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Bioterrorism Preparedness — Smallpox and Related Pox Viruses

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In the event of a major bioterrorist attack involving smallpox, veterinarians, physicians, allied health professionals and the general public must be well prepared. Unlike bioterrorist agents that cause diseases such as anthrax, bubonic plague, tularemia and brucellosis that infect many species, including human beings, smallpox infects only primates. It is the first choice of viral bioterrorist agents; it has killed more people throughout history than any other disease.

Veterinarians, veterinary technicians, animal caretakers and zoo visitors could be greatly affected in the event of a smallpox outbreak among captive sub-human primates. Human beings are the predominant smallpox host, but monkeys may become infected and transmit the virus to other monkeys and possibly people. A smallpox epidemic in Brazil was associated with an outbreak in monkeys; the bodies of dead animals were covered with smallpox pustules. In 1951, an orangutan in a zoo developed smallpox during an outbreak in Djakarta, Indonesia.

In recent years, concerns over diseases such as Ebola have drastically restricted the importation of monkeys. However, large populations exist in research facilities and zoos across the United States. Consequently, human and sub-human primate populations in the United States, which are both susceptible to smallpox, coexist in close and continuous contact.

At one time, almost everyone contracted smallpox. The two forms of smallpox were variola major, which had a 30 percent fatality rate, and variola minor that killed about 1 percent of its victims. Variola virus (smallpox virus) is in the family *Poxviridae*, genus *Orthopoxvirus*. Three out of six other viruses of this genus — cowpox, vaccinia and monkeypox (horsepox,another closely related orthopoxvirus, is also included in older literature) — can infect people. Smallpox is the only one in this genus that readily spreads from person to person. These four viruses are so closely related that infection with one generally confers immunity to the others. For example, vaccination with vaccinia protects human beings against smallpox (the very first effective smallpox vaccine contained cowpox virus); vaccination with vaccinia protects animal caretakers and researchers against monkeypox. Since smallpox has been eradicated, monkeypox is rare but remains the only smallpox-like disease in nature (if transmitted to human beings).

Smallpox Characteristics Made Eradication Possible

How was smallpox eradicated while many other infectious diseases remain? Although smallpox eradication was accomplished after a colossal and persistent global effort, the biologic characteristics of the virus actually made this feasible:

- No wildlife reservoir — Smallpox virus never existed in wildlife. Consequently, it could not become active and be transmitted from wildlife to humans (except for possible temporary transmission from sub-human primates to humans).
- No reservoir or carrier host — Because no other mammals get smallpox (except for short-term infection in subhuman primates), then recover and harbor the virus in their bodies, they cannot serve as carriers of the virus to infect people.
- No persistent infection with recurrent disease and virus shedding in human beings. Once a person recovers from the disease, he/she does not permanently carry that infection in his or her system to infect others or to recur at a later date.

- No subclinical cases — Smallpox cases are easy to recognize. Persons with the virus exhibit fever, skin rash and obvious signs of infection.
- During the prodromal (incubation period from seven to 17 days) stage, a patient was not contagious. After that point, the patient developed a fever for 2 to 3 days, then a rash; the patient was contagious from the onset of the rash through the first seven to 10 days of rash.
- Only one smallpox serotype or strain — In contrast to disease agents that have many strain variations with each requiring a specific vaccine, smallpox has only one type. As a result, only one vaccine was needed.
- An effective vaccine existed.
- Only one dose of vaccine was required for long term protection.
- Early containment of outbreaks was possible by vaccinating human beings in and around an outbreak area (called ring vaccination), isolating persons who may have been exposed (quarantine) and by surveillance to detect new smallpox cases.
- A high level of public concern due to the potential 30 percent mortality rate in unvaccinated persons and severe scarring in those patients who did recover.

Smallpox Risks Remain After Eradication

After 1980, smallpox virus existed only in two World Health Organization laboratories — the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the Institute of Virus Preparation in Moscow, Russia. However, scientists believe that the Soviet Union's bioweapons program produced many tons of smallpox virus annually for delivery in bombs and intercontinental ballistic missiles beginning in 1980. Furthermore, it was reported that Russia expanded this program to produce more virulent and contagious recombinant smallpox strains (strains produced by combining genes from different organisms). Credible experts fear that, since the fall of Communism, these viruses may have fallen into the hands of terrorists to be used as weapons.

