

# Smallpox

Clinical Description &  
Recommendations for a Vaccination Program

## Overview of Smallpox

**SLIDE 1:** Smallpox is the disease caused by the variola virus.

**SLIDE 2:** Smallpox was perhaps the most devastating infectious disease scourge known to mankind,

**SLIDE 3:** causing more deaths and suffering than any other [1].

**SLIDE 4:** 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,

**SLIDE 5:** one year after the global eradication of naturally-occurring disease [2].

**SLIDE 6:** 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, probably contributing to smallpox outbreaks that decimated the tribes. There is strong suspicion that the former Soviet Union produced variola virus specifically for use as a weapon in their bioweapons research program in the 1980's.

**SLIDE 7:** Today, the risk of this extinct disease being used as an agent of biological warfare is deemed to be low, but not negligible for two reasons. First, variola virus is thought to be possessed by unauthorized groups. As a result of a World Health Organization effort, all known existing stocks of variola virus were either destroyed or transferred to one of two facilities by 1984, one of these is the Centers for Disease Control in Atlanta, Georgia, and one in Russia. However, because of the unstable political and economic climate surrounding the subsequent fall of the former Soviet Union, the uncertainty that all stocks were originally accounted for, and recent U.S. intelligence data, there is genuine concern, despite little evidence, that variola virus may reside in the hands of other nations or terrorist groups. [3] Secondly, most of the world's population is now susceptible to the disease.

**SLIDE 8:** Routine vaccination against smallpox ceased in 1972 as the disease had been absent from the U.S. for decades and it was rapidly disappearing from all but a few

endemic pockets in the rest of the world at that time. Less than 20% of the American population now has substantial immunity, making smallpox an attractive weapon to be used by those wishing to cause a high morbidity and mortality [4,5].

**SLIDE 9:** Smallpox afflicts only humans; there are no known animal hosts and no insect vectors. In a largely unvaccinated population, smallpox has a mortality of 25-30%. Although the case fatality rate is likely to be somewhat lower than some other potential bioterrorism agents such as anthrax, smallpox has the potential for secondary spread from person-to-person.

**SLIDES 10/11:** Transmission occurs primarily through close face-to-face contact via droplet nuclei, putting primarily family members at risk.

**SLIDE 12:** However, smallpox can also be transmitted longer distances in the setting of an infected individual with a severe cough, as proven by one outbreak in the 1960's where one patient infected 17 others over 3 floors in a single German hospital. The secondary attack rate is estimated to be 25-40% in unvaccinated contacts, meaning that at least one out of every three or four persons exposed would develop disease. It is expected that 10-20 secondary cases may be generated from a single infected case in a mostly nonimmune population. [4,6].

**SLIDE 13:** Direct inhalation of aerosolized variola virus can also cause smallpox, and is thought to be the most likely route of exposure in the event of a large-scale bioterrorism attack.

**SLIDE 14:** Variola virus is in the *Orthopoxviridae* family of DNA viruses.

**SLIDE 15:** There are 2 variants 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* caused a milder disease and a lower mortality, usually less than 1%, and was the predominant form seen in the United States and Europe in the 20<sup>th</sup> century [7,8]. *Vaccinia* is another Orthopox virus that is used as 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 [2].

**SLIDE 16:** 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 systemic cytokine-mediated inflammatory response is triggered by the viremia and can lead to sepsis, multiorgan failure and death [4,9].

**SLIDE 17:** There are three stages of disease starting with an asymptomatic incubation stage that typically lasts for 10-12 days after exposure to smallpox, with a range of 7-17 days.

**SLIDE 18:** This is followed by a prodromal phase that begins very suddenly with a nonspecific, flu-like illness almost always accompanied by high fevers, headache, back pain and prostration.

**SLIDE 19:** The prodrome lasts for 2-5 days and ends with the eruption of the characteristic rash.

**SLIDE 20:** Patients become infectious approximately one day prior to the appearance of the rash, corresponding to the development of oral mucosal lesions.

**SLIDE 21:** 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 [4,3].

**SLIDE 22-23:** These photographs demonstrate the classic distribution of the rash.

**SLIDES 24-26:** 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 [4].

**SLIDE 27-28:** These photographs show the characteristic grouping where all lesions within a localized area are in the same stage of development.

**SLIDE 29-31:** The progression of smallpox lesions can be observed on these photographs. The lesions start as 2-3 mm macules that progress to papules within 2 days.

