings and tests	Treatment	Prevention
Progressive vaccinia	0.9–1.5	Immune deficiency, especially CMI; uncontrolled viral replication	Primary vaccination site does not heal; several new lesions with no inflammation	Appearance of lesion in a typical host ± a positive viral test result ^a	VIG, up to 10 mL/kg, ± surgical debridement ± cidofovir therapy (as IND)	Do not vaccinate patients with immunodeficiency
Eczema vaccinatum	10.4–38.5	T cell defect and autoinoculation of skin from vaccine site or by viremic spread	Multiple skin lesions that look like the primary site, especially areas of eczema; bacterial infection	Typical lesions, elevated IgE levels and impaired T cell function ± positive viral test result ^a	Prompt VIG therapy, 0.6 mL/kg, ± cidofovir therapy, and ± antibiotic therapy for bacterial infections	Do not vaccinate patient with active or history of eczema or atopic dermatitis
Congenital vaccinia	— ^b	Infection of fetus	Extensive skin lesions at birth that look like the primary vaccine site	Third trimester vaccination or contact, typical lesions, positive viral test result ^a	VIG	Do not vaccinate pregnant patients (but do not terminate pregnancy because of inadvertent vaccination)
Accidental implantation	25.4–529.2	Autoinoculation of any disrupted skin	Lesions that look like the primary vaccine site; onset 7–10 days after autoinoculation	Typical lesions; if extensive, perform immune function and viral testing ^a	For a few lesions, no specific treatment; for multiple lesions, VIG, 0.6 mL/kg	Do not vaccinate patients with extensive skin disease; provide vaccine site care and counseling
Postvaccinial encephalitis	2.9–12.3	Unknown; probably autoimmune disorder	Onset 7–14 days after inoculation; headache, lethargy, and myelitis	Nonspecific findings and CSF with increased pressure and elevated levels of protein and mononuclear cells	Supportive care	No known predisposing condition
Vaccinia keratitis	Unknown	Autoinoculation of the eye and prior eye disease (most patients have no prior eye disease)	Corneal ulcer with onset 7–10 days after inoculation	Corneal ring lesion revealed by slit-lamp examination	Topical vidarabine or trifluridine	Do not vaccinate patients with inflammatory eye conditions; observe strict hygiene; provide prophylactic antivirals ± VIG for lid vaccinia
Generalized vaccinia	23.4–241.5	Presumed viremic spread	Onset 6–9 days after inoculation; lesions look like the primary site but smaller and heal quickly	Small generalized lesions; rule out erythema multiforme	For extensive disease only, VIG	

NOTE. Data are from [19, 24], and [25]. CMI, cell-mediated immunity; IND, investigational new drug; VIG, vaccinia immune globulin; ±, with or without.

^a Viral testing can be done only by the Centers for Disease Control and Prevention (Atlanta, GA) [10].

^b Fewer than 50 cases were reported.

Table 4. Frequency of adverse events due to smallpox vaccination in 1968.

Class of event, event	No. of events per million vaccinees			
	National survey [24]		Ten-state survey [25]	
	All primary ^a vaccinees	Vaccinees ≥1 year old	All primary ^a vaccinees	Vaccinees ≥1 year old
Serious but not life-threatening reactions				
Inadvertent inoculation	25.4	27.1	529.2	532.0
Generalized vaccinia	23.4	17.7	241.5	222.8
Erythema multiforme	NA	NA	164.6	131.3
Total	48.8		935.3	
Life-threatening reactions				
Postvaccinial encephalitis	2.9	2.4	12.3	8.6
Progressive vaccinia (vaccinia necrosum)	0.9	1.0	1.5	1.7
Eczema vaccinatum	10.4	10.6	38.5	41.5
Total	14.2		52.3	
Death	1.1	0.6	1.5	NR

NOTE. Table reproduced, with slight modifications, from Centers for Disease Control and Prevention Web site (<http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp>). Data are from [24–26]. NR, none reported.

^a I.e., first-time vaccinees.

different reports and case series? There are at least 3 factors that contribute to this apparent high variability in rates.

Differences between primary vaccination and revaccination.

The complication rates most commonly quoted are those from the 1968 reports demonstrating that serious adverse events were approximately 5–10-fold greater among patients who received primary vaccination than among patients who were revaccinated: for serious reactions, 1253 versus 108 reactions per million persons vaccinated (0.1% vs. 0.01%), and, for lethal reactions, 1 versus 0.25 reactions per million persons vaccinated [24].

Strain variation. Vaccine prepared from vaccinia virus has been used throughout the world to control smallpox, but many strains of virus have been used. The 2 most common are the NYCBH strain (used by Wyeth, Aventis-Pasteur, and Acambis-Baxter), which is the only strain approved by the FDA for use in the United States, and the Lister strain used in most European countries. The 2 vaccines prepared from these strains provide comparable levels of protection. The NYCBH strain appears to be less reactogenic, but data from truly comparative studies are not available.

Method of data collection. The influence of data collection methods is exemplified by the differences between the findings of the US national survey and the 10-state survey (table 3) [24, 25]. Despite the facts that both studies involved the same vaccine, the same year (1968), overlapping population, and the same authors, there was a 10–20-fold difference in the reported rate of complications because one study used voluntary reporting from physicians and the other used an active survey in which physicians were contacted and urged to report reactions, including less severe reactions [10, 24, 25].

What is progressive vaccinia? The term “progressive vaccinia” is synonymous with “vaccinia necrosum” and “vaccinia gangrenosum.” Progressive vaccinia has typically been seen in patients with severe impairment of immune defenses, primarily impaired CMI, but a few cases were reported in patients with agammaglobulinemia at a time when immunology studies could not readily define CMI [27]. In progressive vaccinia, the vaccine injection site shows progressive enlargement after post-vaccination day 15. This reaction may be restricted to the vaccination site, but most cases are complicated by 10–20 large, painless skin ulcers at other sites that evolve over weeks and expand concentrically without inflammation. Biopsy of the lesions confirms the presence of minimal lymphocytic infiltrates; at autopsy, cultures of organ and skin tissue specimens demonstrate viremic dissemination [24, 28–32]. Progressive vaccinia may occur after primary vaccination or after revaccination and does so with near equal frequency (1–3 cases per million persons vaccinated), according to studies from the 1960s, when smallpox vaccine was routinely given and there were far fewer high-risk patients with CMI defects (e.g., due to organ transplantation, immunosuppressive therapy, or AIDS) [24]. The older reports show that most cases were lethal unless the patient was treated with VIG [10, 33]. Treatment includes administration of VIG in cumulative doses up to 10 mL/kg, but results seem less impressive than those obtained for cases of eczema vaccinatum. For example, Fulginiti et al. [34] reported that 5 of 8 individuals with progressive vaccinia died despite receiving very aggressive therapy that often included VIG, surgical debridement, and exchange transfusions. The role of surgical debridement is unclear.

