Bioterrorism and Smallpox Vaccination: Experience and Considerations

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Smallpox, which is believed to have originated more than 3,000 years ago in India or Egypt, is one of the most devastating diseases known to humanity. For centuries, repeated smallpox epidemics swept across continents, decimating populations in their wake.

The disease, for which no effective treatment was ever developed, killed as many as 30% of those infected. Between 65% and 80% of survivors were marked with deep-pitted pockmarks, most prominently on the face. Blindness was another complication. In 18th century Europe, a third of all reported cases of blindness were because of smallpox.

As late as the 18th century, smallpox killed every 10th child born in Sweden and France. During the same century, every 7th child born in Russia died from smallpox. It wasn't until 1798, when Edward Jenner demonstrated that inoculation with pus from cowpox lesions could protect against smallpox, that there was hope that the disease could be contained through medical means.

In the early 1950s—150 years after the introduction of vaccination—an estimated 50 million cases of smallpox occurred in the world each year, a figure which fell to around 10 to 15 million by 1967 because of vaccination. Based on these encouraging statistics, the World Health Organization (WHO) launched an intensified plan in 1967 to eradicate smallpox—the "ancient scourge" that threatened 60% of the world's population.

Through the success of the global eradication campaign, smallpox was finally pushed back to the horn of Africa and then to a single last natural case, which occurred in Somalia in 1977 (the last case in the United States occurred in 1949 in Texas). There has been only one smallpox-related fatality since: a laboratory-acquired case that occurred in the United Kingdom in 1978. In 1979, WHO certified the global eradication of smallpox—one of the greatest achievements in the history of public health.

With the end of smallpox, the virus went on to survive only in laboratories in the United States and in Koltsovo, Siberia. After the Soviet Union collapsed, reports surfaced alleging that the Soviets had produced variola in large quantities and were attempting to weaponize the virus in the 1970s, 80s, and 90s. Bioterrorism experts began to worry that the Russians might have let the virus slip into the wrong hands, with recent media reports suggesting that at least four countries have hidden stocks of variola. Still, most experts have long discounted the use of variola as a biological weapon, given numerous safety and "effectiveness" considerations. However, after the terrorist attacks on the World Trade Center and the Pentagon on September 11, 2001, many of the nay-sayers did an about-face and recognized that, in the hands of the wrong people, a lethal and socially destabilizing attack using variola was possible, if not likely.

Because of the lingering threat of a terrorist attack involving variola—an attack anywhere in the world could easily result in widespread dissemination before the first case of smallpox is officially diagnosed—a number of health agencies throughout the world have begun the process of reimplementing smallpox vaccination programs. In the United States, both "pre-event" and "post-event" protocols have been set up and there is now enough vaccine available to immunize every U.S. resident. However, there are lingering concerns regarding the use of smallpox vaccination in the United States today, given that a much larger percentage of the general population are immune compromised, including a sizeable percentage of HIV-infected individuals.

What follows is a detailed summary of smallpox and the smallpox vaccine, including the anticipated adverse events (particularly those in HIV-infected individuals with suppressed immune systems) and the various contraindications that need to be considered. Also provided is a review of the pre-event vaccination program currently under way in New York City, along with encouraging smallpox vaccine safety data from Israel and the United States Department of Defense.

Variola: The Basics

Smallpox is caused by variola, a DNA virus belonging to the orthopoxvirus family. It is a brick-shaped virion, approximately 200 nm in diameter—roughly the size of a bacterial spore. Its dumbbell-shaped core contains nucleic acid and is surrounded by a series of membranes. Variola replicates in the cytoplasm of host cells, forming B-type inclusion bodies—Guarnieri bodies—which, unlike many other viruses, replicate in the nucleus.

In terms of its genetic composition, variola carries a single, linear, double-stranded DNA covalently closed at each end. The average variola genome has 200,000 base pairs, which ranks among the largest of the animal viruses.

Smallpox has two main forms: variola major and variola minor. While both forms cause similar lesions, variola major is typically associated with severe disease and high fatality rates, claiming the lives of approximately 30% of those infected. Variola minor, which includes the strains kaffir and alastrim, tends to run a milder course of disease and has a case-fatality rate of less than 1%.

Transmission and Clinical Picture

THE USUAL ROUTE OF VARIOLA ENTRY IS THROUGH THE OROPHARYNGEAL or respiratory mucosa. Secretions from the mouth and nose that become airborne are the most important source of human-to-human transmission, although this generally requires direct and prolonged face-to-face contact (i.e., within six feet). Transmission is also possible through direct contact with body fluids and contaminated objects. Variola is less contagious than measles or influenza and is not known to be transmitted by insects or animals.

Twelve to 14 days after infection, the incubation period typically ends and the first phase of symptoms appear. These include high fevers; severe body aches; abdominal pain, nausea, and vomiting; and finally sores that develop in the mouth and pharynx, where they ulcerate, quickly releasing large amounts of virus into the saliva. It is at this point that the patient is considered to be highly infectious.

Approximately four days after the onset of the first phase of symptoms, the second phase begins. It is during this phase that the hallmark lesions of smallpox appear on the skin and become disseminated, with umbilication of the lesions being a common feature. After the vesicular stage, the lesions become pustular. The pustules are characteristically round, tense, and deeply embedded in the dermis.

With the development of an effective immune response, healing begins. The contents of the pustule become dried out, and reestablishment of the epithelial cell layer occurs between the cavity of the pustule and the underlying dermis. The pustule then becomes a crusty scab. It is not until the scabs fall off that the patient is considered to be no longer infectious, approximately 21 days after the infection was first established.

Death caused by a variola infection is often the result of a cascade of physiological events occurring as a result of overwhelming infection, usually between days 10 and 16 of the illness. These events can lead to disseminated intravascular coagulation, hypotension, and cardiovascular collapse. Smallpox can lead to other serious complications, including respiratory diseases (e.g., bronchitis and pneumonia), bacterial infection of skin lesions, encephalitis, scarring of the skin, and blindness.

Smallpox Vaccination

SMALLPOX VACCINATION EFFORTS DATE BACK TO 10TH CENTURY CHINA AND India, where "variolation" became a popular public health initiative among community healers. Variolation involved taking pus from the pocks of someone suffering from smallpox and rubbing it into incisions made in the skin of people who were not yet exposed to the disease. This, of course, was associated with a number of unfavorable consequences, including full-blown smallpox and death in a number of individuals who underwent variolation.