**SLIDE 32-33:** These then progress to slightly larger vesicles and then pustules over the next 2-5 days.

**SLIDE 34-35:** The pustules persist for 5-8 days then slowly dry and form scabs that separate leaving permanent pockmarks in the majority of cases. Separation of all scabs marks the end of infectiousness. [4,3]

**SLIDE 36:** The vesicles are characteristically deep and tense, often with an umbilicated appearance.

**SLIDE 37:** This classical rash was seen in approximately 90% of all smallpox cases. The severity of the rash correlates with the mortality, where the most severe rashes have the lowest survival rates. A grading system was devised by the WHO, which classified the rash into 3 categories.

**SLIDE 38:** These photos demonstrate these three categories. The discrete version is characterized by fewer lesions with no confluence and was associated with a case fatality rate of <10%.

**SLIDE 39:** Semi-confluent rashes were more severe with 25-50% mortality,

**SLIDE 40:** while the confluent category was the most severe and fatal 50-75% of the time.

**SLIDE 41:** Infrequent complications of smallpox included infection of the eye and subsequent blindness, arthritis, encephalitis and secondary bacterial infections.

**SLIDE 42:** The differential diagnosis for smallpox includes many febrile rash illnesses, although the one disease that is most likely to be misidentified as smallpox is chickenpox.

**SLIDE 43:** Monkeypox is clinically very similar to mild smallpox but is currently limited to areas in Africa.

**SLIDE 44:** Severe drug hypersensitivity reactions are preceded by a new drug exposure and may exhibit eosinophilia.

**SLIDES 45-46:** Generalized vaccinia may occur after administration of the smallpox vaccine.

**SLIDE 47:** Multiple insect bites may have a similar appearance but are rarely accompanied by systemic illness or fever.

**SLIDE 48:** Molluscum contagiosum are benign lesions frequently seen in persons with AIDS that are caused by another related poxvirus that does not progress and is not associated with systemic illness or fever.

**SLIDE 49:** Secondary syphilis has a predilection for the palms and soles but is unlikely to form vesicles or pustules.

**SLIDE 50:** Many other acute viral infections cause an exanthem that may be confused with early smallpox.

**SLIDE 51:** Caused by the varicella zoster virus, chickenpox can be differentiated from smallpox by the distribution, grouping and appearance of the rash as well as other features. The fever associated with chickenpox onsets simultaneously with the rash with little or no prodrome.

**SLIDES 52-54:** The lesions involve the trunk more than the extremities in a centripetal distribution,

**SLIDE 55:** sparing the palms and soles.

**SLIDES 56-58:** Crops of chickenpox lesions are in different stages of development on the same location of the body, and progress quickly from vesicles to scabs within one day. The entire duration of active eruption in chickenpox is usually only 4-6 days. [10,3].

**SLIDE 59:** Non-classical presentations of the smallpox rash are more difficult to diagnose and differ in mortality. The milder, modified type of rash was seen infrequently in non-immune persons but accounted for 25% of presentations in previously vaccinated individuals.

**SLIDE 60:** This variant produces smaller, more superficial lesions and is rarely fatal, making it more difficult to distinguish from chickenpox. This may be the predominant presentation of smallpox in an outbreak setting if mass vaccination is performed prior to any bioterrorist event.

**SLIDE 61:** Other, more ominous variations of the classical rash were also recognized. 5-10% of cases were of the flat, or malignant, type characterized by more severe systemic illness and

**SLIDE 62:** flat, leathery skin lesions that coalesce and fail to form discrete pustules. Mortality was 97% for this variant that may represent fulminant disease in immunocompromised hosts.

**SLIDE 63:** Hemorrhagic smallpox was seen in less than 5% of all cases. Systemic illness progresses more rapidly than the skin lesions,

**SLIDE 64:** which are often hemorrhagic in nature. This variant was usually seen in pregnant women and was uniformly fatal and difficult to diagnose,

**SLIDES 65-66:** mimicking meningococemia and disseminated intravascular coagulation, or DIC.

**SLIDE 67:** 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. However, as most practicing clinicians today have never seen a case of smallpox, the real challenge in diagnosis is in recognizing the first few cases. All clinicians should have a high index of suspicion and should consider smallpox in the differential diagnosis of any patient presenting with the classical rash, or with a suspicious rash and a severe febrile illness without other explanation.

