

SMALLPOX

Introduction

Smallpox is a highly contagious, virulent, and often fatal disease caused by variola virus, a large orthopoxvirus of the family Poxviridae, subfamily Chordopoxvirinae. Four species of the genus Orthopoxvirus cause infection in humans: vaccinia virus, cowpox virus, monkeypox virus, and variola virus. Vaccinia virus is a laboratory virus and used to vaccinate humans against smallpox. Cowpox virus is a virus of rodents that is transmitted to humans by cows or cats. Monkeypox is clinically indistinguishable from smallpox but has a lower mortality rate. The two classic varieties of Smallpox are variola major and variola minor. Variola major was endemic in India for at least 2000 years and spread to China, Japan, Africa, and the Americas. Beginning in the 20th century, the less virulent form of smallpox, variola minor, spread from South Africa to Florida and the Americas, and then to Europe. A world-wide eradication program began in 1956. The case fatality rate of smallpox in unvaccinated patients was 30% or more for variola major and 1% or less for variola minor; significant morbidity was much higher. Routine vaccinations against smallpox were discontinued in the United States in 1972.

History of Infection

It is difficult to imagine that smallpox was one of the most feared diseases in ancient and modern history. After an extensive and successful eradication program, the World Health Assembly certified the global eradication of smallpox infection in 1980. There has not been a single reported case of smallpox infection in over twenty years. However, smallpox was once a deadly disease with the power to decimate whole populations. Successful efforts to prevent the spread of smallpox through vaccination changed the course of the history of Western medicine. The history of smallpox is indeed a fascinating testament to the effect of health and disease on the development of modern civilization.

Ancient Evidence of Smallpox Infection

Literature dating from approximately 3700 BC in Egypt and 1100 BC in China suggests that the original sources of the disease were in Asia and Africa. There is evidence that a major smallpox epidemic occurred toward the end of the 18th Egyptian dynasty. Studies of the mummy of Pharaoh Ramses V (d. 1157 BC) indicate that he likely died of smallpox infection. From ancient Egypt, it appears that traders spread the disease to India. Since there is no animal reservoir for smallpox, it is not surprising that patterns of disease transmission often paralleled human travel and migration patterns.

From these regions, the disease spread to Europe during the Middle Ages. Smallpox was brought to the Americas with the arrival of Spanish colonists in the fifteenth and sixteenth centuries. Many historians argue that smallpox infection killed more Aztec and Inca people than the Spanish *conquistadors* did.

Naming the Disease

In the 6th century AD, a Swiss bishop named the etiologic agent of smallpox "variola", from the Latin *varius*, meaning "pimple" or "spot". Beginning in the 10th century, the Anglo-Saxons used the term *poc* or *pocca*, referring to the scars left behind that resembled "pouches". When syphilis became epidemic in the 15th century, the term smallpox was adopted, to distinguish it from the former "Great Pox".

The First Vaccine Efforts

The idea of intentionally inoculating healthy persons to protect against infection actually dates back to the 6th century AD, in China. For the Chinese physicians, inoculation involved mixing dried, powdered scabs from a smallpox victim with musk and applying the mixture to a cloth that was inserted in the nose. In India, healthy persons 'protected' themselves by sleeping next to a smallpox victim or wearing the shirt of an infected person.

The first successful use of the intentional inoculation method in the Western world took place in 1717 on the six-year-old son of an English ambassador to Constantinople. This process, called variolation, also involved intentional infection of a healthy person with the virus. One version of variolation entailed going to a bathhouse and slapping the skin with branches that were previously used on the skin of a smallpox victim. Care was taken to select a virus donor who manifested a mild form of the disease. The technique won considerable acceptance, and special "pox houses" were opened in numerous countries, including Greece, England, and Russia. However, in some instances, variolation resulted in contraction of full-blown smallpox and even death; one source cites a mortality rate of 1 per 459 persons variolated.