It wasn't until 1721 that variolation was introduced to the western world. Lady Mary Wortley Montagu, a writer and the wife of the British Ambassador to Turkey, learned of variolation while living in Constantinople. After surviving a disfiguring case of smallpox several years earlier, she had her children inoculated through variolation and persuaded some of the British royal family to do the same.

In 1788, a smallpox epidemic erupted in the English county of Gloucestershire. Dr. Edward Jenner, a military-trained doctor who set up his practice in bucolic Berkeley, initiated a variolation campaign to stem the spread of smallpox. However, this effort was met with a great deal of resistance by many of the local residents. Dr. Jenner learned that many of the residents, particularly dairy farmers and milkmaids, had suffered from a mild form of cowpox and appeared to be immune to smallpox. In turn, only a few residents saw the need for risky smallpox variolation.

These observations led to Dr. Jenner's famous experiment in 1796. Modifying the smallpox variolation method, he inserted pus extracted from a cowpox pustule on the hand of a milkmaid, into an incision on the arm of an eight-year-old boy named James Phipps. Roughly two weeks later, he repeated varioloation on Phipps, this time with pus from a smallpox pustule. Phipps developed cowpox but not smallpox, despite close and prolonged exposure to individuals with the disease. After conducting the experiment on 23 different cases, he concluded that those who had suffered cowpox were indeed immune to smallpox. Hence, the term "vaccine" was coined by Dr. Jenner, stemming from the Latin *vacca*—cow.

The modern smallpox vaccine is made from live vaccinia virus—the pathogen identified, many years after Dr. Jenner's experiments, to be the cause of cowpox. The smallpox vaccine does not contain variola virus. Neutralizing antibodies induced by the smallpox vaccine are genus-specific and cross-protective for other orthopoxviruses in addition to variola virus. Although the efficacy of the smallpox vaccine has never been measured precisely in controlled clinical trials, epidemiologic studies demonstrate that an increased level of protection against smallpox persists for up to five years after primary vaccination and substantial but waning immunity can persist for up to 10 years. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Importantly, administration of the smallpox vaccine within the first three to four days after initial exposure to variola can reduce symptoms or prevent smallpox disease.

Two vaccines will be used in the coming years: the calf-lymph vaccine and a tissue culture cell vaccine. Dryvax, the stored calf-lymph vaccine manufactured in the 1970s by Wyeth Laboratories, is freeze dried (lyophilized) and must be reconstituted before use. This vaccine was pro-

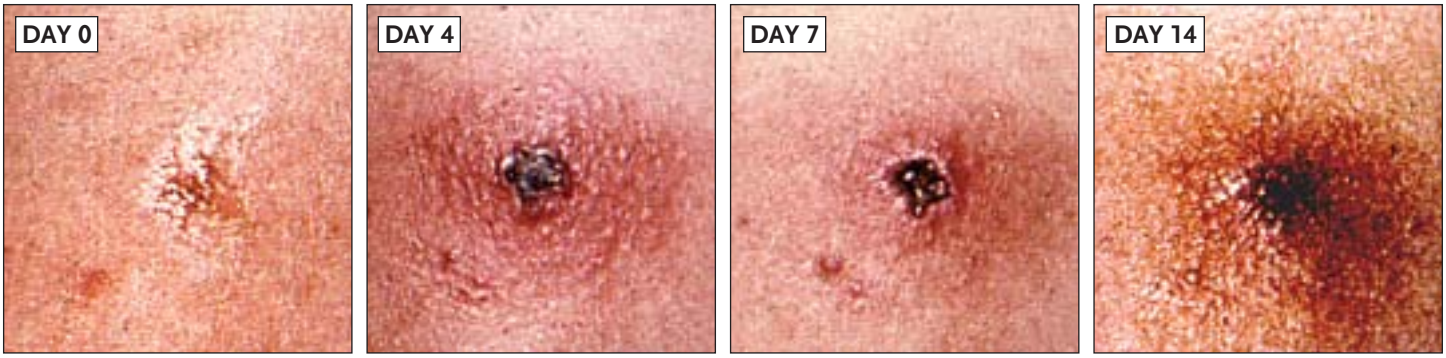

Figure 1. **Successful Response to Smallpox Vaccination.**
Photographs of vaccination site "takes" shot at different intervals over a two week period

Source: John D. Millar; U.S. Centers for Disease Control and Prevention

duced by infection of skin of calves using a strain of vaccinia virus collected by the New York City Board of Health—the NYCBOH strain.

Dryvax is now licensed in the United States. Before use, the vaccine is reconstituted with a diluent that contains 50% glycerin and 0.25% phenol. The licensed vaccine is packaged in multiple dose vials which, when reconstituted, will yield 100 doses per vial.

The licensed vaccine will be used to immunize health-care workers who volunteer to be members of the smallpox response teams being set up around the United States (discussed in greater detail below). Dryvax is also used to immunize laboratory workers who require vaccination to safely conduct research activities involving vaccinia or other orthopoxviruses.

Currently in development are tissue culture cell vaccines, being prepared by Acambis/Baxter Laboratories. Two cell lines were selected for propagation of vaccinia virus; the NYCBOH strain was selected as seed virus.

Vero monkey kidney cells and a human fibroblast cell line (MRC5) were selected as host cells for the preparation of vaccine. Several lots of both vaccines have been prepared and are undergoing testing. It is anticipated that one of these vaccines will supplant calf-lymph vaccine if a more extensive vaccination program is implemented.

The following sections review the official recommendations for using the Dryvax smallpox vaccine in a pre-event vaccination program, including the vaccination program currently under way. These recommendations, including descriptions of the adverse events and contraindications to watch for, were initially published by the Advisory Committee of Immunization Practices in 2001 (CDC, 2001) and recently updated, in their entirety, in April 2003 (CDC, 2003). ACIP remains committed to reviewing these recommendations periodically or more urgently, if necessary.

Vaccination Method

THE SKIN OVER THE INSERTION OF THE DELTOID MUSCLE OR THE POSTERIOR aspect of the arm over the triceps muscle are the preferred sites for smallpox vaccination. Alcohol or other chemical agents should not be used for skin preparation for vaccination unless the area is grossly contaminated. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine by the alcohol.

The multiple-puncture technique uses a presterilized bifurcated needle that is inserted vertically into the vaccine vial, causing a droplet of vaccine 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 to 20 seconds. For individuals being vaccinated for the first time, only three punctures are needed. For individuals who have received the vaccine in the past, a total of 15 punctures are necessary. Any remaining vaccine should be wiped off with dry sterile gauze and the gauze disposed of in a biohazard waste container.