Table 5. Frequencies of serious reactions following primary smallpox vaccination and following revaccination.

Reaction	No. of events per million vaccinees	
	Primary vaccination	Revaccination
Encephalitis	12	2
Progressive vaccinia	1.5	3
Eczema vaccinatum	38.5	4
Generalized vaccinia	241	9
Accidental infection	529	42
Erythema multiforme	165	10
Other	266	39
Total	1253	108

NOTE. Data are from [25].

What is postvaccinial encephalitis? CNS complications of smallpox are rare but serious, and they occur with a frequency that ranges from 1 case per 100,000 to 1 case per 500,000 primary vaccinations [24, 35, 36]. CNS complications are thought to be autoimmune reactions; they typically occur after primary immunization and occur more rarely after revaccination. There are 2 forms: postvaccinial encephalitis and postvaccination encephalomyelitis (PVEM). Postvaccinial encephalitis is most common in children aged <2 years, presents on days 6–10 after vaccination, and manifests as aseptic meningitis with cerebral vascular inflammation changes. Clinical features are fever, mental status changes, and vomiting, which progress in association with focal neurologic signs and seizures. PVEM is most common in children aged >2 years, presents on days 11–15 after vaccination, and has pathologic features similar to those seen in other postinfectious encephalopathies. Clinical features include mental status changes, fever, seizures, and spinal cord signs.

Lumbar puncture may reveal elevated CSF pressure and presence of mononuclear cells and an increased protein concentration in the CSF, or findings may be normal. Treatment is supportive; VIG therapy is not useful for either postvaccinial encephalitis or PVEM. Overall mortality rates are variable but are reported to be as high as 25%, with 25% of the survivors having neurologic deficits [33]. Valid data on the incidence of and the prognosis for postvaccinial encephalitis and PVEM are confounded by the lack of precise diagnostic criteria and the erroneous inclusion of data for other forms of encephalitis. The data summarized in this section are for the experience with DryVax. The European experience has indicated that postvaccinial encephalitis occurred after primary vaccination at a rate of up to 1 case per 4000 adults [37]. There is no clear explanation for the difference in rates, but they likely relate to the different stains of vaccinia used for vaccine.

What is eczema vaccinatum? Eczema vaccinatum occurs

when vaccinees that have an active or a past history of atopic dermatitis (or eczema) develop a specific form of cutaneous vaccinia lesions that is characterized by the occurrence of localized or generalized maculopapular rash, vesicles, or pustules in areas predisposed to eczema; this is accompanied by systemic signs such as fever, malaise, and lymphadenopathy. There may be hundreds of lesions, and they evolve rapidly; by contrast, progressive vaccinia generally is characterized by a much smaller number of cutaneous lesions that evolve over weeks or months. Most cases occur in children as a result of primary vaccination or contact with a vaccinee. Pathologic studies of the skin lesions characteristic of eczema vaccinatum reveal neutrophils, macrophages, and large numbers of viral particles [38]. The severity of the disease is highly variable; some patients have mild disease, and others have extensive lesions that result in a substantial loss of the dermal barrier and need to be managed like a large surface burn. In the 1960s, eczema vaccinatum accounted for ~20% of smallpox vaccine-associated deaths [30, 39]. Treatment with VIG (at dosages of 0.6–1 mL/kg) appears to have reduced mortality substantially; this therapy should be given early in the disease course [30]. Most cases of eczema vaccinatum occur in patients with active eczema, but 3%–20% of cases may occur in patients who do not have eczema lesions at the time of smallpox exposure [40].

What is generalized vaccinia? As the name implies, generalized vaccinia is a generalized rash that resembles the skin manifestations seen at the primary vaccination site. The incidence is 200–800 cases per million persons who receive primary vaccination, and it typically occurs in children following primary vaccination [24]. The suspected pathophysiologic mechanism is vaccinia viremia rather than autoinoculation. Generalized vaccinia typically presents as multiple, disseminated, maculopapular-vesicular lesions that appear to be at the same stage of development as and are usually smaller than the lesion at the primary vaccination site. The onset is generally on days 6–9 after vaccination, and the lesions usually heal rapidly, possibly because of immunity induced by the primary vaccination. Despite the sometimes striking appearance of the rash, it is typically a benign process. The differential diagnosis of generalized vaccinia includes eczema vaccinatum, progressive vaccinia, erythema multiforme, accidental inoculation vaccinia, smallpox, and chickenpox. Most patients do not appear seriously ill and do not require any treatment, but occasional severe cases have been treated with VIG.

What is accidental inoculation vaccinia? This is the inadvertent transfer of vaccinia virus from the vaccination site to another anatomical site, most commonly to a skin site that has been disrupted by a lesion, and disease severity is often dependent on the extent of the predisposing condition. Mucous membranes may be uniquely susceptible, since many cases involve the eyelids, the mouth, the lips, the nose, and the vulva

[41–43]. These lesions are usually seen on days 7–10 after vaccination, and they evolve like the lesion at the primary site or somewhat more rapidly because of immunity [44].

What are the ocular complications of vaccinia? These include blepharitis, blepharo-conjunctivitis, and keratitis occurring as complications of autoinoculation or contact vaccinia. Previous ocular inflammation may predispose to these conditions, but most cases occur in previously healthy eyes. The greatest concern is vaccinia keratitis, which is uncommon but serious. This typically begins ~10 days after inoculation and progresses with pain, inflammation, and a characteristic central grayish corneal ulcer that is best detected by means of a slit-lamp examination. With progression, there may be deep corneal ulceration and residual vision loss. Ocular vaccinia should be managed by an ophthalmologist. Topical administration of trifluridine or vidarabine is used for treatment of vaccinia keratitis; this should be considered in order to protect the cornea when there is orbital infection or accidental exposure. VIG therapy should not be used for isolated keratitis, because there is no evidence of benefit, and studies involving rabbits indicate increased rates of residual corneal scarring [45]. However, VIG therapy should not be withheld if otherwise indicated, including for treatment of severe ocular disease without keratitis [10, 46–49].