To use this virus as a weapon, it is necessary to deliver that agent to its target. Smallpox virus dispersed by missiles or bombs could be devastating. Such a release could spread widely because only a small dose is

Smallpox in History

The last endemic case of smallpox occurred in Somalia in October 1977. Before this, smallpox killed more people than any other infectious disease — more than 300 million — and those who recovered were permanently scarred. Some of these deaths occurred when smallpox was used as a biologic weapon.

British forces in North America were probably the first to use smallpox as an offensive weapon during the French and Indian War (1754-1767). Blankets used by smallpox patients were distributed for the sole purpose of starting outbreaks among American Indians, who were a totally susceptible population. As a result, more than 50 percent of exposed and affected tribes were killed.

The origins of inoculation to prevent disease actually began with centuries-old observation that individuals who survived certain diseases did not have recurrences. In ancient China and later in western Asia, fluid from vesicles (sores) of persons with smallpox was inoculated (introduced) into the skin of noninfected individuals in an attempt to specifically protect against smallpox. In 1721, Lady Mary Wortley Montague, wife of the British ambassador to Turkey, is credited with introduction of variolation (inoculation with smallpox virus) into England. This practice of inoculation with virulent smallpox virus from even mildly infected patients was very risky, resulting in significant disease and mortality. By 1840, the practice of variolation was banned.

In the late 1700s in England, it was common folk knowledge that cowpox infection in milkmaids protected against smallpox. Noting this observation, Benjamin Jesty, a Dorsetshire farmer, reportedly inoculated his wife and children with cowpox in 1774. However, no scientifically based study was undertaken until May 1796, when Edward Jenner, a young Gloucestershire physician, inoculated a young boy named James Phipps with cowpox. The boy later proved immune to smallpox. Jenner published "An Inquiry into the Causes and Effects of Variolae Vaccinae" in 1798. His medical peers thereafter accepted this vaccination method as a valid tool for preventing smallpox.

The worldwide dissemination of cowpox inoculation reduced the likelihood that smallpox would be used as a biologic weapon and set the stage for the eventual eradication of the disease. Jenner's work also started the use of the term "vaccination" that comes from the Latin word "vacca," which means cow. Coined originally to refer to inoculation of smallpox vaccine, it now is used to apply to any immunizing procedure for which an antigen is injected.

By 1978, a global vaccination program had successfully rid the world of smallpox. In 1980, the World Health Assembly recommended that all countries stop vaccination.

needed to cause disease and because the variola virus in aerosol form is relatively stable. In addition, each case of smallpox during the December to April period of highest transmissibility could produce 10 to 20 additional cases.

Spreading smallpox virus by an infected, individual terrorist may not be as likely since the disease would be so severe by the time the smallpox virus was contagious that the terrorist would no longer be ambulatory. Also, the pox lesions all over the body would be noticeable to observers and impossible to hide. However, another point of view is that the possible spread of smallpox by infected terrorists is the most plausible introductory method. Nevertheless, the diagnosis of even a single case of smallpox cannot be minimized; it would be of extreme concern and should be handled as a possible international health emergency.

Countermeasures

The likely countermeasures to a smallpox virus bioterrorist attack would include:

- More rapid identification of cases — Normally, there would be one to two weeks from release until the first index case because of a long incubation period. A long, undetected incubation period allows an outbreak to become too widespread.
- Isolation and vaccination in a wide area around an outbreak of presumed infected and exposed individuals (ring vaccination).
- Surveillance of exposed individuals and their contacts.
- Decontamination procedures (ordinary disinfectants like hypochlorite [bleach] and quaternary ammonia products inactivate smallpox). Deceased smallpox patients should be cremated. Because smallpox does not live longer than two days in the environment, even under the most ideal conditions, by the time the first case is diagnosed, no environmental virus contamination would likely be present from the original terrorist release to cause any new cases.

Although smallpox virus in scabs may be viable for as long as 13 years, it is not thought to be contagious. The scab prevents the virus from being transmitted through inhalation, which is its normal method of spread. Also, smallpox has a long incubation period (12 to 14 days, seven to 17 day range) and is not contagious until a rash appears. If vaccination is performed within the first few days (and perhaps as late as four days) of exposure, illness from smallpox may be significantly reduced.