In 1796, Edward Jenner observed that milkmaids who had contracted cowpox, an orthopox virus similar to variola, had a lower incidence of smallpox infection. Using the theory that infectious material from an individual with a milder disease could protect against a more severe disease, Jenner developed the first vaccine, using bovine serum containing the cowpox virus. The word vaccination was actually coined from *vacca*, the Latin word for cow. Jenner successfully tested his vaccine in 1796 and repeated his test successfully on another patient two years later. Vaccination has been used to represent immunization of other diseases in honor of Edward Jenner.

Vaccination using Jenner's method proved instrumental in decreasing the number of smallpox deaths. For example, for the period 1899-1908, in countries with mandatory vaccination, the smallpox mortality rate ranged 0.27 per million in Sweden to 91.08 per million in France, while in countries without mandatory vaccinations, the rate was considerably higher: 310.71, 394.08, and 567.28 per million in Greece, Spain, and Russia, respectively. As more and more countries adopted mandatory vaccination, the number of countries with endemic smallpox decreased to 58 by 1957. However, even in countries without endemic smallpox, outbreaks initiated by the arrival of an infected person from abroad were not uncommon.

The Global Eradication of Smallpox

In 1956, the World Health Organization (WHO) began a program to eradicate smallpox by vaccination. The nature of smallpox infection made this a difficult undertaking for the following reasons:

Duration of immunity: Smallpox vaccination does not grant lifelong immunity to smallpox, nor does contracting the disease itself. In fact, immunity lasts on average from 5-7 years.

As a result, vaccination campaigns had to incorporate significant revaccination efforts. Revaccination results in a boost, which may extend neutralizing antibody levels for up to 30 years.

Subclinical cases: In addition, those who have been vaccinated against smallpox, especially those whose immunity to smallpox is present but diminishing, often still contract the disease but in a milder, less recognizable form-frequently absent are such key symptoms as fever and rash. Thus, transmission of the disease by undiagnosed vaccinated persons was probably a frequent occurrence.

For these reasons, the World Health Organization's first attempt to eradicate smallpox was not successful. In the late 1960s, the WHO modified its strategy to involve two critical components: (1) a mass vaccination campaign in each country involved, and (2) a system that contained outbreaks by vaccinating the close contacts of index smallpox cases (ring vaccination).

This new approach, called the Global Intensified Eradication Program, proved to be more effective. The drop in the number of cases was particularly dramatic in India, the country with the highest smallpox morbidity, which experienced 27,407 cases in 1972; 87,240 cases in 1973; 188,003 cases in 1974; but only 1,436 cases in 1975. In 1976, the only cases of smallpox were isolated cases in Ethiopia. The last recorded naturally occurring case of smallpox occurred in Somalia in 1977, and on May 8, 1980, the WHO declared the global eradication of smallpox.

History of Development as Weapon

The concept of using variola virus in warfare is an old one. During the French and Indian Wars (1754-1767), British colonial commanders distributed blankets that were used by smallpox victims in order to initiate an epidemic among Native Americans. The mortality rate associated with these outbreaks was as high as 50% in certain tribes. Scholars have also debated the possibility that smallpox was used as a weapon during the Civil War. In the years leading up to and during World War II, the Japanese military explored smallpox weaponization during the operations of Unit 731 in Mongolia and China.

Remaining Stocks of Smallpox Virus

In general, the worldwide practice of smallpox immunization greatly diminished the fear of an epidemic caused by a deliberate release of the virus. Although the disease was declared eradicated in 1980, stores of smallpox virus officially exist at two WHO-approved repositories. The first is at the Centers for Disease Control and Prevention in Atlanta, USA. The second is the State Research Center for Virology and Biotechnology (also known as "Vector") at Koltsovo, in the Novosibirsk region of Siberian Russia. In June of 1995, WHO inspected the Koltsovo facility and determined that it was an acceptable storage facility after the virus stocks were moved there from the original storage site at the Institute of Viral Preparations in Moscow. All other laboratories in the world were required to destroy their remaining stores of smallpox virus.

Despite the provisions of the World Health Organization and the 1972 Biological Weapons Convention, the former Soviet Union maintained a sophisticated and large-scale research and development program for biological weapons implementation. It is now known that the Soviet Union successfully developed and adapted smallpox virus for use in strategic weapons. The industrial capacity of this effort is astounding when one considers that the Soviet Union was able to produce and store hundreds of tons of weaponized smallpox virus. In addition, defectors from Soviet programs have stated that research was performed to

produce recombinant strains that are more virulent, contagious and capable of evading vaccination.

