Abstract: Smallpox as a Biological Weapon: Medical and Public Health Management

Inglesby TV, Henderson DA, Bartlett JC, et al. Journal of the American Medical Association, June 9, 1999; vol. 281, no. 22: 2127-2137.

In 1999, a working group of 21 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of smallpox as a biological weapon on civilian populations. Their consensus recommendations covered five main areas:

1. Smallpox Vaccination
2. Therapy
3. Postexposure Isolation and Infection Control; Home Care
4. Hospital Epidemiology and Infection Control; Decontamination of the Environment
5. Additional Research Needs

These recommendations and a brief overview of smallpox disease are presented below. This information is taken from an article published under the same title in the June 9, 1999, issue of the *Journal of the American Medical Association*.

Historical Perspective/Background

- The occurrence of smallpox was once worldwide in scope. A global campaign, begun in 1967 under the auspices of the World Health Organization (WHO), succeeded in eradicating naturally acquired smallpox in 1977. In the United States, routine vaccination ceased in 1972.
- Before 1972, smallpox vaccination was recommended for all U.S. children at 1 year of age. Most states required evidence of vaccination for school entry. Vaccination was also required for military recruits and tourists visiting other countries. Few persons younger than 27 years have been vaccinated. In 1998, the U.S. Census reported approximately 114 million persons were age 29 years or younger and, most likely, not vaccinated against smallpox.
- WHO proposed in 1986 that all laboratories destroy their variola stocks or transfer them to one of two WHO reference labs: the Institute of Virus Preparations in Moscow, Russia, or the Centers for Disease Control and Prevention in Atlanta, Georgia. All countries reported compliance. However, it was reported that, beginning in 1980, the Soviet government embarked on a successful program to produce smallpox virus in large quantities and adapt it for use in weapons. This report is cause for some concern because funding for Russian labs has declined and existing expertise, stocks, and equipment could migrate to other countries.

Forms of the Disease

- Smallpox is a DNA virus, a member of the genus orthopoxvirus. There are two epidemiologically distinct types of variola—major and minor—based largely on mortality rates. Variola minor is in some cases caused by a virologically distinct virus (variola "alastrim" minor), and in other situations is speculated to have been "minor" because of the population (immunity) status.
- In general, the illness associated with variola minor is milder with a sparse rash. Pre-eruptive or prodromal stages of major and minor are similar, but constitutional symptoms after rash onset are less severe in minor than in major. Although the quantity of lesions in minor could

equal the number seen in a major case, flatpox forms of disease were not seen with variola minor, and hemorrhagic forms were rare. A more rapid evolution of rash, over 6 to 7 days to crust stage, is observed in variola minor. Secondary fevers, common in variola major, are less frequently seen in variola minor. Ultimately, an outbreak of variola minor could be differentiated from variola major only after evaluation of the mortality rate. Outbreaks of minor had mortalities of ~1%. A milder form of disease is also seen among those who have residual immunity from prior vaccination. In partially immune persons, the rash tends to be more scant and evolution of lesions more rapid.

- Two rare forms of smallpox that can be difficult to recognize are hemorrhagic and malignant or flat-type. Both are characterized by a somewhat shorter incubation period and severely prostrating prodromal illness with fever, headache, and backache. Hemorrhagic smallpox is uniformly fatal; pregnant women appear to be unusually susceptible. Death usually occurs on the fifth or sixth day after the onset of rash. Malignant smallpox is frequently fatal. Constitutional symptoms are similar, but lesions develop slowly and do not progress to the pustular stage, remaining soft, flat, and velvety to the touch. If the patient survives, the lesions disappear without forming scabs, or, in severe cases, large amounts of skin may peel away.

Transmission

- Natural infection occurs following implantation of the virus on the otolaryngeal or respiratory mucosa. The infectious dose is unknown but believed to be only a few virions.
- Smallpox spreads from person to person primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. Contaminated clothing or bed linens can also spread the virus. There are no known animal or insect vectors.
- The risk for transmission does not occur until the onset of rash, following a period of high fever and malaise. Secondary cases are most often seen in those immediately caring for the patient, who is most infectious from the onset of the rash through the first 7 to 10 days of the rash. As scabs form, the risk of infecting others rapidly wanes. Even though scabs contain large amounts of viable virus, it appears not to be especially infectious, presumably because the virions are tightly bound in the fibrin matrix.