Evidence of Immunity

APPEARANCE OF NEUTRALIZING ANTIBODIES AFTER VACCINATION WITH LIVE vaccinia virus indicates an active immune response that includes the development of antibodies to all viral antigens and increased vaccinia-specific cell-mediated immunity. In a person with normal immune function, neutralizing antibodies appear approximately 10 days after primary vaccination and seven days after revaccination. Clinically, persons are considered fully protected after a successful response or major reaction is demonstrated at the site of vaccination (see Figure 1).

The vaccination site should be inspected six to eight days after vaccination and the response interpreted at that time. Two types of response have been defined by the World Health Organization (WHO) Expert Committee on Smallpox. The first type of response is a "major reaction," defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer. A major reaction indicates that virus replication has taken place and vaccination was successful. There is also an "equivocal reaction," defined, somewhat vaguely, as all responses other than major reactions. An equivocal reaction indicates a possible consequence of immunity adequate to suppress viral multiplication or allergic reactions to an inactive vaccine without production of immunity. If an equivocal reaction is observed, vaccination procedures should be checked and the vaccination repeated by using vaccine from another vial or vaccine lot, if available.

Side Effects and Adverse Reactions

SMALLPOX VACCINATION IS GENERALLY CONSIDERED TO BE A SAFE AND effective preventive measure against smallpox. However, in a number of individuals, smallpox vaccination can result in untoward effects and adverse reactions. Most are totally benign, if frightening in appearance. Some are serious, but treatable. A few, which rarely occur, are potentially fatal.

Inadvertent Inoculation: In terms of less severe adverse events, inadvertent inoculation at other sites is the most frequent complication of smallpox vaccination and accounts for approximately half of all complications of primary vaccination and revaccination (see Figure 2). Inadvertent inoculation usually results from autoinoculation of vaccinia virus transferred from the site of vaccination. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. While most lesions heal without specific therapy, vaccinia immunoglobulin (VIG) can be used to manage cases of ocular implantation. However, if

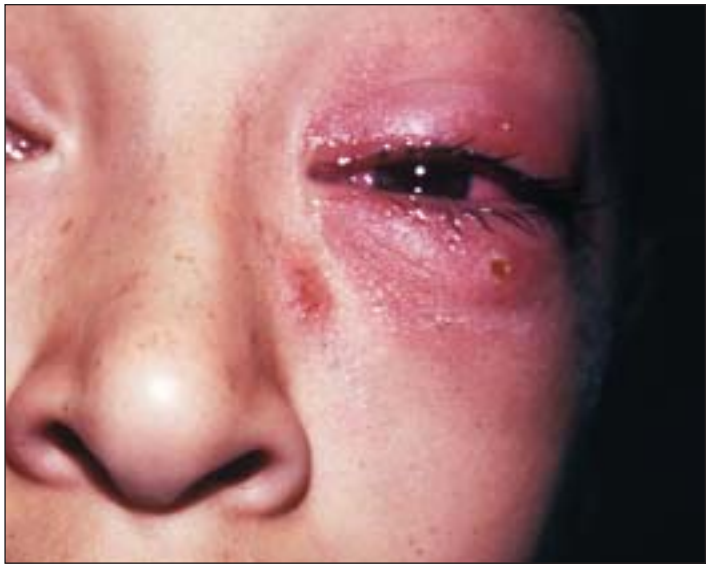

Figure 2. **Inadvertent Autoinoculation**

Inadvertent autoinoculation of the cornea in a 12-year-old male.
Source: U.S. Centers for Disease Control and Prevention

vaccinial keratitis is present, VIG is contraindicated because it might increase corneal scarring.

Rash: Erythematous or urticarial rashes can occur approximately 10 days after primary vaccination and can be confused with generalized vaccinia. However, the vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within two to four days. Rarely, bullous erythema multiforme (i.e., Stevens-Johnson syndrome) occurs (see Figure 3).

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, generalized vaccinia, progressive vaccinia, and postvaccinial encephalitis. These complications are rare but are more likely to occur among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults.

Eczema Vaccinatum: Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus among persons who have eczema or a history of eczema or other chronic or exfoliative skin conditions (e.g., atopic dermatitis). Usually, illness is self-limited, but it can be severe or fatal (see Figure 4).

Generalized Vaccinia: Generalized vaccinia is the result of the systemic spread of virus from the vaccination site (see Figure 5). Despite the appearance of the lesions, it is usually a benign complication of primary vaccination that is self-limited except in some individuals with underlying immune suppression. Other post-vaccination rashes—examples include nonspecific autoimmune rashes, eczema vaccinatum, and lesions of inadvertent inoculation—have been diagnosed as generalized vaccinia, making it difficult to determine the true frequency of this complication.

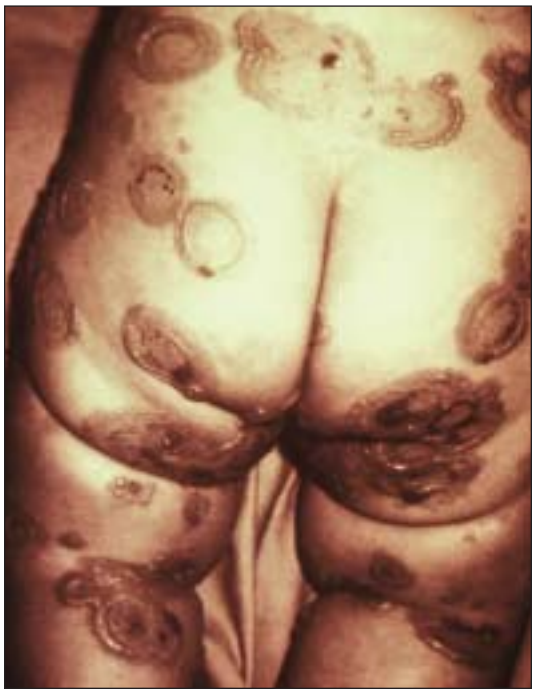

Figure 3. **Erythema Multiforme**

This eight-month-old patient displayed erythema multiforme lesions two weeks after his primary smallpox vaccination.

Souce: Arthur E. Kaye; U.S. Centers for Disease Control and Prevention

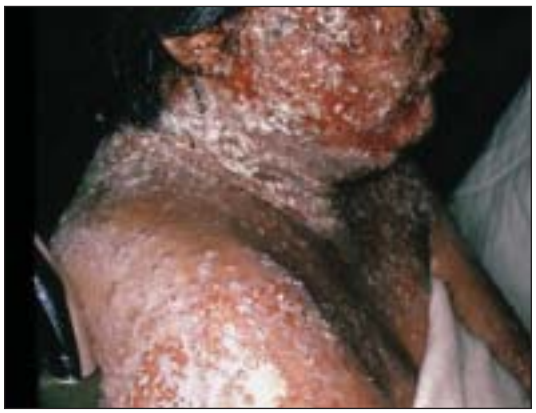

Figure 4. **Eczema Vaccinatum**

A 22-year-old woman with eczema vaccinatum acquired from her boyfriend. She became critically ill, with nearly total involvement of her body, and required thiosemicarbazones, as well as large doses of VIG.