Remaining Stocks of Smallpox: a Current Debate

A 1980 WHO resolution also indicated that smallpox vaccination should no longer be required except for "investigators at special risk", and that the WHO would maintain seed lots of vaccinia virus as well as stocks of 200 million doses of prepared vaccine in case of outbreak. In 1981 smallpox was removed from the WHO's list of diseases covered under the International Health Regulations, which detail notification requirements and measures that should be taken to contain an outbreak, although smallpox is still under international surveillance.

Considerable debate has ensued regarding the two officially remaining stores of variola virus. Since 1986, the WHO *Ad hoc* Committee on Orthopoxvirus Infections has consistently recommended destruction of remaining reserves of the smallpox virus. The initial proposal was to destroy the remaining stocks in December 1990. However, the fact that smallpox had been developed into a biological weapon and a new concern exists about possible access to the virus by terrorist organizations, the scientific community continues research on the pathogen. To date, a consensus on destruction of all remaining smallpox stores has not been reached among scientists and those responsible for military and public health policy.

Evaluation of the Current Threat of Smallpox Biological Weapons

Since many of the laboratories involved in biological weapons research and development in the former Soviet Union were working with decreased funding in the early 90s, particularly in the areas of staff and support, there evolved concern that bioweapons resources and expertise may spread to other countries. A report from the Washington Center for Strategic and International Studies states that at least ten countries are involved in biological weapon research programs.

The ability of a group to acquire variola and develop it as a biological weapon is limited by the following factors:

- Specialized skills are required to grow smallpox in effectively large quantities and to adapt it for use as an aerosol-based weapon. It is unlikely that small, technically-limited fanatical or dissident groups would use smallpox as a weapon.
- The open use of a biological weapon by any nation or political state would undoubtedly illicit severe retaliation.
- Smallpox virus is not as readily available as other agents of biological terrorism such as anthrax (*Bacillus anthracis*) or plague (*Yersinia pestis*).

Evaluation of these and other factors have led bioweapons experts to conclude that well-financed and highly organized subnational groups and politically/state sponsored terrorist groups would be the most likely to use smallpox as a biological weapon.

The following characteristics make smallpox virus an excellent candidate for use as a biological weapon:

- An aerosol suspension of smallpox virus is quite stable and has a very low infectious dosage. In general, the dissemination of a pathogen by aerosol droplet is the preferred deployment method for biological weapons.

- There are no large-scale civilian smallpox vaccination requirements at this time. Thus, there is a large susceptible population at risk for smallpox infection. (Note that both military and civilian planners are evaluating the merits of expanding vaccination to much larger populations).
- Smallpox is a highly contagious disease, spread through droplet inhalation or ingestion.
- The incubation period in naturally occurring cases (droplet infection) averages 7-14 days. However, this period could be shortened to 3-7 days especially in the cases of aerosol application (in biological weapons).
- People may be contagious during the late stages of the incubation period, even though they are minimally symptomatic.
- Depending on the climate, corpses of smallpox victims remain infectious for days to months. Bodies should be cremated, if possible.
- The duration of disease is long. Coupled with the complex isolation and protection requirements of smallpox treatment, each infected person will require the efforts of several medical and support personnel.

Epidemiology

Naturally Occurring Infection

Humans are the only natural reservoirs of variola virus. Person-to-person transmission of smallpox occurs by aerosol droplets expelled from the oropharynx of infected persons, or by direct contact with an infected person. The virus can also be spread through contaminated bedding and clothing.

Despite the fact that smallpox is less contagious than influenza or measles, it is still considered a highly contagious disease. The infectious dose 50, the amount of agent inhaled in aerosol form that is required to cause manifest illness in 50% of susceptible humans, is less than 100 viral particles. The patient can be already infectious in the last day of incubation period, and remains contagious until the scabs separate. The virus can remain viable for months on objects from the victim's surroundings. Though smallpox is spread most readily during dry, cool winter months, the disease can be transmitted in any climate and in all parts of the world.