What is contact vaccinia? Contact vaccinia is an inadvertent vaccinia virus infection in a person other than the vaccine recipient; it is the result of the spread of vaccinia from a vaccination site to another person. The incidence of contact vaccinia is reported to be 20–60 cases per million vaccinations, although this probably represents substantial underreporting, with bias toward the more serious cases. Most cases occur because of contact with a person who received primary smallpox vaccination, and most involve children with exposure to a family member in the home [40]. A national survey of 139 cases of contact eczema vaccinatum found that 81 cases (58%) occurred in siblings of vaccinees, 16 (12%) occurred in playmates of vaccinees, and 13 (9%) occurred in adult members of the families of vaccinees [40]. Occasional cases occur because of transmission in the hospital; such cases accounted for 4 (2%) of the 223 cases included in data combined from 2 surveys [39, 40]. Sepkowitz [42] has recently reported 85 cases of nosocomial spread on the basis of 12 reports from 1907 to 1975, but most of these cases occurred in hospital settings very different from those of today. Nearly all fatal cases involve children <1 year of age [50–53]. Historically, eczema vaccinatum accounted for nearly all of the serious cases of contact vaccinia; 2 national surveys found incidences of 8.7 cases per million vaccinations [23] and 10.7 cases per million vaccinations [24].

Is contact vaccinia a greater concern now than it was in the 1960s and 1970s, during the global eradication program? Many of the reports from the 1960s and 1970s were

based on very large surveys of results for vaccination with the same vaccinia strain that is to be used in the smallpox vaccination effort, and these studies were performed by well-qualified investigators. However, studies based on surveys often suffer from underreporting, inconsistent reporting, and reporting bias that favors more serious forms of disease. The risk that this disease will develop may have increased substantially, because the prevalence of eczema during the years 1950–1970 was 3%–6%, but it is now believed to be 6%–22% [54–57]. The proportion of patients with immunodeficiency, especially defective CMI, has increased substantially because of the currently large number of persons with HIV infection (550,000–900,000); patients who have undergone organ transplantation (184,000); patients with rheumatologic disease who are receiving immunomodulatory therapy (2.1 million); persons with a history of cancer and receipt of chemotherapy (8 million); and asthmatic patients (14 million), many of whom take systemic or aerosolized steroids. Finally, primary vaccination imparts a more significant risk for contact vaccinia than does revaccination, and most Americans <33 years old have not been vaccinated.

Can vaccinia be spread by aerosols or respiratory droplets from the pharynx of recent vaccinees? A recent review raised the possibility that, on very rare occasions, vaccinia might be disseminated by aerosols or respiratory droplets [42]. This review described cases of contact vaccinia in which the mechanism of transmission was unclear, and most of them involved children with dermatologic conditions who were treated in hospital conditions that would not be seen today. The possibility of aerosol dissemination was based primarily on 2 reports published in 1936, which describe secondary cases that occurred in a hospital ward that housed a bedbound source patient [58, 59]. In these cases, the possibility of fomite-based spread via health care workers could not be excluded. Despite these rare exceptions and theoretical concerns, contact vaccinia is nearly always traced to direct contact [10].

What other forms of skin reactions may follow smallpox vaccination? Minor skin reactions are common following smallpox vaccination, take a variety of forms, and must be distinguished from vaccinia virus infection (including generalized vaccinia, eczema vaccinatum, accidental inoculation and progressive vaccinia). A recent review of primary vaccination in 665 healthy vaccine recipients aged 18–32 years found rash distant from the vaccination site in 37 persons (5.6%) at day 7–9 after vaccination and in 67 persons (10.1%) at day 10–12 [7]. Most common were pustular or vesicular rashes on the chest and back. Maculopapular and urticarial rashes were also relatively common. These rashes are thought to be immune mediated, are not usually associated with fever, and usually resolve spontaneously in 2–4 days. In the recent study, 2 patients had erythema multiforme. The 10-state survey from 1968

found that erythema multiforme occurred following 0.16% of primary vaccinations [25]. Erythema multiforme can be a potentially serious reaction. It is characterized by distinctive target-patterned lesions (a central papule with surrounding erythema), severe pruritis, and diagnostic histology [60]. Another serious manifestation is Stevens-Johnson syndrome, which is characterized by widely disseminated purpuric macules and blisters, with prominent involvement of the trunk and face.

Compared with the more serious vaccinia-associated rashes (such as eczema vaccinatum or vaccinia necrosum), these non-specific rash reactions occur earlier, are more frequently associated with extensive erythema, are less likely to evolve as does the primary vaccination site, are not associated with fever, and resolve spontaneously in 2–4 days. In some cases, the distinction between these and the more serious rash reactions can only be made by detection of the virus. With respect to management, there is no need for specific forms of therapy, except to administer antibiotics to treat bacterial cellulitis and antihistamines to treat pruritis, which may be severe. Patients with Stevens-Johnson syndrome require hospitalization and supportive care.

How are vaccinia infections external to the vaccination site diagnosed and managed? The diagnosis is usually based on the appearance of the lesion, the temporal relationship with the date of vaccination, and the previously described host factors, primarily immune deficiency or eczema. With lesions that involve vaccinia, it is important to remember that the same recommendations for fastidious wound management apply; these include daily observation, use of a dressing with a semiocclusive cover, and instruction of the patient to avoid touching the sites of the lesions. Vaccinia virus can be detected by means of electron microscopy or PCR, but these tests are currently available only through the CDC [10]. Guidelines for specimen collection are available at the CDC Web site (<http://www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp>). Specific interventions with VIG or cidofovir are reviewed below.

CONTRAINDICATIONS TO SMALLPOX VACCINATION

What are the major contraindications to vaccination? In the event of confirmed, imminent, or likely exposure to the smallpox virus, there are no absolute contraindications to vaccinia vaccination. However, in the current circumstances, given the potential for serious adverse reactions to the vaccine, there are number of risk groups for which vaccination is contraindicated.

According to CDC recommendations [61], the following conditions and therapies are contraindications for smallpox vaccination at this time.