The United States maintains a stockpile of at least 15.4 million doses of smallpox vaccine, enough to vaccinate about 7 percent of the population. The government is making every effort to expand the vaccine supply. Recent experimental work at the National Institute of Allergy and Infectious Diseases, Baylor College of Medicine in Houston and two other institutions has demonstrated that the standard vaccinia vaccine against smallpox is potent even when diluted to one-fifth strength. The researchers are optimistic that adequate protection may even be possible with vaccine used at a 1 to 10 dilution. These studies are scheduled to be published in the *New England Journal of Medicine* in late April 2002 (http://www.nejm.org).

Researchers have reportedly found approximately 90 million long-forgotten doses of smallpox vaccine in the freezers at Aventis Pasteur, a French drug firm in Pennsylvania. Most of this vaccine has been donated to the U.S. government. Baylor College of Medicine researchers in Houston are designing a study to test the effectiveness of the newly-found vaccine.

In addition, the U.S. government has contracted with Acambis/Baxter to produce 209 million doses of a "second-generation" (made not directly from an animal but from cell culture) vaccinia vaccine. As a result, by the end of 2002, it is estimated that a total of at least 286 million doses of vaccine will be stockpiled.

The Disadvantages of Vaccination

Vaccination does have drawbacks. In addition to the estimated one person per million that would likely die from the vaccine, an estimated total of 250 persons per million inoculated will suffer reactions to the available vaccine. These reactions may be severe enough to require administration of Vaccinia Immune Globulin (VIG, an antidote). However, VIG is in short supply and is cumbersome to administer since large doses are

Smallpox Experts are Now Very Optimistic about Preparedness Options

"Expanding our existing smallpox vaccine stockpile ensures that we are well prepared in the event of a bioterrorist attack using smallpox. This new contract gives us the insurance that we will have more than enough vaccine for any outbreak that might occur." — Dr. D.A. Henderson, director of the Office of Public Health Preparedness, U.S. Department of Health and Human Services, and leader of the World Health Organization's successful worldwide program to eradicate smallpox, 2002

"These encouraging results [studies on diluted vaccine] suggest that we can do more with less and thereby extend our capacity to contain a potential smallpox outbreak." — Dr. Anthony S. Fauci, director, National Institute of Allergy and Infectious Diseases, 2002

required (0.3 to 0.6 ml/kg IM in divided doses over 24 to 36 hour period — 21 to 42 ml in a 70 kg [154 pound] person). VIG may also prevent or modify smallpox if given within 24 hours of exposure. Currently, the CDC provides vaccinia vaccine and VIG through state health departments only to persons in special risk categories such as laboratory workers directly involved with smallpox or closely related viruses.

How long does protection last in those previously vaccinated for smallpox? Routine vaccination in the United States stopped in 1972. Since at least 42 percent of the American population (those younger than 30 years old) has never been vaccinated and few persons alive today have been vaccinated more than once, most scientists believe that almost everyone in the United States is susceptible to smallpox infection. However, this is another issue regarding smallpox that continues to be debated.

Future Needs for Smallpox Preparedness

To prepare for a bioterrorist attack with smallpox, the United States needs, first, a rapid, simple oropharynx (throat) swab test to identify the smallpox virus before any clinical signs develop (eg. polymerase chain reaction [PCR] test). Prompt vaccination of individuals who test positive to the infection early in the incubation period would help prevent spread.

Second, a vaccine that produces fewer adverse reactions is needed. The "second-generation" vaccine that the government has contracted to be produced is made in cell culture, rather than calf skin. The newer vaccine, to be available by the end of 2002, will be as effective but still retains the risks of traditional vaccinia vaccines. Consequently, scientists are now focusing on developing a safer "third-generation" vaccine.

Third, an alternative to VIG is needed because it is difficult to produce and administer (it requires large amounts of antidote per person). An immune globulin containing monoclonal antibodies against smallpox and produced in human cell culture has been suggested as a possible replacement. Antiviral drugs that are already on the market or near approved status could also be tested for use against smallpox.

For more information

Centers for Disease Control and Prevention web site, *http://www.bt.cdc.gov.*

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