Source: U.S. Centers for Disease Control and Prevention

Progressive Vaccinia: Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions (see Figure 6). If allowed to progress, progressive vaccinia can lead to superimposed systemic fungal infections and/or bacterial infections, including bacteremia and endotoxic shock with or without disseminated intravascular coagulation.

Massive doses of VIG are necessary to control viremia in patients with progressive vaccinia. Up to 10 ml/kg of intramuscular VIG has been used. In the event VIG is not available or is not effective in managing progressive vaccinia, the CDC lists cidofovir (Vistide)—a intravenously administered antiviral approved for the treatment of cytomegalovirus disease—as an alternative. Studies evaluating the effectiveness of cidofovir in patients with life-threatening vaccinia reactions are not available; however, *in vitro* and animal studies involving orthopoxviruses have yielded encouraging results. Surgical removal of massive lesions has also been performed to reduce viral mass, usually following VIG treatment. And in patients with bacterial or fungal superinfections, antibiotic therapy is often warranted.

Postvaccinial Encephalitis: Another serious complication is postvaccinial encephalitis. In the majority of cases, it affects primary vaccinees. According to the CDC, occurrence of this complication was influenced by the strain of vaccine virus and was higher in Europe than in the United States. The principal strain of vaccinia virus used in the United States—the NYCBOH strain—was associated with the lowest incidence of postvaccinial encephalitis. Approximately 15% to 25% of affected vaccinees with this complication die, and 25% have permanent neurologic complications. The risk of this serious complication is highest among children less than one year of age.

Cardiac Complications: Finally, there are possible cardiac complications to consider. At the February 2003 PRN meeting, when the notable adverse events of smallpox vaccination were reviewed by Drs. Weisfuse, Sepkowitz, and Danon, reports of cardiac problems among vaccinees had not yet surfaced. However, on March 28, the CDC described cases of cardiac adverse events among vaccinated persons in the *Morbidity & Mortality Weekly Report* (MMWR) (CDC, 2003a). At the time of this report, a total of 10 cases of myopericarditis had been documented among approximately 240,000 primary vaccinees in the military vaccination program, and two such cases (one of myocarditis and one of pericarditis) had been reported among civilian vaccinees. No cases of myopericarditis had been reported among approximately 110,000 military revaccinees. Patients whose cases were reported to the U.S. Department of Defense had onset seven to 12 days after vaccination and had illness diagnosed based on clinical features, laboratory studies, and electrocardiographic or echocardiographic features. Compared with the rate reported in an unvaccinated military population during 1998 to 2000, the rate of myopericarditis is substantially elevated.

As for cardiac ischemic events, a total of five reports had been reported to the CDC as of March 28, including three patients with myocardial infarctions and two patients with angina. The five patients with ischemic events ranged in age from 43 to 60 years, and four of the

five were aged >54 years; four were women. Four of the five had underlying cardiovascular risk factors. One had known cardiovascular disease, and two others had histories of chest pain (not clearly identified as cardiac in origin on the basis of available information). Two patients died, both from myocardial infarctions with out-of-hospital cardiac arrests. Onset of cardiac symptoms occurred 4, 4, 5, 9, and 17 days after vaccination in the five patients; the patient who experienced a cardiac arrest 17 days after vaccination had symptoms of nausea, dizziness, shortness of breath, fever, and productive cough five days after vaccination. Two patients were revaccinees, but the previous vaccination status of the other patients is unknown; all were children at a time when the majority of children in the United States received smallpox vaccine. The two deaths due to cardiac disease among civilian vaccinees are similar to the numbers expected among persons in these age groups in the general population in the absence of vaccination. The military reported an additional case of a myocardial infarction and out-of-hospital cardiac arrest in a man aged 55 years with multiple cardiac risk factors; the cardiac arrest occurred five days after vaccination.

These data are consistent with a causal relation between myocarditis/pericarditis and smallpox vaccination, but no causal association between the ischemic cardiac events and smallpox vaccination has been identified.

In summation, fatal complications caused by smallpox vaccination have historically been considered rare, with approximately one death per million primary vaccinations and 0.25 deaths per million revaccinations—usually because of either progressive vaccinia or postvaccinial encephalitis. However, there are lingering concerns that the risk of serious adverse events, including death, will be higher today, given the larger proportion of patients with immune suppression currently living in the United States (and elsewhere) than in decades past.

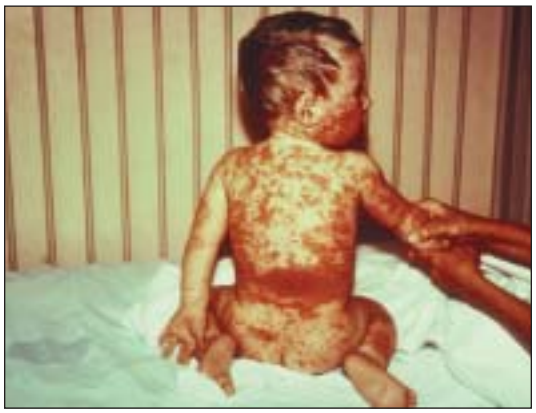

Figure 5. **Generalized Vaccinia**

This child manifested generalized vaccinia after receiving a primary smallpox vaccination.

Arthur E. Kaye; U.S. Centers for Disease Control and Prevention

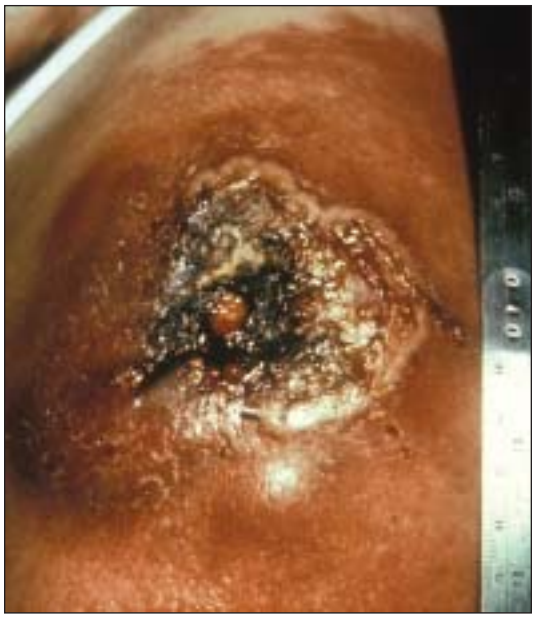

Figure 6. **Progressive Vaccinia**

This adult manifested progressive vaccinia, shown here as progressive necrosis of the vaccination area, after receiving a primary smallpox vaccination.