1. Pregnancy or intended pregnancy within 4 weeks after vaccination
2. Immunodeficiency
 - a. HIV infection (at any stage or CD4 count)
 - b. Congenital or acquired immunodeficiency disorder
 - c. Organ, marrow, or stem cell transplantation
 - d. Generalized malignancy
 - e. Leukemia
 - f. Lymphoma
 - g. Agammaglobulinemia
 - h. Autoimmune diseases
3. Immunosuppressive therapy
 - a. Long-term corticosteroid therapy (≥ 20 mg/day of prednisone [or equivalent dose of other steroids, including topical and inhaled steroids] for ≥ 14 days)
 - b. Radiotherapy
 - c. Antimetabolite therapy
 - d. Alkylating agent therapy
 - e. Chemotherapy
 - f. Therapy with immunomodulatory medications for patients with organ transplants or autoimmune diseases: for example, corticosteroids, azathioprine, mycophenolate mofetil, cyclosporin, tacrolimus, and etanercept
4. Eczema/atopic dermatitis (active disease or prior history)
5. Skin diseases (active) or lesions
 - a. Burns
 - b. Wounds
 - c. Contact dermatitis
 - d. Recent surgical incisions
 - e. Chickenpox
 - f. Shingles
 - g. Herpes
 - h. Psoriasis
 - i. Darier disease
 - j. Severe acne
6. Conjunctival or corneal diseases; florid inflammation or pruritic lesions of the eye
7. Allergy to a component of DryVax (polymyxin B, streptomycin, chlortetracycline, neomycin, or phenol)
8. Contact: close contact with a person with any of the conditions listed here (i.e., household contact)

Some health care institutions and public health agencies have also chosen to exclude persons who have not been previously vaccinated, because of the higher risk of serious adverse events, and/or persons living with children <1 year of age, because of the higher risk of contact vaccinia.

How many individuals are expected to be excluded from vaccination in the current US smallpox vaccination program because of confirmed or suspected contraindications? One analysis concluded that ~15% of the US population will be

excluded on the basis of contraindications 1–7 (as listed in the previous section, above). An additional 10% will be excluded because they regularly come into household or close contact with persons who have ≥ 1 of the contraindication (see contraindication 8, above). These groups combined would total ~25% of the US population [62]. Recent information suggests that 25% may even be an underestimate. The military vaccination program began on 13 December 2002; of the first 276 persons screened, 102 (37%) were exempted for medical reasons. Approximately one-half of them were exempted because of a contraindication in a household contact [63]

What are the pregnancy-related concerns regarding smallpox vaccine? The primary concern is for the fetus. There appears to be no established risk to the mother, unless she has a concurrent contraindication. Maternal safety with smallpox vaccination is established on the basis of studies that included thousands of pregnant women who received smallpox vaccine [64, 65].

The most complete information on fetal risk is a report by Levine [66] summarizing a series of 20 anecdotal case reports of fetal vaccinia reported from 1932 to 1974. Mothers of the affected fetuses received the vaccine during weeks 3–24 of gestation. Of the 20 cases, 18 occurred in women who were vaccinees themselves, and 2 occurred in women with contact vaccinia. At least 13 of the 20 women were primary vaccinees, and 3 had been revaccinated; the vaccine status of the other 4 was unspecified. The outcome was stillbirth or abortion in 11 cases and live birth in 10 cases (there was 1 set of twins). Of the 10 infants born alive, 3 survived. None of the infants showed teratogenic defects. Pathologic examination of the fatal cases revealed placental changes, skin lesions, and disseminated vaccinia with multiple organ involvement [67–69].

The data in these reports [66–69] are based on anecdotal case reports and do not address the issue of incidence. In this regard, of 11 prospective studies, which included a combined total of 8599 pregnant smallpox vaccine recipients and 11,104 control subjects, only 2 reports showed an increase in the rate of fetal death [70, 71]. Naderi [72] subsequently reviewed an additional 1522 consecutive pregnant women who received smallpox vaccine for comparison with 2024 control subjects. There was no difference between the 2 groups in rates of stillbirth, premature birth, and congenital abnormalities. Also, attempts to cultivate vaccinia from the specimens of fetal and placental tissue after abortions were uniformly unsuccessful in 334 reported cases [66, 73]. These data show that smallpox vaccination poses no identified risk to the mother and that the risk to the infant is very low.

What should be stated about pregnancy in the informed consent process for vaccination? Potential vaccinees should be counseled that (1) vaccination is voluntary; (2) fetal vaccinia appears to be very rare but can be fatal to the fetus; (3) if they

are pregnant or might become pregnant during the 4 weeks after vaccination, they should not be vaccinated; in addition, (4) potential vaccinees who are of child-bearing potential and accept vaccination should be counseled on abstinence and/or contraceptive use to reduce pregnancy risk before vaccination and for 4 weeks after vaccination. According to Amstey and Gall [65], who were the obstetrician representatives on the CDC task force that defined the recent smallpox vaccination recommendations, the decision to set the time period at 4 weeks was based on the recommendation for rubella vaccine, which was recently changed from 12 weeks to 4 weeks. If a pregnant woman is inadvertently given smallpox vaccine, the CDC recommendations are to provide counseling on the risk of fetal vaccinia, but “this should not ordinarily be a reason to terminate pregnancy” [65, p. 1356].

Should pregnancy testing be done as a contingency for vaccination? The CDC recommendation is that any woman who wants to be tested should have access to tests at the screening site and at the vaccination site, but “routine pregnancy testing of women of child-bearing age is not recommended” [65 {p. 1356}, 4]. Despite this, some health care institutions may make smallpox vaccination contingent on negative pregnancy test results and require that the recipient have a negative urine pregnancy test result for the first morning-voided urine on the day scheduled for vaccination.

What is fetal vaccinia? Fetal vaccinia is a vaccinia infection of the fetus that typically results in fetal death or live birth with disseminated skin lesions that have the characteristics of those associated with generalized vaccinia or progressive vaccinia. It is unclear whether the pathophysiologic characteristics of this infection are more analogous to those of generalized vaccinia, with generalized cutaneous lesions, or to those of progressive vaccinia, with widespread infection of organs and skin. Fetal vaccinia usually causes intrauterine death or death shortly after birth. The diagnosis is established by the history of potential exposure (i.e., exposure of the mother by vaccination or by contact) and the occurrence of typical lesions. The diagnosis of fetal vaccinia can be confirmed by viral culture results. It should be emphasized that vaccination during pregnancy is not associated with any unique risk to the mother and does not cause congenital abnormalities and that the risk of fetal vaccinia is real, but extremely low.

Is there a diagnostic test to detect intrauterine fetal vaccinia infection? No.