Clinical Presentation

- Following infection, the virus migrates to the regional lymph nodes and multiplies. The patient develops asymptomatic viremia on about the third or fourth day, followed by multiplication of the virus in the spleen, bone marrow, and lymph nodes. Secondary viremia begins on about the eighth day, followed by fever and toxemia. The virus, contained in leukocytes, then localizes in small blood vessels of the dermis and beneath oral and pharyngeal mucosa and subsequently infects adjacent cells.
- At the end of the 12-to-14-day incubation period (range: 7 to 17 days), the patient typically experiences high fever, malaise, and prostration with headache and backache. Severe abdominal pain and delirium are sometimes present. A maculopapular rash then appears on the mucosa of the mouth and pharynx and on the face and forearms; the rash then spreads to the trunk and legs. Within 1 to 2 days, the rash becomes vesicular and, later, pustular. Pustules are characteristically round, tense, and deeply embedded in the dermis. Crusts begin to form on about day 8 or 9. As the patient recovers, the scabs separate and characteristic pitted scarring gradually develops.

- The rash is centrifugal in distribution, most dense on the face and extremities. Lesions develop during a 1-to-2-day period and evolve at the same rate. On any given part of the body, they are generally at the same stage of development. This characteristic is in contrast with chickenpox (varicella), the disease most often confused with smallpox. With varicella, new lesions appear in crops every few days, and lesions at very different stages of maturation can be adjacent; varicella lesions are more concentrated on the trunk than on the face and extremities and are almost never found on the palms and soles.
- Except for lesions in the skin and mucosa and reticulum cell hyperplasia, other organs are seldom involved. Secondary bacterial infection is not common. Death, most common during the second week of illness, most likely results from the toxemia associated with circulated immune complexes and soluble variola antigens. Encephalitis sometimes ensues and is indistinguishable from the acute perivascular demyelination observed as a complication of infection.
- Neutralizing antibodies can be detected by day 6 of the rash and remain at high titers for many years. Hemagglutinin-inhibiting antibodies can also be detected about day 6 of the rash or about 21 days after infection, and complement-fixing antibodies appear about 2 days later.

Diagnosis/Laboratory Confirmation

- Laboratory confirmation of the diagnosis is important. Visualization of an orthopoxvirus particle, to suggest a diagnosis of smallpox infection, can be quickly accomplished by electron microscopic examination of vesicular or pustular fluid or scabs.
- Specimen collection should be done by personnel who are knowledgeable and who have been vaccinated. Contact precautions should be observed, with the additional use of a facemask. Guidance for proper specimen collection procedures can be obtained from the CDC.
- State and local health department labs should be immediately contacted, as examination requires high-containment facilities and should be undertaken only by those with appropriate training and equipment. Definitive lab identification and characterization of the virus involves growing the virus in cell culture or on chorioallantoic egg membrane and performing various biologic assays, including PCR (polymerase chain reaction) technique and restriction fragment-length polymorphisms. PCR studies can be completed within a few hours at CDC.

Recommendation 1: Smallpox Vaccination

- Because of the small quantities of vaccine and vaccinia immune globulin (VIG) maintained by CDC, a preventive vaccination program is not an option at this time.
- VIG is recommended to treat severe cutaneous reactions to vaccination. It is estimated that 250 of every 1 million persons vaccinated might require VIG treatment.

Procedures

- When available, vaccination is normally done with a bifurcated needle. A sterile needle is inserted into an ampoule of reconstituted vaccine and, on withdrawal, a droplet of vaccine sufficient for vaccination is held by capillarity between the two tines. The needle is held at right angles to the skin; the wrist of the vaccinator rests against the arm. Fifteen perpendicular strokes of the needle are rapidly made in an area about 5 mm in diameter. The strokes should result in a trace of blood at the site after 15-30 seconds. After vaccination, excess vaccine should be wiped from the site with gauze that should be

discarded in a hazardous waste receptacle. The site should be covered with a loose, nonocclusive bandage to deter the individual from touching the site and perhaps transferring virus to other parts of the body.

Efficacy

- After about 3 days, a red papule appears at the vaccination site and becomes vesicular on about day 5. By day 7, it becomes the typical Jennerian pustule—whitish, umbilicated, multilocular, containing turbid lymph and surrounded by an erythematous areola that may continue to expand for 3 more days. Regional lymphadenopathy and fever is not uncommon. As many as 70 percent of children have 1 or more days of temperature higher than 39°C (100°F) between days 4 and 14. The pustule gradually dries, leaving a dark crust, which normally falls off after 3 weeks.
- Successful vaccination for those with partial immunity may manifest responses along a gradient from that described above to an accelerated reaction in which there is little more than a papule surrounded by erythema that reaches a peak within 3-7 days.
- A response that peaks in erythema within 48 hours represents a hypersensitivity reaction and does not signify that virus growth has occurred. Revaccination is indicated.

