



## **Smallpox September 2003**

Smallpox is the disease caused by variola virus.

Smallpox was perhaps the most devastating infectious disease scourge known to mankind, causing more deaths and suffering than any other. As a result of possibly the greatest achievement of modern public health, there have been no cases of smallpox since a laboratory accident in 1978, one year after the global eradication of naturally-occurring disease. There is precedence, however, to be concerned about smallpox as a biological weapon. It was used in the French and Indian War when blankets known to have infectious materials on them were given to Native Americans, leading to smallpox outbreaks among the tribes. More recently, its production in the former Soviet Union specifically for the use as a biological weapon was confirmed. The potential of its use as a bioweapon, however, is contingent upon the availability of the virus and this is a question of debate. There are officially only two stocks of virus in existence -- one at the CDC in Atlanta, Georgia and the second at a similar biological lab in Russia. However, the security of the stock that has been in Russian hands is in question because of the fallout from the collapse of the former Soviet Union. Because it is estimated that less than 20% of the United States population has substantial immunity, smallpox is an attractive weapon to be used by those wishing to cause a high mortality. For these reasons, there is legitimate concern that an extinct disease poses a substantial risk.

Smallpox afflicted only humans, as there are no known animal hosts. In a largely unvaccinated population, smallpox had a mortality of 25-30%. Although the case fatality is lower than other potential bioterrorism agents such as anthrax, smallpox has the potential for secondary spread from person to person. Transmission occurs primarily through close face-to-face contact via droplet nuclei. However, smallpox can also be transmitted via an airborne route in the setting of an infected patient with a severe cough, and from direct aerosol inhalation. One of the most concerning things about smallpox is that there is person to person transmission, and the secondary attack rate would likely be 25-40% in unvaccinated contacts, meaning that at least one of every three or four persons

exposed would develop disease. Historically, three to four contacts were infected per index case. However, it is expected that up to 10-20 contacts in a mostly nonimmune population could be infected. There is very high potential for nosocomial spread as evidenced by several cases occurring throughout a hospital where an infected patient with a cough was kept in an isolation room.

Variola virus is in the *Orthopoxviridae* family of DNA viruses. There are 2 strains including *Variola major*, which was the cause of the majority of fatal disease with a mortality of 25-30% and was prominent in India, Asia and Northern Africa. *Variola minor* is a second strain with a milder disease and a lower mortality, usually less than 1%, which was the predominant form seen in the United States and Europe in the 20<sup>th</sup> century. *Vaccinia* is another *Orthopox* virus, and the virus used for the current smallpox vaccine. Cowpox, used by Jenner in his first vaccinations against smallpox, and monkeypox are other *Orthopox* viruses that rarely cause disease in humans.

The pathogenesis of smallpox begins when the virus lands on respiratory or oral mucosa. Macrophages engulf the organism and carry it to the regional lymph nodes where a primary transient viremia develops. The reticuloendothelial organs are invaded and overwhelmed leading to a secondary viremia. White blood cells are subsequently infected and then migrate to capillaries and invade the dermis causing dermal cell infection and an influx of additional leukocytes and mediators that lead to the formation of deep vesicles. A further inflammatory response occurs systemically which is triggered by the viremia and leads to sepsis, multiorgan failure and often, death.

There are three stages of disease starting with an asymptomatic incubation stage that typically lasts 12-14 days, with a range of 7-17 days. This is followed by a prodromal phase that begins very acutely as a nonspecific, flu-like illness almost always accompanied by fevers and prostration. The prodrome lasts for 3-5 days and ends with the eruption of the characteristic rash. Patients become infectious approximately one day prior to the appearance of the rash, corresponding to the development of oral mucosal lesions. The classical smallpox rash is characteristic and can be distinguished from other rashes based on its distribution, its grouping and the deep tense vesicles that are formed.

This photograph of an infant shows the classic distribution of the rash. It appears in a centrifugal pattern where the lesions first occur on the head and face and then the distal arms and legs including the palms and soles with relative sparing of the trunk.

This photograph shows the characteristic grouping where all lesions within a localized area are in the same stage of development. This is unlike chicken pox where crops of lesions in different stages of development are noted in the same location. The vesicles are also deeper and more tense than chickenpox. The severity of the rash correlates with the mortality, where the most severe rashes have the lowest survival rates.

The progression of smallpox lesions can be noted on this slide. The earliest stage is maculopapular, leading to deep vesicles, then pustules and finally scabs that then separate leaving a permanent scar. Scab separation marks the end of the period of infectiousness.

The one disease that is most likely to be misidentified as smallpox in the setting of an outbreak is chicken pox. In addition to the grouping of the lesions, the critical differentiation can be made by the distribution of the rash. Chickenpox is distributed centripetally, starting on the trunk and sparing the palms and soles.