Which transplant recipients are excluded from vaccination? The CDC recommends exclusion of organ and stem cell transplant recipients [4]. The major risk in these patients is related to the immunosuppression conferred by drug therapy. This risk is specific to the drug, the dosage of the drug, and the duration of treatment in each situation. The major agents of concern are corticosteroids, mycophenolate mofetil, cyclo-

porin, and tacrolimus. The greatest concern for serious reaction would be in the early posttransplantation period; low doses of drug therapy at times of clinical stability would, in theory, pose less risk, and transplant recipients who are not receiving immunosuppressants should, in theory, have essentially no risk. However, there are no data to support these conclusions, because organ transplantation was in its early stages of development when smallpox vaccination was discontinued in the United States in 1972. The conservative approach is to exclude all transplant patients, including recipients of organ, marrow, or stem cell transplants. No restrictions should apply to recipients of cartilage, bone, or joint transplants.

What are the risks associated with vaccination for patients with HIV infection? Routine smallpox vaccination of civilians was ended in the United States in 1972. AIDS was first reported in 1981, and serologic testing for HIV was introduced in 1985. The reported experience of adverse reactions to the vaccine is limited to a single case in a 19-year-old military recruit with AIDS, who was not known to have HIV infection until he developed progressive vaccinia following smallpox vaccination in May 1984 [31]. This patient received extensive treatment with 12 weekly doses of VIG. The progressive vaccinia ulcers completely healed. The patient, who also had cryptococcal meningitis, died ~18 months later from what appeared to be an HIV-related complication. This case occurred before the institution of routine testing of military recruits for HIV. A more recent analysis by the military estimates that at least 350 other military recruits with HIV infection had received smallpox vaccination without apparent incident. These data, a wealth of clinical experience, and common sense suggest that the risk of progressive vaccinia is low for HIV-infected patients and is presumably CD4 cell count–dependent and that receipt of HAART and concomitant immune reconstitution would decrease the likelihood and severity of complications from smallpox vaccination [74]. Nevertheless, the conservative approach, based on the paucity of cases, is to exclude all persons with HIV infection from the current smallpox vaccination program.

Are negative results of HIV serologic tests required as a contingency for vaccination? The CDC recommends that HIV serologic testing be readily available to individuals who volunteer to be vaccinated in the smallpox vaccination program and who wish to be tested [4]. Universal testing is not recommended or mandatory. A quick survey of leading hospitals suggests that most will “recommend” or “strongly recommend” the performance of HIV serologic tests prior to smallpox vaccination (T. Perl, personal communication). There are ~25,000 health care workers in the United States with HIV infection [40].

If screening HIV serologic testing is done, what test should be performed? Standard serologic tests for HIV have sensitivities and specificities approaching 100%. Informed consent

is required for performance of these tests. With standard tests, results take 2–7 days to obtain, but the SUDS test (Murex Diagnostics) and the OraQuick test (OraShure Technologies) can provide results in 20 min. The OraQuick test no longer requires interpretation by a Clinical Laboratory Improvement Amendments–certified lab technician, which means that the test usually can be read on-site. Negative results of the EIA screening test for routine serologic testing and negative results of the SUDS or OraQuick tests are considered definitive for excluding the diagnosis of HIV infection; positive results require confirmation by a standard serologic test.

What patients with congenital or acquired immunodeficiency are at highest risk for progressive vaccinia? Defective CMI appears to be most important risk factor for progressive vaccinia, as indicated by case reports of progressive vaccinia, including one of a case in a patient who had defective CMI but a normal humoral response [75]. Prior reports also indicate that most cases of progressive vaccinia occur in children with severe defective CMI function [34, 76, 77]. Conditions that are associated with defective CMI and therefore would be associated with high risk of progressive vaccinia after vaccination are as follows: severe combined immune deficiency syndrome (SCID), Wiskott-Aldrich syndrome, ataxia telangiectasia, cartilage hair hypoplasia, and purine nucleoside phosphorylase deficiency. Common variable immunodeficiency is associated with normal or near normal CMI and poses a theoretical risk, but a small one. Hypogammaglobulinemia is a lesser risk, but a case of progressive vaccinia has been reported in a patient with Bruton-type agammaglobulinemia [27]. Conditions that would not appear to pose risk, on the basis of current understanding of CMI and the risk of complications, are complement defects, neutropenia, IgA deficiency, and chronic granulomatous disease. It is anticipated that vaccination would be safe for patients with these conditions, but there is no published experience to confirm this impression.

Should there be screening for congenital or acquired immune deficiencies? Most persons with serious immunodeficiencies manifest serious sequelae of infections before they reach adulthood. The most relevant exception is persons with common variable immunodeficiency, because these individuals are often unaware of the condition until they are >20 years old. It is not clear that this group is at significant risk, because most have normal or near-normal CMI, but lack of risk is not established. Clues in a patient’s medical history that would suggest common variable immunodeficiency include serious infections (such as osteomyelitis and pneumonia) involving at least 2 noncontiguous anatomical sites, autoimmunity, and a family history of the disorder. The appropriate screening test for persons suspected of having common variable immunodeficiency is a serum quantitative immunoglobulin assay. Another diagnostic concern relates to children with as yet un-

detected SCIDs. More than 80% of children with SCID receive the diagnosis in the first year of life, so the greatest concern is the group of children with undiagnosed SCID who are <1 year old. In the current smallpox vaccination program, children are not being vaccinated, so the concern is children with undiagnosed SCID, who could contract contact vaccinia. It should be emphasized that SCID is rare (estimated prevalence, 1 case per 100,000 to 1 case per million children), and contact vaccinia is also rare. If SCID is suspected, the appropriate screening test would be a complete blood cell count with a lymphocyte count. Given the rarity of SCID, routine performance of screening is unrealistic; however, some hospitals are not administering smallpox vaccination to persons with household contacts that include children aged <1 year.

What is the definition of atopic dermatitis? Atopic dermatitis is a chronic inflammatory skin condition commonly associated with other atopic disorders (e.g., asthma and allergic rhinitis) that is characterized by defective CMI and acutely pruritic, erythematous patches on the face, scalp, and extremities.

How does atopic dermatitis affect the risk of a serious reaction to smallpox vaccination? Atopic dermatitis poses a risk with smallpox vaccination because of its association with eczema vaccinatum, which was the most common life-threatening complication of smallpox vaccination in the 1960s [24]. Patients with active lesions are at greatest risk, but 3%–23% of patients who develop eczema vaccinatum have a history of atopic dermatitis but no active lesions at the time of exposure [40].