Physical protection, early vaccination, and isolation of infected patients are the only effective protection against the disease. Patients vaccinated within 2 or 3 days of exposure, will most likely not develop the disease. Vaccination 4 or 5 days after exposure may significantly reduce mortality, but will less effectively reduce morbidity.

Classification and Etiology

Smallpox virus particles, or virions, have a characteristic brick-shape and appear as smooth, rounded rectangles by electron microscopy, measuring approximately 302-350 nm by 244-270 nm. The smallpox genome is 186 kbp and consists of a single linear double-stranded DNA molecule with a hairpin loop at each end. Smallpox virion replication occurs in the cytoplasm. Smallpox virion replication uses viral-associated DNA-dependent RNA polymerase. Viral envelopes are made of modified Golgi membranes containing viral-specific polypeptides. Both enveloped and nonenveloped virions are infectious. The molecular pathogenesis of poxviruses is largely based on the studies of monkeypox virus and mousepox virus.

Organ and System Pathogenesis

Smallpox virus enters the body through the respiratory tract, though it can also enter through the conjunctivae. The virus then probably attaches to the epithelial cells of the oropharyngeal and pulmonary mucosa. These cells, within the upper respiratory tract, are the site of virus accumulation and active replication. Early in infection, the patient is highly contagious via aerosol droplet transmission, because of the high concentration of viral particles replicating in the upper respiratory tract. Transmission to others is generally through coughing of virus particles suspended in oropharyngeal secretions. Though highly contagious, the patient may not yet have pox lesions during these early stages.

Primary Viremia

From the upper respiratory tract, the virus is thought to migrate to regional lymph nodes, where continued replication takes place. This is associated with primary, asymptomatic viremia three to four days after infection.

Secondary Viremia

The virus migrates to sites of immune cell generation—the liver, spleen and bone marrow—where it replicates inside mature leukocytes. About 24 hours after infection of the liver and spleen, a high concentration of virus is released into the bloodstream. This produces a secondary viremia that is associated with toxemia and fever.

Infected macrophages localize in small dermal vessels, resulting in characteristic maculopapular lesions. These primary dermal lesions progress to vesicular, pustular lesions that form preferentially on the face and distal extremities. The reason for the preferential lesion formation is unknown.

Likely sites for viral replication are the lymphoid organs (spleen, bone marrow, and lymph nodes), but extensive necrosis does not occur in those sites. It is our understanding that the virus in the blood is largely associated with monocytes macrophages and other immunocompetent cells. It is not currently understood why the migration of the virus from the upper respiratory tract to the lymphatic and dermal vessels does not involve any major organ systems other than the lymphoid organs.

The development of fatal systemic smallpox infection is associated with disseminated intravascular coagulation, hypotension, and cardiovascular collapse. In hemorrhagic smallpox, these events are exacerbated by failure of the blood to clot.

Cellular and Molecular Pathogenesis

Poxviruses replicate in the cytoplasm of infected cells. The viral genome encodes several enzymes that are required for biosynthetic processes and for the regulation of a precursor pool of macromolecules. These viruses have a very complex morphogenesis involving the *de novo* synthesis of virus-specific membranes and inclusion bodies. Poxvirus genomes also encode several proteins that interact with host processes at both the cellular and organ/system level.

Poxviruses have evolved numerous strategies to evade host immune and inflammatory response. They have accomplished this by acquiring and modifying host immune/inflammatory response modulating genes. Many of these virulence genes encode homologues of host cytokines and chemokines and their receptors. These include soluble interferon, IL-1b, and TNF-a receptor homologues that block the host cytokines. Other virulence gene products interfere with interferon signaling within cells and prevent the formation of biologically active IL-1b by cleavage of its precursor protein. Clearly, there is much research, which needs to be performed on the cellular pathogenesis of smallpox and host cell-mediated immunity to smallpox infection.