The diagnosis of smallpox is a clinical one and in the setting of an outbreak, the classic syndrome and rash are all that is necessary for confirmation. Any suspicious rash during the setting of an outbreak must be considered smallpox until proven otherwise.

Traditional confirmatory methods have included electron microscopy of vesicle fluid that can rapidly confirm the presence of an *Orthopoxvirus* but does not prove variola is the species. This requires culture on chick membrane or cell culture, which is specific but slow. Newer rapid tests including PCR are available at reference labs.

The management of confirmed or suspected cases consists primarily of supportive care for those infected, and isolation. There is no specific antiviral treatment for those already showing symptoms. Supportive care is critical including careful attention to electrolyte and volume status, and ventilatory and hemodynamic support. Antibiotics are only required in the uncommon setting of secondary bacterial infections, such as *Staphylococcus aureus* cellulitis. Isolation of the patient is a vital component of the management of smallpox. Vaccination does not provide benefit to those truly infected who are already symptomatic, but can be considered in the treatment regimen in case the diagnosis of smallpox is wrong in a patient who was at risk of exposure.

Post exposure prophylaxis should be provided to those who have suspected exposure prior to symptom onset. This would include persons exposed to an original aerosol or contacts of cases, defined as those in the same household or who have had direct face-to-face contact with the patient after fever onset. Vaccine is partially protective if given within 3-4 days of exposure and may reduce the incidence of disease by 2-3-fold and mortality by 50%. Administration of *Vaccinia* immune globulin (VIG) in conjunction with vaccination may provide up to 70% greater protection versus incidence and death versus vaccination alone if given within the first few days after exposure. The passive immunity lasts for approximately two weeks, and presumably provides protection until active immunity from the vaccine develops. The antiviral agent cidofovir can prevent disease in animals exposed to other pox viruses and may be effective as a post exposure prophylactic option for smallpox if given within two days of exposure.

The smallpox vaccine used in the United States, called Dryvax, consists of live attenuated *Vaccinia* virus. Although new, improved vaccine supplies are entering production, there is currently enough of the original vaccine for every U.S. citizen. In an outbreak setting, vaccination can reduce the secondary attack rate by ten-fold. It has the highest efficacy in those who are vaccinated multiple times. Duration of efficacy of a single immunization is unknown but is likely to provide substantial protection for at least 3-5 and possibly up to 10 years, and to have at least a 3-fold decrease in mortality for 20 years. Revaccination can grant 30+ years of immunity that may persist life long.

The vaccine does have serious complications with up to 3 in 100,000 vaccinees reporting significant adverse reactions and nearly 1 in 1,000,000 deaths. Likelihood of adverse effects are 3-4-fold higher in infants and in primary vaccinees.

Most of the adverse effects of the vaccine are attributable to *Vaccinia* viremia. Encephalitis is the most feared adverse effect, occurring in 1 out of every 300,000 primary vaccinees. Mortality from this complication, for which there is no treatment, is 25%, and those who do survive often have permanent neurological sequelae. *Vaccinia gangrenosum* and *Vaccinia necrosum* are also highly feared serious adverse effects with mortality nearing 100% in those who are untreated. Eczema vaccinatum, which occurs in vaccinees or their contacts who have a history of eczema, is manifested by vaccinia lesions that appear in areas of skin involved by eczema. Mortality can be up to 40% in children less than 2 years old. All complications except encephalitis can be treated successfully with VIG.

This photograph shows an infant with *Vaccinia necrosum* at the inoculation site who died of this complication.

There are several critical infection control issues to be considered in the setting of a smallpox outbreak. They involve the proper handling of infected patients and case contacts. First, all suspected cases must be isolated following standard, contact and airborne precautions requiring the placement in a negative pressure room with HEPA filtration, and the use of gowns, gloves and N95 masks. If the clinical situation allows, home isolation is an option, especially during a large outbreak. When possible, only recently vaccinated caregivers should be assigned to suspected cases.

Contacts of suspected smallpox cases must first be correctly identified based on the fact that the period of infectiousness effectively begins with the eruption of the rash, and lasts until all lesions have scabbed over. Because the rash is preceded by a fever, a temperature greater than 38.0°C is an adequate trigger to isolate a case contact. Persons at risk include those exposed to a suspected case after fever onset via direct contact with secretions or face-to-face contact within 3 meters. Also, because of the high risk of nosocomial spread, all patients and staff in a hospital containing a suspected case should be considered contacts. All contacts should be immediately vaccinated (with concomitant VIG for those with relative contraindications) and observed 17 days for the development of fever. Isolation is not necessary before a fever is detected. Quarantining of patients or contacts may be necessary from a public health standpoint.