Source: Arthur E. Kaye; U.S. Centers for Disease Control and Prevention

Contraindications

ACCORDING TO THE ACIP, THE SMALLPOX VACCINE SHOULD NOT BE ADministered for pre-event indications if any of the contraindications reviewed below are present or if the vaccinee lives with or has close physical contact (e.g. persons with prolonged intimate contact with the potential vaccinee, including the potential for direct contact with the vaccination site) with someone who has one of these conditions (CDC, 2003). However, in the event of a smallpox outbreak, if exposure to the variola virus has occurred or there is a high risk of exposure to a patient, these contraindications would not apply. In these situations, the benefit of vaccination outweighs the risks of potential adverse events.

Eczema, Atopic Dermatitis, Darier's Disease, or Other Skin Conditions: Because of the increased risk for eczema vaccinatum, the smallpox vaccine should not be administered to persons with eczema or any degree of atopic dermatitis, to those with a past history of eczema or atopic dermatitis, or to those whose household contacts have active eczema or atopic dermatitis or a history of these skin conditions. Persons with other acute, chronic, or exfoliative skin conditions (e.g., burns, impetigo, or varicella zoster) might also be at higher risk for eczema vaccinatum and should not be vaccinated until the condition resolves.

Pregnancy: Because of the remote possibility of intrapartum vaccinia infection of the infant, the smallpox vaccine should not be administered to pregnant women for routine pre-event immunization indications. Women who are vaccinated should avoid getting pregnant for four weeks after vaccination.

Immune Suppression: Replication of vaccinia virus can be enhanced among persons with HIV infection and other immunodeficiency diseases, including those being treated with immunosuppressive drugs (e.g., as occurs with leukemia, lymphoma, generalized malignancy, solid organ transplantation, stem cell transplantation, cellular or humoral immunity disorders, or therapy with alkylating agents, antimetabolites, radiation, or high-dose corticosteroid therapy). Persons with such conditions or whose household contacts have such conditions should not receive the smallpox vaccine.

HIV Infection: Risk for severe complications after smallpox vaccination for persons infected with HIV is unknown and there hasn't been any evidence concluding that smallpox vaccination accelerates the progression of HIV-related disease, particularly among patients with undetectable HIV-RNA levels. However, the degree of immune suppression that would place an HIV-infected person at greater risk for adverse events is unknown. Because of this uncertainty, until additional information becomes available, not vaccinating persons—under routine pre-event conditions—who have HIV infection is advisable.

Allergy to Vaccine Components: The currently available smallpox vaccine contains trace amounts of polymyxin B sulfate, streptomycin sulfate, chlortetracycline hydrochloride, and neomycin sulfate. Persons who experience anaphylactic reactions (e.g., hives, swelling of the mouth and

throat, difficulty breathing, hypotension, and shock) to any of these antibiotics should not be vaccinated. The smallpox vaccine does not contain penicillin. Future supplies of the smallpox vaccine will be reformulated and might contain other preservatives or stabilizers. Refer to the manufacturer's package insert for additional information.

Infants and Children: Before the eradication of smallpox, smallpox vaccination was administered routinely during childhood to those over 12 months of age. However, smallpox vaccination is no longer indicated for infants or children for routine immunization.

Cardiovascular Problems: While not a part of the original list of contraindications published by the ACIP, it is now recommended that persons be excluded from the pre-event smallpox vaccination program who have known underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking) (CDC, 2003a). In response to these updated recommendations, prevaccination screening forms and other materials have been revised and provided to state health departments. At the present time, there are no recommendations for special medical follow-up for persons with cardiovascular risk factors who have been vaccinated. Persons with risk factors or known atherosclerotic coronary artery disease should be cared for and monitored by their physicians.

HIV and Smallpox Vaccination

THE HEIGHTENED RISKS OF SMALLPOX VACCINATION AMONG HIV-POSITIVE people are not hypothetical. In April 1984, a 19-year-old African-American male from the mid-southwestern United States began basic training at an Army military base (Redfield, 1987). He received multiple immunizations—adenovirus 4 and 7, measles, rubella, bivalent influenza, trivalent poliomyelitis, tetravalent meningococcal, tetanus, and diphtheria—within the first three days of basic training, followed by a primary smallpox vaccination at the end of the first week.

He participated fully in basic training until two and a half weeks after the smallpox vaccination, when fever, headache, neck stiffness, and night sweats developed. The diagnosis was cryptococcal meningitis and, after further evaluation, it was determined that he had a CD4+ count of fewer than 25 cells/mm^3. HIV was then isolated from PBMCs and antibodies to the virus were detected by Western blot.

Four weeks after receiving the smallpox vaccination, while the conscript was being treated for cryptococcal meningitis at the Walter Reed Army Medical Center, an ulcer approximately 4 centimeters in diameter developed at the vaccination site, with a smaller satellite ulceration developing nearby. Over the next two to three days, approximately 80 to 100 pustular lesions appeared on the buttocks and the legs, many of which became ulcerated. Generalized vaccinia was determined to be the cause and 12 weekly doses of VIG were prescribed. The ulcers gradually epithelialized and were completed healed by mid-August. The patient subsequently died, probably as a result of progressive neurological disease, in December 1985.

Another noteworthy report was published in 1991 in *The Lancet* (Guillaume, 1991). The report involved the experiences of 12 HIV-positive patients who underwent therapeutic administration of autologous lymphocytes that were infected with a recombinant HIV-vaccinia virus. Eight of the 12 patients had fewer than 150 CD4+ cells/mm^3 and three of them developed symptoms of progressive vaccinia and subsequently died. These complications were not recognized as such and VIG was not administered.

As explained by Dr. Kent Sepkowitz, of the five notably adverse events of smallpox vaccination—autoinoculation, generalized vaccinia, eczema vaccinatum, progressive vaccinia, and encephalitis—generalized vaccinia and progressive vaccinia are the most likely to occur in greater frequency in HIV-positive vaccinees.