Pathologic Anatomy

In addition to the obvious cutaneous lesions, the mucous membranes of the respiratory and digestive tracts are affected, although the lesions are less obvious. Lesions are most common on the pharynx, tongue, and upper part of the trachea and esophagus, consisting of hemorrhages and pseudomembranes. Endothelial cells lining the sinusoids of the liver are often swollen and sometimes necrotic. Reticuloendothelial hyperplasia is seen in bone marrow and spleen. The kidneys may be hemorrhagic and liver heavier than normal. Encephalitis occurs rarely.

Clinical Manifestations and Diagnosis

Three types of smallpox have been described:

1. Typical Variola Major: The prototypical disease described here occurred in ca. 95% of infections. Mortality was ca. 3% in vaccinated and 30% in unvaccinated individuals.
2. Flat-Type: Seen in 2-7% of subjects, almost always in unvaccinated individuals. The majority of cases occurred in children. This variant was characterized by severe systemic toxicity and the evolution of flat, focal skin lesions. Characterized by very high mortality.
3. Hemorrhagic-type: Seen in fewer than 3% of patients, typically in adults. Occurred equally in vaccinated and unvaccinated individuals, it was characterized by intense toxemia and mucosal hemorrhage. Characterized by very high mortality.

Duration

Subjective and objective clinical symptoms characteristic of the following four periods in the progression of smallpox infection are discussed:

- 1) Incubation period: virus actively replicating and spreading to lymph nodes and target tissues; patient is generally asymptomatic. The onset of high fever marks the end of the incubation period.
- 2) Prodromal period: marked by the beginning of subjective, nonspecific clinical symptoms. Patients are most infectious during the first week of this period. Once the fever subsides, the rash usually appears.
- 3) Manifestation period: development of smallpox lesions and characteristic objective symptoms.
- 4) Outcome period: associated either with recovery or severe toxemia and death.

Types of smallpox, their details are given below:

1) Typical (variola major)

- Incubation Period : 7-14 days for natural infection
1-5 for infection due to deliberate release of aerosolized virus*
- Prodromal Period : 2-3 days
- Manifestation Period : 8-9 days
- Period of Outcome : 2nd week of illness

2) Hemorrhagic

- Incubation Period : 7-14 days
- Prodromal Period : 1-2 days
- Manifestation Period : 5-6 days
- Period of Outcome - N/A

3) Flat

- Incubation Period : 7-14 days
- Prodromal Period : 1-2 days
- Manifestation Period : 2-3 days
- Period of Outcome - N/A

Subjective Symptoms

The symptoms, their description and period are given below:

1) Fever : Sudden onset, 38.5° C and 40.5° C. High fever has been associated with delirium in some smallpox cases. Subsides after 2-3 days, at whichpoint the characteristic smallpox rash usually appears. Occurs during prodromal period (rash marks the end of prodromal and start of manifestation).

2) Pain: Headache - may be severe - during early prodromal

3) Pain: Other: - severe backaches, occasional abdominal pain - during prodromal period

4) Fatigue/Malaise - common - during prodromal period

5) **Nausea** - occasional - during prodromal period

Objective Symptoms

Although the pathogenesis of smallpox involves (lymph nodes, etc.), objective clinical manifestations of the disease are usually limited to the characteristic lesions of the skin and mucous membranes.

The organ/system symptoms, their description and period are given below:

1) **Skin Rash**

- Erythematous ("rose") rash associated with early viremia during late prodromal period
- Centripetally distributed purpuric or petechial eruption developing on an erythematous background near the groin or other flexures, also associated with early viremia. Extensive petechial rash is associated with hemorrhagic smallpox - late prodromal, early manifestation.
- Maculopapular rash develops on the mucosa of the mouth, pharynx, face, and forearms. The rash then spreads to the trunk and legs - during manifestation
- Within 1-2 days after appearance, the maculopapular rash becomes vesicular, then pustular. Pustules are characteristically round and deeply embedded in the dermis - during manifestation
- After 8-9 days, crusts begin to form on pustules. As the patient recovers, the scabs separate and characteristic pitted scarring gradually develops. The scars are most evident on the face and result from the destruction of sebaceous glands, shrinking of granulated tissue, and fibrosis.