Complications

- The frequency of complications with the vaccine used throughout the United States and Canada (the New York Board of Health strain) is the lowest for any vaccinia virus strain, but the risks are not inconsequential.
- Complications can include postvaccinal encephalitis, progressive vaccinia (vaccinia gangrenosa), eczema vaccinatum, generalized vaccinia, inadvertent inoculation, and a variety of other complications, usually rashes.

Contraindications

- Groups at special risk for complications include persons with eczema or other significant exfolliative conditions; patients with leukemia, lymphoma, or generalized malignancy who are receiving therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids; patients with HIV infection; persons with hereditary immune disorders; and pregnant women. If available, VIG may be given simultaneously with vaccination in a dose of 0.3 mL/kg body weight. If VIG is not available, vaccination may still be warranted, given the far higher risk of an adverse outcome from smallpox than from vaccination.
- VIG may also be administered to patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and periocular infections resulting from inadvertent inoculation. It is administered in a dose of 0.6 mL/kg body weight, given intramuscularly in divided doses over a 24-to-36-hour period and may be repeated in 2 to 3 days if improvement does not occur. Because VIG quantities are limited, it should be reserved for the most serious cases.

Immunity

- The immune status of those vaccinated more than 27 years ago is not clear. Studies done on those remotely vaccinated have demonstrated persistence of T-cell and humoral responses, but absolute levels of neutralizing antibodies decline substantially during a 5-to-10-year period post-vaccination. Epidemiologic studies during endemic smallpox

suggested (remote) vaccination could ameliorate disease but did not prevent disease in a majority of cases with high-risk exposures.

Vaccine Stockpile

- In November 2001, the Department of Health and Human Services (HHS) contracted with Acambis, Inc., and their subcontractor, Baxter International, for 155 million doses of smallpox vaccine by the end of 2002. This order will supplement the 15 million doses of vaccine currently available in the stockpile and the 54 million doses previously ordered from Acambis and scheduled for production in 2002.

Recommendation 2: Therapy

- No antiviral substances have *proven* effectiveness for smallpox treatment.
- Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.
- Currently there is no cure for smallpox. Smallpox patients should be offered supportive therapy plus antibiotics as indicated to treat occasional secondary bacterial infections.

Recommendation 3: Postexposure Isolation and Infection Control; Home Care

- As soon as the diagnosis of smallpox is made, all those suspected of being infected should be immediately isolated and all persons in the household and others who have had face-to-face contact with the infected individual after the onset of fever should be vaccinated and placed under surveillance. Patients should be isolated while infectious.
- Because persons who have had contact with an infected individual would not be contagious until the onset of rash, they should take their temperatures at least once daily, preferably in the evening. Any temperature higher than 38°C or 101°F during the 17-day period following last exposure to the infected patient would suggest the possible development of smallpox. This would be cause for immediate isolation until it can be determined clinically and/or by laboratory examination whether the person has smallpox.
- Cooperation from most patients and persons who have had contact with patients can likely be ensured through counseling and persuasion. There may be some for whom forcible quarantine is required.
- In the event of an outbreak, the following high-risk groups should be given priority for vaccination: 1) persons exposed to the initial release of the virus; 2) contacts of suspected or confirmed smallpox patients; 3) personnel selected for direct medical or public health evaluation, care, or transportation of suspected or confirmed smallpox patients; 4) laboratory workers selected for the collection or processing of possible smallpox specimens; 5) other persons who may be in contact with infectious material, such as hospital laundry or medical waste, and mortuary workers; 6) other groups essential to response activities such as selected law enforcement, emergency response, or military personnel; and 7) all individuals present at a hospital during the time that a smallpox patient is present and not isolated appropriately. Employees for whom vaccination would be contraindicated should be furloughed.

Recommendation 4: Hospital Epidemiology and Infection Control; Decontamination of the Environment

- In the event of a limited outbreak, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air (HEPA) filtration.

- To limit nosocomial infections, authorities should consider designating a specific hospital or hospitals for smallpox care.
- Standard precautions using gloves, gowns, and masks should be observed. All laundry and waste should be placed in biohazard bags and autoclaved before being laundered or incinerated. Surfaces that may be contaminated with smallpox virus can be decontaminated with disinfectants that are used for standard hospital infection control, such as hypochlorite and quaternary ammonia.
- Patients who die should be cremated whenever possible.

Recommendation 5: Additional Research Needs

- Priority should be given to three areas: vaccines, immunotherapy and drugs, and diagnostics.
- Continued efforts are needed to ensure a sufficient smallpox vaccine stockpile (see **Recommendation 1: Smallpox Vaccination – *Stockpile***).
- The frequency of complications is sufficiently great to recommend the development, if possible, of a more attenuated strain.
- Production of VIG should be a high research priority. An alternative to VIG is also needed.
- A simple, rapid diagnostic test to identify variola virus during the prodrome is also needed.