What are the clinical features of atopic dermatitis? In children, the characteristic skin lesions are intensely pruritic, red patches with papules and scaling on the face, scalp, extremities, and/or trunk. In adults, the lesions often show lichenification with a predilection for flexor surfaces (e.g., the antecubital fossa and the popliteal fossa), the face, wrists, and forearms. Other clinical features are onset at an early age (by age 5–7 years), a family history of atopy, and a chronic recurring course [78].

How does one make the formal diagnosis of atopic dermatitis? There are no pathognomonic diagnostic tests. The diagnosis is made on the basis of the clinical features, as defined in the previous paragraph and as formalized by diagnostic criteria in 1982 [79]. The formal diagnosis requires that 3 of 4 major criteria be met. They are as follows:

1. Pruritis
2. Dermatitis involving flexural surfaces, in adults, and involving the face and the extensors, in infants
3. Chronic or relapsing dermatitis
4. Personal or family history of cutaneous or respiratory atopy

The minor criteria are as follows:

1. Features of “atopic facies”: face pallor or erythema, hypopigmented patches, infraorbital darkening, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, and anterior neck folds
2. Triggers of atopic dermatitis: foods, emotional factors, environmental factors, and skin irritants (wool, solvents, and sweat)
3. Complications: susceptibility to cutaneous viral and bacterial infections, impaired CMI, immediate skin test reactivity, elevated IgE level, keratoconus, and anterior subcapsular cataracts
4. Other: early age at onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris, hand and foot dermatitis, nipple eczema, white dermatographism, and perifollicular accentuation

As a practical matter, how should the health care provider screen for atopic dermatitis in persons who are considering smallpox vaccination? Most health care providers have not in the past and do not now distinguish between eczema and atopic dermatitis, so smallpox vaccination should not be administered to patients with either current manifestations or a history of either condition. As noted in the previous subsection (above), there are no specific tests for atopic dermatitis; it is diagnosed clinically on the basis of the criteria listed above. The ACIP has suggested 2 screening questions:

1. Have you or a member of your household ever been diagnosed with eczema or atopic dermatitis?
2. Eczema/atopic dermatitis usually is an itchy, red, scaly rash that lasts >2 weeks and often comes and goes. Have you or a member of your household ever had a rash like this?

A positive answer to either question is a contraindication to smallpox vaccination, in the current vaccination program [5].

What are the pathophysiologic characteristics of atopic dermatitis? The pathogenesis is poorly understood but involves immune deficiency (i.e., reduced CMI) and atopy (elevated IgE levels and positive results of immediate skin tests of foods and inhaled allergens) [80]. There is a family history of respiratory atopy (asthma or allergic rhinitis) for 50% of patients, and genetic studies suggest inheritance on chromosome 11 [81].

Why is atopic dermatitis so important with regard to smallpox vaccination? Atopic dermatitis predisposes to eczema vaccinatum (see above), and eczema vaccinatum was the most common serious complication of smallpox vaccination in the 1960s. Atopic dermatitis is now expected to be the most common exclusion criterion for smallpox vaccination because of its reported prevalence (6%–22% of the US population), and the prevalence of the condition has been increasing for the past 3 decades. In addition, there will be difficulty in distinguishing it from other chronic inflammatory skin conditions [40,

54–57]. The risk applies to the vaccinee with atopic dermatitis and to household contacts with active or inactive atopic dermatitis.

What type of allergy to the vaccine components should be a contraindication to vaccination? This issue could be the source of significant confusion. Many patients report “allergy” to topical neomycin, a common ingredient in antibiotic ointments and lotions. Patch testing for allergy to neomycin and other aminoglycosides reveals reactions indicating hypersensitivity in 4%–13% of healthy adults [82–84]. Patch testing for neomycin allergy is performed because it is a component of a standard battery of allergy tests or because of concern about reactions to topical antibiotics [85]. However, patients with a topical reaction to neomycin may be treated with parenteral neomycin or other aminoglycosides without consequences, so the relevance of this topical allergy to the safety of smallpox vaccination is not clear. This observation may be analogous to the experience with lidocaine: patch testing commonly detects hypersensitivity to the drug, but it is well tolerated when injected. The individual clinician must use his or her judgment about reported allergies; if a patient has manifested symptoms that suggest a true allergic response to components of the vaccine (streptomycin, neomycin, polymyxin, chlortetracycline, or phenol), vaccination should be avoided, in this voluntary vaccination program.

TREATMENT OF VACCINE-RELATED COMPLICATIONS

What is vaccinia immune globulin (VIG)? VIG is a sterile solution of globulins derived from blood samples donated by persons who previously underwent smallpox vaccination. It contains 15%–18% proteins with $\geq 90\%$ γ -globulin and glycine as a stabilizing agent and antibacterial agent. VIG was originally prepared in the 1950s and 1960s from pooled plasma obtained from ≥ 1000 vaccinated volunteer recruits [86]. It was separated by Cohn fractionation and contained 15–17 g of protein per 100 mL. It was required to be stored at 2°C–8°C. Vaccinia neutralization titers at the time that VIG was first prepared were $\geq 1:640$. The rate of use was 100 doses per million primary vaccinations, and it was virtually never used for revaccination. The usual dose was 0.6 mL/kg (100 mg/kg) given intramuscularly. For a 70-kg adult, this translated to 42 mL given intramuscularly (usually in the buttock or anteriorlateral thigh) in divided doses to reduce local reactions. In some cases, cumulative doses of up to 10 mL/kg were given to treat eczema vaccinatum and progressive vaccinia. There is one case report in which a 20-month-old child with Bruton agammaglobulinemia and progressive vaccinia was given 335 mL of VIG, 135 mL of which was given intravenously with exchange transfu-

sions (in combination with surgical debridement); the child survived [34].

Does VIG effectively treat vaccine-related complications? VIG was never subjected to a controlled clinical trial. All available information is anecdotal. Nevertheless, VIG is considered first-line therapy for serious vaccination-related complications that are caused by continued replication of vaccinia virus. The most impressive results are the reduction in the mortality associated with eczema vaccinatum [30, 87].