2) **Mucous Membranes** : Mucosal hemorrhage occurs as a result of extensive, confluent maculopapular rash in hemorrhagic smallpox infection - during manifestation

3) **Systemic reactions** : Toxemia associated with circulating immune complexes and soluble variola antigens is the usual cause of death in smallpox patients. This toxemia appears especially severe in cases of hemorrhagic and flat (malignant) smallpox - during outcome period. Secondary bacterial infections are rare.

To view an illustration of the usual clinical course of smallpox, [click here](#).

Differential Diagnosis

Smallpox is most frequently misdiagnosed as *varicella*, or chickenpox, which is caused by a herpes virus. The most effective criteria for distinguishing the two infections is an examination of the following characteristics of the lesions:

- **Time and pattern of appearance**: The most obvious distinction between the two infections involves the time period over which the skin lesions appear. In chickenpox infection, the lesions occur in successive "crops". It is possible, when examining a

patient, to observe several different stages of lesion maturation and development at the same time. In smallpox infection the lesions appear more or less simultaneously.

- **Density and location:** Chickenpox lesions tend to be denser over the trunk (centrifugal distribution), while smallpox lesions are denser on the face and extremities (centripetal distribution). Chickenpox lesions are almost never seen on the palms or soles of the feet. Smallpox lesions, especially in severe cases, can often be found in these areas.
- **Physiology:** Chickenpox lesions tend to be superficial, while smallpox lesions are much deeper, affecting the sebaceous glands and leaving pitted, fibromatous scars.

Monkeypox is another infection to be considered in the differential diagnosis of smallpox infection. Patients with monkeypox develop fever, respiratory symptoms, and synchronized lesions like patients with smallpox. However, patients with monkeypox seem more prone to develop inguinal and cervical lymphadenopathy and appear to have a lower mortality rate (3%-10%). Pneumonia secondary to monkeypox has a 50% mortality rate.

The CDC has prepared a poster to assist in the differential diagnosis of smallpox. To view the poster, click here: [Part1](#) | [Part2](#)

Diagnostic samples and related biosafety issues

The most important step in confirming a case of smallpox is laboratory diagnosis. Someone who has recently been vaccinated and who wears gloves and a mask must collect the specimens. To obtain vesicular or pustular fluid, it is often necessary to open lesions with the blunt edge of a scalpel. The fluid can then be harvested on a cotton swab. Scabs can be picked off with forceps. Specimens should be deposited in a primary sterile vacutainer tube sealed with tape, packed with absorbent padding in a secondary "screw-top" container and then in a United Nations approved shipping carton, in accordance with 49CFR172. See www.iata.org and www.dot.org for additional information on shipment of diagnostic specimens and etiologic agents.

As always, state or local health department laboratories should immediately be contacted regarding the shipping of specimens. Laboratory examination and diagnosis requires high-containment (Biosafety Level-4) facilities and should be undertaken only in designated laboratories where appropriately trained personnel and equipment are available.

Smallpox infection can be rapidly confirmed in the laboratory by electron microscopic examination of vesicular or pustular liquid or scabs. Definitive laboratory identification and characterization of the virus involves growth of the virus in the cell culture or on chorioallantoic egg membrane and characterization of strains by use of biologic assays, including the polymerase chain reaction (PCR), restriction fragment-length polymorphism analysis (RFLP) and ELISA. Confirmation using these methods can be accomplished in a few hours.

Mortality and Survivability

Note that for typical smallpox, there is a low mortality rate in vaccinated persons.

Ordinary (typical) smallpox
Unvaccinated – 30%
Vaccinated – 3%

Hemorrhagic smallpox

Unvaccinated – 99%
Vaccinated – 94%

Flat (malignant) smallpox
Unvaccinated – 95%
Vaccinated – 66%

Protection/Isolation/Notification Measures

The discovery of a single suspected case of smallpox must be treated as an international health emergency and be brought immediately to the attention of national officials through local and state health authorities.

As soon as the diagnosis of smallpox is made, all individuals in whom smallpox is suspected should be isolated immediately and all household and other face-to-face contacts should be vaccinated and placed under surveillance. Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other non-hospital facilities whenever possible. Home care for most patients is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy. Strict quarantine with respiratory isolation should be applied for 17 days to all personnel in direct contact with the index case or cases, especially the unvaccinated.