"Simply put, we don't know what the risks are and I sincerely hope that we won't ever find out." As for autoinoculation, Dr. Sepkowitz does not foresee an increased risk compared to HIV-negative persons. There is also no reason that exzema vaccinatum would be more common in HIV, except in someone with sustained chronic dermatitis of some sort. "We don't see as much folliculitis as we used to," he said. "We don't see as many chronic skin conditions as we did in pre-HAART days. That said, one can imagine that someone with diffused Kaposi's sarcoma or diffused skin conditions could get into big trouble from being vaccinated. But the biology of HIV would not, in itself, predispose someone to higher rates of vaccinatum." There's also little reason to believe that encephalitis rates would be any higher among HIV-positive vaccinees than HIV-negative vaccinees.

In terms of generalized vaccinia, Dr. Sepkowitz reckons that there would almost certainly be increased rates among HIV-positive vaccinees. "However, this is very manageable with VIG and is not one of those oh-my-God-drop-everything sort of infections. They can become that, but they sound much more cinematic that they actually are in the clinic." Progressive vaccinia remains Dr. Sepkowitz's biggest fear. "Anyone with underlying immune dysfunction can develop this," he warned. "Progressive vaccinia has occurred, in the past, in one in a million vaccinees. We'd expect a much higher rate in a million immune-suppressed vaccinees. While we might be able to determine which of our diagnosed HIV-positive patients have suppressed immune systems, we also know that there are many people walking around with undiagnosed HIV infection and possible immune suppression. We can pretty much bank on increased progressive vaccinia in today's day and age."

Because of these fears, HIV-positive individuals, irrespective of their CD4+ cell counts, are being excluded from the current pre-event smallpox vaccination program. However, there are encouraging data to suggest that, in the event of a "pre-event" to "post-event" vaccine strategy that includes the immunization of HIV-positive people, the adverse event rate will remain relatively low. Dr. Sepkowitz pointed out that the Department of Defense (DOD) and the CDC have estimated that between 500 and 1,000 undiagnosed HIV-positive conscripts received smallpox vaccination in the 1980s, with an adverse event rate of less than 0.2%. "However," Dr. Sepkowitz added, "most people who join the army are relatively healthy, so this estimate doesn't accurately reflect what we'd expect to see in sicker HIV-positive individuals with suppressed immune systems."

The possible scenario doesn't end with data from the DOD. Dr. Sepkowitz reminded PRN members that HIV-positive individuals with well-controlled infection safely benefit from MMR, yellow fever, and Varivax immunizations—all live-virus vaccinations—with adverse event rates on a par with HIV-negative individuals.

While numerous steps—including HIV-antibody testing—are in place to prevent HIV-infected individuals from erroneously receiving the smallpox vaccine as a part of the pre-event smallpox vaccination program, there is still some concern that HIV-infected individuals will be inadvertently infected with the vaccinia virus through contact with a recently vaccinated person. Fortunately, Dr. Sepkowitz suspects that contacts of vaccinees—even those with suppressed immune systems—are unlikely to

experience either progressive vaccinia or encephalitis if they are infected. "What we're likely to see are cases of inoculation, eczema vaccinatum, and possibly generalized vaccinia," Dr. Sepkowitz said.

To better understand nosocomial spread of vaccinia virus, Dr. Sepkowitz performed a literature search spanning 100 years of smallpox vaccination and yielded 12 key reports from around the world (Sepkowitz, 2003). In short, these reports detailed the experiences of 85 secondary cases of vaccinia infection, 23 of which involved direct contact with a vaccinee. Approximately 75% of these secondary cases were children and 9/85 (11%) died of complications related to secondary vaccinia infection.

Information regarding the vaccinees—the sources of the secondary vaccinia cases—was provided in the 12 reports reviewed by Dr. Sepkowitz. In five of the reports, the sources were children experiencing eczema vaccinatum. "A child with eczema vaccinatum is simply oozing virus," he said. "The child is misdiagnosed and is put on to a ward with other children with eczema. From there, it spreads from person to person by the hands of a health-care worker. It's very easy to see how this can happen." As for the other seven sources, two cases were adults with generalized/disseminated vaccinia, one was a burn patient, one involved a contaminated urinary catheter (an infant with dysuria received a urinary catheter, which was subsequently removed and placed into a pan with other catheters, resulting in vaccinia infection of 23 other children), and two cases involved individuals participating in a community vaccination program. Only in one report was information involving the vaccinee not known.

In terms of risk factors associated with secondary infection, all of the cases reviewed by Dr. Sepkowitz involved individuals with an underlying skin disorder. For example, a large percentage of secondary vaccinia cases were in patients with eczema at the time of infection. Pemphigus foliaceous was a preexisting condition in some adults with secondary vaccinia disease. Other documented skin disorders believed to increase suspectibility to secondary vaccinia infection included burns, Mycosis fungoides, scabies, secondary syphilis, impetigo, and acne.

All in all, Dr. Sepkowitz believes that HIV-infected individuals with well-controlled disease will tolerate smallpox vaccination, as well as other live vaccines. "However," he added in his concluding remarks, "there are lessons from TB to be learned here. Even though we're dealing with an extremely familiar and predictable disease, it's always possible that it will become extremely unfamiliar and unpredictable in people with HIV infection."

The New York City Smallpox Vaccination Program

GIVEN THE CONCERNS THAT SMALLPOX MAY USED BY TERRORIST GROUPS OR rogue nations as a component of biological warfare, the federal government announced plans on December 13, 2002, for a voluntary smallpox vaccination program for hospital-based health care personnel who, in the event of an outbreak, would be available and willing to care for the initial patients with suspected or confirmed smallpox. In addition to these smallpox response teams, the federal government also announced plans to begin vaccinating public health response teams and select military personnel.

There's little doubting the need for a vaccination campaign to protect "first response" health-care workers. For evidence of this, one doesn't need to look much further than the SARS epidemic. A number of health-care workers have come down with symptoms of SARS after treating patients with the disease and have subsequently gone on to infect others. As a result, some hospitals have been forced to shut down or to reduce vital services—including those intended for HIV-infected patients—in order to grapple with the spread of SARS. Clearly, little good can come of health-care providers being unprotected against a contagious disease.

The pre-event smallpox vaccination plan outlined by the federal government consists of three waves. The first wave involves the vaccination of 500,000 hospital-based health-care workers and public health response teams nationwide. [EDITOR'S NOTE: *According to a* New York Times *editorial published on May 12, 2003, federal health officials are now suggesting that perhaps 50,000 vaccinated health care workers will be enough to complete the first wave of vaccinations.*] The second wave currently calls for the vaccination of 10 million health-care workers, along with first responders (e.g., police, firefighters, and emergency medical service staff) not covered in the first wave. In the third wave of the program, vaccination will be made available to the general population.