How can VIG be acquired? VIG is available as an investigational new drug from the CDC (for information, telephone [877] 554–4625). Since it is available only for investigational new drug treatment, there must be institutional approval and signed informed consent, and follow-up information must be reported to the CDC. CDC has indicated that it will provide VIG on an expedited basis for serious reactions attributed to uncontrolled replication of vaccinia virus [10].

How much VIG is available for treatment of vaccine-related complications? Until recently, the CDC held only 600 vials of VIG. The supply is now being augmented by donors who recently have been vaccinated and subsequently have undergone plasmapheresis. A VIG supply sufficient to treat ~3700 serious reactions is now part of the NPS, and a supply of VIG sufficient to treat 30,000 serious reactions is expected by August 2003. The newer product has the advantages that it can be administered intravenously (VIGIV therapy) and does not contain thimerosal.

What are the indications for VIG administration? Indications include progressive vaccinia, eczema vaccinatum, congenital vaccinia, and, in some cases, generalized vaccinia. It may be used to treat severe blepharitis or blepharo-conjunctivitis, but VIG therapy should be avoided for patients with keratitis alone and given with caution if keratitis accompanies another condition for which VIG is indicated. It is not indicated for postvaccinial encephalitis (which may be autoimmune mediated) and most cases of generalized vaccinia (since most cases have a benign prognosis). The main reason to give it to patients with orbital vaccinia is to protect the cornea.

Why is VIG administered intramuscularly and not intravenously? The current preparation of VIG is given intramuscularly (VIGIM therapy) because of the high proportion of aggregated protein in the VIG from the 1960s. It is expected that new supplies of VIG will be appropriate for intravenous administration (VIGIV therapy). Given the high volume required per dose, use of the intravenous route will notably facilitate administration.

Does VIG play any role in prophylaxis? VIG has been advocated as prophylaxis for patients who have contraindications to the vaccine and are exposed to either vaccinia or smallpox [88]. This proposed use is based on experience with the use of other hyperimmune globulins, such as varicella immune

globulin, following exposure to varicella zoster. Concerns regarding VIG used in this fashion are the lack of data regarding efficacy, the limited national supply, and side effects associated with VIGIM therapy (local pain and swelling, headache, fever, myalgia, gastrointestinal symptoms, back pain, and/or anaphylaxis) and with VIGIV therapy (anaphylaxis, renal failure, and/or aseptic meningitis) [10].

Is antiviral therapy useful and available for vaccine-related complications? There are no antivirals that have been proven effective for treatment of vaccinia-related complications. There is speculation that cidofovir might be useful, although supporting clinical data are lacking. Cidofovir is active against most poxviruses in vitro, including smallpox and vaccinia [89–91]. It has been used successfully in topical preparations to treat infection with another poxvirus, *Molluscum contagiosum* [92]. Studies involving mice demonstrated that cidofovir has good in vivo activity against cowpox infection if given within 24 h after challenge, but it failed to prevent death if the animals were severely immunosuppressed or if the infection was established prior to drug administration [89, 93–95]. The FDA has approved the use of cidofovir with probenecid plus hydration for treatment of CMV infection, as an alternative to ganciclovir and foscarnet. Use for vaccinia would be considered experimental. Nephrotoxicity is a concern, and caution should be exercised, especially for patients with preexisting renal disease. It should be emphasized that the animal data indicate a need to treat within 24 h after vaccination, and the clinical experience is that complications of vaccinia are not apparent until 1–2 weeks after vaccination.

Ribavirin also shows in vitro activity against vaccinia virus. There is one case report of its use (ribavirin 400 mg q8h iv for 5 days) to treat a patient with chronic lymphocytic leukemia who had progressive vaccinia after inadvertent vaccination with vaccinia melanoma oncolysate. The report indicates the patient responded, but conclusions are not possible, because it is a single case and the patient was also treated with low-dose VIG [96].

LIABILITY ISSUES RELATED TO SMALLPOX VACCINATION

Does US law give liability protection to health care providers who administer the smallpox vaccine? Section 304 of the Homeland Security Act of 2002 (codified at 42 USCS §233(p)) was included specifically to provide liability protection to individuals and entities involved in the administration of the smallpox vaccine. It does so by deeming “covered persons” to be employees of the US Public Health Service and by amending a few provisions of the existing Public Health Service Act. Under federal law, regular employees of the US Public Health

Service cannot be sued in their individual capacity for damages for personal injury and death when acting within the scope of their employment. The federal government substitutes itself as defendant and accepts liability through the Federal Tort Claims Act.

What does the Homeland Security Act say about liability?

As of late January 2003, liability protection is afforded to (1) a “covered person” with respect to a claim (2) alleging personal injury or death arising out of the administration of a “covered countermeasure” that is (3) used to prevent or treat smallpox, or VIG, if used to control or treat the adverse effects of a vaccinia vaccine, and if administered by (4) a qualified person to (5) specified categories of people during (6) a time period specified in a declaration issued by the Secretary of the US Department of Health and Human Services (DHHS). If all of these requirements are met, people who experience adverse events after receiving smallpox vaccination and most people who are unintentionally inoculated should be able to sue only the federal government, for most types of claims. However, because this is a new law, there can be different interpretations, and, ultimately, those differences might have to play out in the courts.

Liability protection is triggered when the Secretary issues a declaration that concludes that an actual or potential bioterrorist incident (or other actual or potential public health emergency) makes vaccination advisable. On 24 January 2003, Secretary Tommy Thompson issued the first such declaration (“Declaration Regarding Administration of Smallpox Countermeasures” [hereafter, “Smallpox Declaration”; codified at 68 FR 4212] and declared its effective period to be from 24 January 2003 until and including 23 January 2004.

What treatments and interventions (“countermeasures”) are covered under the Smallpox Declaration? The Secretary identified 3 covered countermeasures that can be administered: (1) vaccinia (smallpox) vaccination, including Dryvax; (2) cidofovir and derivatives thereof; and (3) VIG.

Who are the covered persons shielded from liability under the Homeland Security Act?

Under this act, the term “covered person” includes 4 categories of individuals or entities: (1) manufacturers or distributors of a covered countermeasure, (2) health care entities under whose auspices a covered countermeasure is administered, (3) a qualified person who administers a covered countermeasure, and (4) an official agent or employee of a “person” described in (1), (2), or (3). A “qualified person” is defined as a licensed health professional or other individual who is authorized to administer the countermeasure under the law of the state where the countermeasure is administered. “Health care entities” include, but are not limited to, hospitals, clinics, state and local health departments, and contractors of those entities who (1) administer covered countermeasures; (2)

designate officials, agents, or employees to receive or administer covered countermeasures; or (3) are identified by state or local government or the DHHS to participate in the vaccination program.