The rationale for vaccinating all individuals suspected to have smallpox in case of an aerosol release and a subsequent outbreak is to ensure that misdiagnosed patients are not placed at risk of acquiring smallpox. Vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness. An emergency vaccination program is also indicated that would include all health care workers at clinics or hospitals that might receive patients; all other essential disaster response personnel, such as police, firefighters, transit workers, public health staff, and emergency management staff; and mortuary staff who might have to handle bodies. It is recommended that all such personnel for whom vaccination is not contraindicated should be vaccinated immediately irrespective of prior vaccination status. In late 2002, the U.S. government implemented plans to vaccinate military personnel and relevant civilian healthcare workers.

Public health implications

Strict quarantine with respiratory isolation should be applied for 17 days to all personnel in direct contact with the index case or cases, especially the unvaccinated.

Public health notification requirements

According to the Centers for Disease Control and Prevention's Bioterrorism Preparedness protocols, a local health official who suspects that cases of illness are due to a biological terrorist incident must first inform their State Health Department. The Health Department will notify the Centers for Disease Control and conduct a formal investigation. As soon as laboratory diagnosis confirms the presence of a particular threat agent, the Federal Bureau of Investigation (FBI) must be contacted. Discovery of a case of smallpox would be considered a threat to international public health.

Along with the State Health Department, local public health leaders should have predetermined emergency response partners that should also be contacted.

Vaccination

Smallpox vaccine (vaccinia) is a live virus vaccine, currently approved by the U.S. Food and Drug Administration for use in persons in special-risk categories, including laboratory workers directly involved with smallpox or closely related orthopoxviruses. WHO has long recommended immediate and widespread vaccination, under epidemic circumstances. In 2002, the U.S. Department of Defense announced a plan to reinstate vaccination of select military populations and the administration announced a plan to vaccinate a minimum of 500,000 emergency responders and healthcare providers.

This vaccine has been safely administered to millions of individuals worldwide in the past. However, there are certain groups for whom elective vaccination has not been recommended because of the risk of complications. Contraindications include 1) immunosuppression, 2) human immunodeficiency virus infection, 3) history or evidence of eczema, 4) current close contact with individuals possessing conditions above or 5) pregnancy. Under epidemic circumstances, the above contraindications would have to be weighed against the risk posed by smallpox. If available, vaccinia immune globulin (VIG) can be given concurrently with vaccination in such persons, but the risk of attenuating the immune response must be considered.

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Ordinary (typical) smallpox

Unvaccinated – 30%
Vaccinated – 3%

Hemorrhagic smallpox

Unvaccinated – 99%
Vaccinated – 94%

Flat (malignant) smallpox

Unvaccinated – 95%
Vaccinated – 66%

Post-exposure prophylaxis and 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. Recent studies in tissue culture and in mice have suggested the possibility that cidofovir, a nucleoside analog DNA polymerase inhibitor, might prove useful in preventing smallpox infection if administered within 3 or 4 days after exposure. Initial studies in a very small number of non-human primates attempting to demonstrate the therapeutic efficacy of cidofovir were unsuccessful; however, the drug was effective as a pretreatment. At this time, there is no evidence that cidofovir is more effective than vaccination in this early period. The drawbacks of cidofovir use are a requirement for intravenous (IV) administration and potentially severe associated renal toxicity.

Supportive therapy with antibiotics is indicated for treatment of secondary bacterial infections associated with smallpox.

Promising research on prophylaxis and therapy

Recent studies on tissue culture, mice, and a small number of monkeys have suggested the possibility that cidofovir, a nucleoside analog DNA polymerase inhibitor, might prove useful in preventing smallpox infection if administered within 1 or 2 days after exposure. At this time, there is no evidence that cidofovir is more effective than vaccination in this early period. The drawbacks of cidofovir use are a requirement for intravenous (IV) administration and severe associated renal toxicity.