In the event of a smallpox attack, it is impossible to predict where the first cases may present for their care. Therefore, the goal of this smallpox vaccination program is to ensure that all acute-care hospitals who volunteer to participate in this program have pre-vaccinated staff ready to respond if a patient with smallpox presents to their institution.

Each hospital's health-care smallpox response team consists of volunteer health-care worker staff who would be prevaccinated against smallpox and have agreed to be available to 1) evaluate and manage patients who present to their hospital with suspected smallpox, and 2) provide in-room medical care for the first 7 to 10 days for these initial suspected or confirmed smallpox patients until additional hospital staff have been successfully vaccinated.

The initial plans in New York City called for approximately 100 to 200 health-care workers at each of the 74 acute-care hospitals—between 750 to 1500 vaccinations in total—to be included in the New York City Department of Health and Mental Hygiene (NYC DOHMH) smallpox vaccination plans. The workers are being recruited to serve on these health-care smallpox response teams as a part of the first wave of the vaccination program. Health-care workers are being selected based on those job categories that would be required to care for the initial smallpox cases (e.g., medical and nursing staff who work in the emergency department, intensive care unit, adult and pediatric wards, as well as respiratory therapists, radiology technicians, security, housekeeping, and other clinical support staff). The vaccine is voluntary; however, any person agreeing to be vaccinated should be willing to serve on the hospital's health-care smallpox response team to provide direct care for the initial suspected or confirmed smallpox case(s) in the event of an outbreak. As the incidence of vaccine adverse effects is less among persons who have previously received smallpox vaccine, efforts are being made to target persons who have received at least one prior dose of smallpox vaccine.

The NYC DOHMH, working closely with hospitals, began administering smallpox vaccinations in March. As of May 9, 2003, a total of 319 persons have received the smallpox vaccination in New York City. As explained by Dr. Weisfuse in a recent interview, there has been very low acceptance of the vaccinations, with the number of volunteers being substantially lower than expected. "This experience mirrors that in the rest of the country," he said. Participating in and plans for the second wave of vaccinations will be reassessed after completion of the first wave.

In order to minimize the number of adverse events, all potential volunteers are being educated about the contraindications to the vaccine. The NYC DOHMH is currently working with hospitals to ensure that educational sessions are offered to all potential vaccinees prior to starting smallpox vaccinations. The NYC DOHMH is also providing information on where potential volunteers may obtain free, confidential, or anonymous HIV counseling and testing, and pregnancy testing, if indicated.

HIV counseling and testing is strongly recommended for all persons considering smallpox vaccination in New York City.

Monitoring for any vaccine-related adverse events and arranging for rapid treatment will be an essential component of the NYC DOHMH vaccine program. The NYC DOHMH has mailed information to all New York City health-care providers and posted information on the NYC DOHMH website (http://www.nyc.gov/health/smallpox) that highlights the recognition, clinical management, and reporting of suspected smallpox vaccine adverse events, all of which have been reviewed in this article. Prevaccination of health-care smallpox response teams is just one component of the NYC DOHMH smallpox preparedness. Also important has been the ability of health-care workers to rapidly recognize and respond to the initial suspect cases of smallpox. New York City hospitals are expected to implement measures outlined in a NYC DOHMH and New York State Department of Health document, "Guidelines for Management of a Suspect Case of Smallpox in Acute Care Hospitals in New York City," which is available through the NYC DOHMH Web site cited above.

These guidelines provide detailed information on measures that should be put into place to ensure rapid recognition, isolation, and appropriate management of suspected smallpox patients, including the need for strict adherence to infection control measures. Isolation of suspected or confirmed smallpox patients and ensuring that all staff adhere to appropriate infection control precautions will also help prevent transmission of the variola virus and protect those who can not, or chose not to, be vaccinated.

The Israeli Experience

ROUTINE VACCINATION AGAINST SMALLPOX IN ISRAEL WAS INITIATED IN 1924 and subsequently halted in July 1980. In August 2002, the Israeli Ministry of Health dusted off its stockpile of smallpox vaccines and began immunizing thousands of citizens, most of them health-care personnel—first responders who would likely be involved in an immediate response to a biological attack. At the time of Dr. Yehuda Danon's PRN presentation, 17,700 Israeli citizens had received the vaccine and safety data were available for more than 7,000 vaccinees.

The smallpox vaccine being used by the Israeli Ministry of Health is based on the Lister strain of the vaccinia virus, grown on the chorioallantoic membrane of fertilized eggs. The bifurcated needle approach used in the United States to administer the vaccine is considered to be too costly in Israel, where the administration equipment of choice is the helicopter pipette. "The helicopter pipette is widely available, has high utilization in routine medical practice, and is associated with good take results," Dr. Danon explained.

Vaccine contraindications in Israel are similar to those in the United States. These include individuals with diseases or conditions that cause immunodeficiency, such as HIV, AIDS, leukemia, lymphoma, generalized malignancy, agammaglobulinemia, or are being treated with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids. Also excluded are individuals who have ever been diagnosed with eczema—even if the condition is mild or not presently active—as well as individuals with acute or chronic skin conditions such as atopic dermatitis, burns, impetigo, or varicella zoster.

Much like the pre-event vaccination program in the United States, Israeli health-care workers who receive the vaccine will be permitted to continue direct patient care, provided that vaccination site remains covered.

To date, roughly 70% of vaccinees have exhibited signs of a successful take, which is on a par with take rates observed in the past. Dr. Danon pointed out that all of the Israeli residents who have received the vaccine had been vaccinated in the past. "We did not want to use a vaccine-naive population," Dr. Danon explained. "We didn't have any VIG in Israel. The only VIG available was through the World Health Organization, and there was concern that some of these were infected with hepatitis B or hepatitis C. Because of this, we needed to make sure that we were being very careful about who received the vaccine in order to reduce the risk of adverse events."

To replenish its VIG stock, the Israeli Ministry of Health has asked that all successfully vaccinated individuals donate plasma—two or three times—three to six weeks after vaccination. Plasma samples collected any sooner than three weeks increase the risk of viremia, whereas plasma collected more than 90 days post-vaccination won't likely contain high enough titers of antibodies to be of therapeutic benefit.

The most common symptoms accompanying vaccination in 7,100 evaluable vaccinees were fatigue and weakness (31%), headaches (28%) muscle pain (22.5%), nausea (12%), shivering (12%), and fever (8%). Looking at the larger population of vaccinees, only ten adverse events were documented as of early May 2003. No vaccine-related deaths have thus far been reported to the Israeli Ministry of Health. In terms of adverse events, there have been two cases of contact vaccinia, one of which resulted in disseminated vaccinia. There have been two cases of erythema multiforme among vaccinees, one case of polymyalgia, one case of Stevens-Johnson optic neuritis, once case of peripheral neuropathy, two cases of myopericarditis, and one case involving a patient with both optic neuritis and vasculitis.