**SLIDE 68:** Confirmation of the diagnosis can be made by testing of clinical specimens including vesicular or pustular fluid, lesion swabs or biopsy. Visualization of brick-shaped viruses by electron microscopy can rapidly confirm the presence of an *Orthopoxvirus* and rule out chickenpox, but it does not prove variola is the species. This

traditionally requires culture on chick membrane or cell culture, which is specific but slow. Newer rapid and specific diagnostic tests including polymerase chain reaction, or PCR, and immunohistochemical stains, are available at reference labs [4]. Serologic testing is also being developed. [3]

**SLIDE 69:** The first step in the management of suspected cases is isolation to prevent secondary transmission. There are no specific antiviral treatments once symptoms are present. Supportive care is necessary for those with confirmed infection and severe disease, and includes careful attention to electrolyte and volume status, as well as ventilatory and hemodynamic support. Antibiotics are only required in the uncommon setting of secondary bacterial infections, such as *Staphylococcus aureus* cellulitis. Vaccination does not provide benefit to those truly infected who are already symptomatic, but should be considered in the treatment regimen in case the diagnosis of smallpox is wrong in a patient who was at risk of exposure [4].

**SLIDE 70:** Post exposure prophylaxis should be provided to those who have had suspected exposure in the previous week but have not yet developed symptoms. This would include persons exposed to an original aerosol release or those who are contacts of suspected cases. Contacts are defined as living in the same household or having direct face-to-face interaction with a suspected case after the onset of the fever [4]. Vaccination provides substantial protection if given within 3-4 days of exposure, reducing the incidence of disease by 2-3-fold and mortality by at least 50% [11]. 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 in humans if given within two days of exposure [4,12]. Cidofovir is a nephrotoxic drug that requires close monitoring.

**SLIDE 71:** Prior infection grants lifelong immunity. For those not previously infected, the smallpox vaccine used in the United States, called Dryvax, consisting of live attenuated *Vaccinia* virus, is highly protective. The stock is controlled by the CDC and is still viable despite being more than 20 years old [13]. It can be diluted up to 10 fold while maintaining greater than 95% efficacy, signified by the appearance of a primary reaction called a Jennerian pustule that confirms successful vaccination. [14] Newer, tissue culture-derived vaccines are being developed.

**SLIDE 72:** In an outbreak setting, vaccination can reduce the secondary attack rate by ten-fold [15]. It has the highest long-term efficacy in those who have been vaccinated multiple times. Duration of efficacy of a single immunization is unknown but it is likely to provide substantial protection for at least 3-5 years and possibly up to 10 years, and to have a modest decrease in mortality for up to 20 years. Revaccination can grant 30+ years of immunity that may persist life long [4,16,17].

**SLIDE 73:** The vaccine does have serious complications with up to 3 in 100,000 vaccinees reporting significant adverse reactions. Approximately 1 in 1,000,000 vaccinations results in death. Likelihood of adverse reactions are 3-4-fold higher in infants and in primary vaccinees who are receiving vaccine for the first time [18].

**SLIDE 74:** There are no absolute contraindications for vaccination in the outbreak setting, however relative contraindications that mandate close observation include age less than one year old, pregnancy, immunocompromised states and history of eczema or other chronic skin disorders. Persons with these relative contraindications, or those who live with such persons should not be routinely vaccinated in a non-outbreak setting.

**SLIDE 75:** 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.

**SLIDE 76:** Progressive vaccinia (previously called vaccinia gangrenosum or vaccinia necrosum) is another highly feared serious adverse effect with mortality nearing 100% in those who are untreated. Eczema vaccinatum, which occurs in vaccinees or their contacts who have a history of eczema or other chronic skin disorders, 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.

**SLIDE 77:** Less severe, but more common, complications include generalized vaccinia and accidental inoculation that may involve the eye. All severe complications except encephalitis can be treated successfully with vaccinia immune globulin, or VIG, which is obtained from the serum of recently immunized individuals [9,18].

**SLIDE 78:** A further discussion regarding the adverse effects of smallpox vaccination is available later on the disc.

**SLIDE 79:** There are several critical infection control issues that need 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 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 [4,19]. Further details can be found in the specific infection control section on this disc.

**SLIDE 80:** Contacts of suspected smallpox cases must be correctly identified based on the fact that the period of infectiousness begins with the eruption of oral lesions, generally one day before the rash is evident, and lasts until all lesions have scabbed over. Because the rash is preceded by a fever, a temperature greater than 38.3°C or 101°F 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. All contacts should be immediately vaccinated and observed 17 days for the development of fever. Isolation is not necessary before a fever is detected. Also, because of the high risk of nosocomial spread, all patients and staff in a hospital

containing a suspected case of smallpox should be vaccinated. Quarantining of patients or contacts may be necessary from a public health standpoint [4,19].