Sources of Further Information

- The Centers of Disease Control and Prevention [Bioterrorism Preparedness Homepage Recommendation of the Immunization Practices Advisory Committee](#)
- The Johns Hopkins University Center for Civilian Biodefense Studies (<http://www.hopkins-biodefense.org>)
- Smallpox Fact Sheet (<http://www.hopkins-biodefense.org/pages/agents/agentsmallpox.html>)
- Articles and Official Statements on the Destruction of Remaining Smallpox (<http://www.hopkins-biodefense.org/pages/news/destruction.html>)

<http://www.bt.cdc.gov/agent/smallpox/index.asp>
<http://jama.ama-assn.org/issues/v281n22/ffull/jst90000.html>
<http://www.nlm.nih.gov/medlineplus/smallpox.html>
<http://www.who.int/emc/diseases/smallpox/factsheet.html>
<http://www.who.int/emc/diseases/smallpox/>
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm>
<http://www.acponline.org/journals/annals/15oct97/smallpox.htm>
http://www.nativeweb.org/pages/legal/amherst/lord_jeff.html (smallpox blankets)
<http://www.nyc.gov/html/doh/html/cd/smallmd.html>
<http://www.library.ucla.edu/libraries/biomed/smallpox/>
<http://cryptome.org/smallpox-wmd.htm> (New Yorker article)
<http://www1.umn.edu/cidrap/content/bt/smallpox/>
<http://www1.umn.edu/cidrap/content/bt/smallpox/biofacts/smlpx-summary.html>
http://abcnews.go.com/sections/wnt/DailyNews/Iraq_smallpox021203.html
<http://news.bbc.co.uk/1/hi/health/2534909.stm>
<http://www.cnn.com/2002/HEALTH/conditions/11/26/smallpox.vaccine/>
<http://www.nlm.nih.gov/medlineplus/ency/article/001356.htm>
http://www.sph.unc.edu/about/webcasts/2001-12-13_smallpox/
http://www.afip.org/Departments/infectious/sp/text/1_1.htm (excellent - army site)
<http://www.doh.wa.gov/BioTerr/smallpox.htm> (dept of health)
<http://www.aap.org/terrorism/index.html> (am acad pediatrics)
<http://edcp.org/html/smallpx.html> (Maryland's page)
<http://www.dhmh.state.md.us/html/smallpox.htm>
<http://www.slu.edu/colleges/sph/bioterrorism/quick/smallpox01.pdf>
<http://www.tdh.state.tx.us/bioterrorism/facts/smallpox.html> (good diff diag)
<http://www.nature.com/nsu/011213/011213-15.html>
<http://www.nature.com/nsu/020318/020318-3.html>
<http://www.merck.com/pubs/mmanual/section13/chapter162/162f.htm>
<http://www.lib.uiowa.edu/hardin/md/smallpox.html> (small collection of sites)
<http://www.hist.umn.edu/~rmccaa/vircatas/vir6.htm> (spanish conquest)
<http://www.noah-health.org/english/illness/infect/smallpox.html>
<http://www.hhs.gov/smallpox/>
<http://www.niv.ac.za/features/smallpox1.htm> (south africa's site)

<http://www.medinfo.ufl.edu/year2/mmid/bms5300/bugs/smallpox.html>
http://www.bernco.gov/departments/environmental_health/about_smallpox.pdf
<http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/FieldManuals/medman/SmallPox.htm>
<http://www.hhs.gov/news/press/2001pres/20011128.html>
<http://www.niaid.nih.gov/factsheets/btsmallpox.htm>
<http://www.usuhs.mil/cbw/smallpox.htm>
http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Smallpox
<http://www.stanford.edu/group/virus/pox/2000/smallpox.html>
<http://www.lcs.mgh.harvard.edu/bioterrorism/smallpox.htm>
<http://www.news.harvard.edu/gazette/1999/05.20/waterhouse.html>
http://www3.baylor.edu/~Charles_Kemp/smallpox.htm
<http://www.biotech.law.lsu.edu/blaw/by/smallpox/svlaw.htm>
<http://www.bt.cdc.gov/agents/smallpox/diagnosis/pdf/spox-poster-full.pdf>
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