In terms of successful vaccine takes, there were no differences among patients who had received either one, two, three, or four vaccinations in the past. Also of interest, the rates of successful takes were similar in all age groups. In terms of serologies, Dr. Danon noted that individuals who had high vaccinia antibody titers on the day of vaccination were the least likely to have successful takes. In contrast, 93% of those who had low titers on the day of vaccination went on to have successful takes.

The Israeli Ministery of Health still has its work cut out for it. "Ever since we began the vaccination program in August 2002, we've had a low level of motivation and compliance among physicians," Dr. Danon reported. "We can't explain why this is, because many of the doctors who have experience in administering the smallpox vaccine and are wary of its side effects are now in retirement. We have many younger physicians who do not have much experience administering the smallpox vaccine and are now being trained, but they're still wary of the potential for adverse events. Conversely, we've had a relatively high level of motivation among nurses."

The Department of Defense Experience

DATA INVOLVING THE U.S. ARMED FORCE'S EXPERIENCE WITH SMALLPOX vaccinations were not available at the time of the February 2003 PRN meeting but have since been released by the Department of Defense (DOD, 2003). As of March 28, 2003, the DOD has vaccinated 350,000 operational forces and military health-care workers against smallpox—many of whom were naive to the vaccine prior to vaccination. Similar to the Israeli experience, DOD smallpox vaccine recipients have experienced the temporary symptoms expected after smallpox vaccination (e.g., itching, swollen lymph nodes, fever, malaise). Approximately 1% of vaccine recipients developed "flat" rashes that are not dangerous and not contagious. These vaccinees have been treated according to their symptoms (such as itching) and have remained on the job with their units. These rashes are

consistent with known responses after smallpox vaccination.

There have been 29 cases of inadvertent auto-inoculation, none of which were severe. There have also been 25 cases of generalized vaccinia, most of which were treated as outpatients. There have been two instances in which VIG was prescribed, both of which involved patients with generalized vaccinia. There have been 14 cases of myocarditis and/or pericarditis among the 350,000 smallpox vaccinees, with symptoms ranging from mild to severe (all have since recovered). No cases of eczema vaccinatum or progressive vaccinia have been reported, and there have been no deaths associated with smallpox vaccination. There have been 10 cases of vaccinia being transferred to contacts. However, none of these cases were severe and primarily involved inadvertent inoculation.

"Our smallpox vaccination program expanded rapidly and effectively to include more than 350,000 people," says Dr. William Winkenwerder, Jr., Assistant Secretary of Defense for Health Affairs. "The program continues to go well, and has been administered in a thorough, careful and professional manner. We continue to experience the types of reactions that we expected overall. Close monitoring has afforded these individuals prompt, effective care. We have adjusted our screening guidelines to defer those with a history of cardiac disease, based on guidance from the CDC and other medical experts. DOD's Smallpox Vaccination Program provides service members and the Nation an enhanced level of preparedness against the threat of smallpox."

Conclusion

ALTHOUGH THE CAMPAIGN TO VACCINATE 500,000 HEALTH-CARE WORKERS against smallpox appears to getting off to an unexpectedly slow start, adverse event data collected thus far paint an encouraging picture (see Sidebar). HIV-infected civilians are still being excluded from the pre-event smallpox vaccination program. At the present time, the greatest threat to HIV-infected patients is secondary vaccinia transmission by a vaccinee. However, as this issue of *The PRN Notebook* went to press, no cases of vaccinia transmission to contacts have been reported to the CDC—an indication that correct measures are being taken to reduce the risk of adverse events.

It is with hope that smallpox never reemerges from the shadows of history. Should the day come, it is comforting that mechanisms are in place to curtail the spread of disease and to protect those who have long been at the greatest risk of walking onto the frontlines of epidemics in their earliest stages: health-care providers and other emergency personnel. prn

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Status of the Smallpox Vaccination Program

State-by-state vaccination numbers, as of May 16, 2003

State/ Program	No. of Individuals Vaccinated	State/ Program	No. of Individuals Vaccinated
Alabama	481	Missouri	1,253
Alaska	95	Montana	101
American Samoa	0	Nebraska	1,457
Arizona	39	Nevada	10
Arkansas	976	New Hampshire	323
California	1,509	New Jersey	657
Chicago	56	New Mexico	158
Colorado	224	New York	659
Connecticut	634	New York City	330
Delaware	107	North Carolina	1,235
District of Columbia	98	North Dakota	414
Florida	3,623	No. Mariana Islands	0
Georgia	135	Ohio	1,760
Guam	0	Oklahoma	335
Hawaii	181	Oregon	95
Idaho	200	Palau	0
Illinois	228	Pennsylvania	198
Indiana	765	Puerto Rico	9
Iowa	486	Rhode Island	29
Kansas	448	South Carolina	859
Kentucky	767	South Dakota	735
Los Angeles	219	Tennessee	2,429
Louisiana	1,107	Texas	4,145
Maine	39	Utah	282
Marshall Islands	0	Vermont	121
Maryland	719	Virgin Islands	0
Massachusetts	94	Virginia	843
Michigan	716	Washington	512
Micronesia	0	West Virginia	734
Minnesota	1,475	Wisconsin	745
Mississippi	404	Wyoming	409

Total Number of Individuals Vaccinated (as of May 16, 2003) **36,662**

Adverse Events Associated with Smallpox Vaccination Among Civilians (Total number of adverse events associated with smallpox vaccination, as of May 9, 2003.)

Adverse Event	Total number of Cases (as of 5|9)	Adverse Event	Total number of Cases (as of 5|9)
Eczema vaccinatum	0	Ocular vaccinia	3
Erythema multiforme/ Stevens-Johnson syndrome	0	Postvaccinial encephalitis	1
Fetal vaccinia	0	Progressive vaccinia	0
Generalized vaccinia	2	Pyogenic infection of vaccination site	0
Inadvertent inoculation, nonocular	13	Vaccinia transmission to contacts	
Myocarditis/pericarditis	24	In health-care settings	0
		In other settings	0

Source: U.S. Centers for Disease Control Prevention. State-by-state vaccination numbers and adverse events numbers will be updated every Thursday by 12:00 PM EST and can be accessed through the World Wide Web (http://www.cdc.gov/od/oc/media/spadverse.htm).