The Homeland Security Act only affords liability protection to covered persons for claims arising out of the administration of a covered countermeasure. "Administration of a covered countermeasure" is broadly defined in the Declaration to include "the physical administration of a covered countermeasure; education and screening of covered countermeasure recipients; monitoring, management, and care of the covered countermeasure site; evaluation of covered countermeasure 'takes;' and contact transmission of vaccinia."

Who can be vaccinated under the Smallpox Declaration?

Under the Smallpox Declaration, 4 categories of individuals can be vaccinated or treated with a covered countermeasure: (1) health care workers who monitor or treat other eligible vaccinees and most cases of contact vaccinia; (2) members of Smallpox Response Teams or similar teams identified by state or local government or the DHHS; (3) public safety personnel, including, but not limited to, law enforcement officers, firefighters, security, and emergency medical personnel who assist these Smallpox Response Teams; and (4) personnel associated with certain (unspecified) federal government facilities abroad.

If a provider is vaccinated and unintentionally inoculates a patient, is the provider shielded from liability? Yes, assuming that the other requirements of the Homeland Security Act have been met.

If a provider vaccinates a patient and that patient unintentionally inoculates someone else, is the provider shielded from liability? Yes, assuming that the other requirements of the Homeland Security Act have been met. However, it is conceivable that a provider could be held liable if multiple generations of contact vaccinia occur, such that the vaccinia virus is spread from person A (the original vaccinee) to person B (the first case of contact vaccinia) to person C (the second case of contact vaccinia), and so on. However, the likelihood of these events is small, and they would probably be difficult to trace back to the provider.

Can liability protection be lost? Yes. For example, under the Homeland Security Act, the provider is explicitly required to cooperate with the government in the processing and defense of a claim. If the provider fails to cooperate, the federal court can remove the government from the case and replace the provider as the defendant. In addition, if the government makes a payment to a claimant, whether by administration determination, settlement, or court judgment, the government can recover from the provider that portion of the payment, as well as interest and any costs of litigation, resulting from the pro-

vider's gross negligence, reckless or illegal conduct, or willful misconduct.

THE RECENT ISRAELI SMALLPOX VACCINATION SERIES

Israel recently vaccinated ~15,000 of its citizens, including 14,000 health care workers and 1000 military personnel. Here we summarize the protocol and the preliminary results. (The information about the logistics of the program was provided as a personal communication by Dr. Ravit Boger [Johns Hopkins University, Baltimore, MD] and Dr. Y. L. Danon [Kipper Institute of Immunology, Tel Aviv University, Israel]).

What was the Israeli vaccination protocol?

- Most exclusion criteria were similar to those enumerated by the CDC: immunodeficiency, HIV infection, atopic dermatitis, pregnancy, receipt of a transplant, receipt of systemic steroid (but not inhaled steroid) therapy, leukemia, lymphoma, eczema or history of eczema, et cetera.
- Having household contacts who had risk factors for infection was not a contraindication for vaccination, but vaccine recipients were intensely counseled about transmission risk.
- No screening tests were mandated, but HIV serologic testing and pregnancy testing were offered.
- Volunteers completed a questionnaire that asked about contraindications; an instructional video followed.
- Informed consent from the patient and assent from the patient's treating physician were required.
- Vaccination was performed as follows: 0.25 mL of vaccine was placed on the arm, then 15 punctures were made with a size G23 needle or, less commonly, with a dermojet. (The bifurcated needle was not used, in part because of its cost: US\$0.22 per bifurcated needle vs. US\$0.01 per G23 needle.)
- The lesion was covered by a simple bandage unless there were risks of contact vaccinia due to occupation (e.g., care of immunosuppressed patients) or living arrangements (e.g., children in the home), in which case the injection site was covered by a gauze and taped on all 4 sides.
- Vaccine recipients returned on day 6–9 after vaccination to assess whether there was a vaccination take.
- Recipients who did not have a take were revaccinated.
- Vaccine recipients were expected to donate blood for VIG.
- There was no policy granting administrative leave from work or work reassignment.

Additional differences between the Israeli and American smallpox vaccination protocols include the following:

- The vaccine used in Israel is derived from the Lister strain

of vaccinia, which is grown in chorioallantoic membrane of fertilized eggs and delivered with an inoculum of approximately 1×10^7 pfu/mL. By contrast, the United States currently uses DryVax (NYCBH strain) with an inoculum averaging 1.6×10^7 pfu/mL [7].

- In Israel, many individuals have received >3 prior smallpox vaccinations, which could decrease the incidence of vaccine-related complications.
- Israel continued smallpox vaccination of its general public until 1978 and of its military until 1996. Thus, Israel's population is more antigenically experienced than is the population of the United States, which could decrease the risk of complications from the vaccine.

What were the preliminary results of the Israeli vaccination program? The take rate with initial vaccination was 76%, which is considerably lower than the 97%–99% take rate reported in the United States by Frey et al. [7]. This difference may reflect the differences in vaccine products, vaccination techniques, and/or rates of primary vaccination and revaccination status between study groups, or other factors. The number of serious side effects was low: there were 2 cases of contact vaccinia (1 spouse and 1 grandchild) and 1 case of erythema multiforme. Another patient had pericarditis develop after vaccination, but this was thought to be unrelated to the vaccine itself.

ADDITIONAL INFORMATION ONLINE

The following are additional useful online sources of information for clinicians regarding the smallpox vaccination program.

1. CDC. Smallpox vaccination and adverse reactions: guidance for the clinician. *MMWR Recomm Rep* **2003**;52:1–29. Available at: http://www.cdc.gov/mmwr/mmwr_rr.html.
2. The CDC Web site has smallpox information: <http://www.bt.cdc.gov/agent/smallpox/index.asp>.
3. A CDC Web page shows images of adverse reactions to the smallpox vaccine: <http://www.bt.cdc.gov/training/smallpox-vaccine/reactions/adverse.html>.
4. The White House Web site answers frequently asked questions regarding smallpox vaccination: <http://www.whitehouse.gov/news/releases/2002/12/20021213-3.html>.
5. The Johns Hopkins Web site has series of short articles reviewing issues related to the major contraindications to smallpox vaccination in more detail: <http://www.hopkins-biodefense.org/>.

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