Smallpox and biological warfare: a disease revisited

Stefan Riedel, MD, PhD

This is the second article in a series of papers addressing issues related to biological warfare and bioterrorism. As outlined in the historical review of biological warfare (1), smallpox is one of the most devastating diseases that could potentially be used as a biological weapon. In fact, smallpox was for many centuries devastating to mankind. However, the remarkable efforts of the World Health Organization led to its eradication in 1977. With the developments in more recent years, the threat of biological and chemical warfare has reemerged. In particular, the events surrounding the attack on the World Trade Center on September 11, 2001, as well as the recent developments in Afghanistan and the Middle East, have shown that the threat of biological weapons is real and present in today's time.

The Centers for Disease Control and Prevention (CDC) in Atlanta has classified various organisms and diseases that could potentially be used as biological weapons. These diseases are grouped in three categories according to their possibility of use and their impact on public health *(Table 1)*. Smallpox is listed in group A, indicating that it is easily disseminated and transmitted from person to person and results in high mortality rates.

Table 1. Bioterrorism agents/diseases as classified by the Centers for Disease Control and Prevention

Category	Organism/disease
A	Smallpox
	Anthrax
	Tularemia
	Plague
	Botulism
	Viral hemorrhagic fevers
B	Brucellosis
	Glanders
	Ricin toxin
	Typhus fever
	Q fever
	Staphylococcal enterotoxin B
	Viral encephalitis (alphavirus: VEE, EEE, WEE)
	Water safety threats (e.g., *Vibrio cholerae, Cryptosporidium parvum*)
C	Emerging infectious diseases such as Nipah virus and Hantavirus

In this article, I outline the epidemiology, microbiology, and clinical features of a disease not known to many people in the 21st century. The recommendations and conclusions are based on extensive research and the summary statement of the Working Group on Civilian Biodefense. Those recommendations presented herein represent the best professional judgment of the working group at the time the data were published. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

BRIEF HISTORY OF SMALLPOX

Smallpox was introduced to Europe sometime between the fifth and seventh centuries and was frequently epidemic during the Middle Ages. Smallpox continued to be a problem throughout the 17th and 18th centuries, affecting populations on a large scale. Variolation was a semi-effective measure to prevent the disease; however, the procedure was not without risk. With Edward Jenner's demonstration in 1796 that inoculation with cowpox provided protection against smallpox, the potential threat of the disease was greatly diminished (2). The procedure of vaccination, as Jenner named it, was rapidly introduced in England, Europe, and North America. In later years, it was also introduced in many of the other European colonies. The history of smallpox and variolation is discussed in more detail in the companion piece to this article (3).

The threat of smallpox being used as a biological weapon in war was greatly diminished when a large part of the European population was vaccinated. However, during the second half of the 19th century, it was realized that vaccination did not confer lifelong immunity and that subsequent revaccination was necessary. The mortality from smallpox had declined, but the regular occurrence of epidemics indicated that the disease was still not under control. In the 1950s many countries implemented various control measures, and smallpox was finally eradicated in many areas in Europe and North America (4).

The process of worldwide eradication of smallpox was set in motion when the World Health Assembly received a report in 1958 of the catastrophic consequences of smallpox in 63 coun-

From the Department of Pathology, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Stefan Riedel, MD, PhD, Department of Pathology, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: docriedel@aol.com).

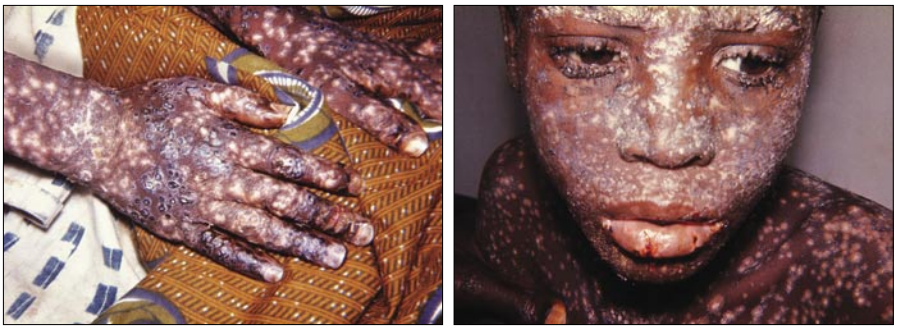

Figure 1. Hand and face of a patient with severe smallpox in Accra, Ghana, 1967. Photo courtesy of the Centers for Disease Control and Prevention Public Health Image Library.

tries, mostly in Asia and Africa *(Figure 1)*. In 1967, a global campaign was begun under the guardianship of the World Health Organization (WHO), which finally succeeded in eradicating smallpox in 1977. On May 8, 1980, the World Health Assembly announced that the world was free of smallpox and recommended that all countries cease vaccination.

A WHO expert committee recommended the worldwide destruction of stocks of variola virus in all laboratories. Two reference laboratories were said to retain stocks of the virus for future research: the Institute of Virus Preparations in Moscow, Russia, and the CDC in Atlanta, Georgia. All countries reported compliance in 1981. The WHO committee later recommended that all virus stocks be destroyed by June 1999, and the 1996 World Health Assembly concurred with this decision (4). In 1998, an expert committee of the Institute of Medicine concluded that continuing and future research on the variola virus was needed and that the virus should be retained at the two approved facilities (5). The WHO expert panel agreed to these recommendations. The virus is still kept at the approved facilities in Moscow and Atlanta.

More recently, allegations brought forth by Ken Alibek, a former deputy director of the Former Soviet Union's bioweapons program, have raised concerns among Western countries that smallpox could be used as a biological weapon. According to Alibek, the Former Soviet Union expanded its bioweapons research program during the 1980s and was eventually able to weaponize smallpox. This research was conducted at remote facilities in Siberia. However, very little information is available about the extent and outcome of this research and where it was conducted (6). Since the financial support for Russian laboratories has substantially declined in recent years, there are increasing concerns that the existing expertise and equipment might fall into non-Russian hands. With the recently increasing terrorist activities worldwide, the concerns raised in the late 1990s become more real.

EPIDEMIOLOGY OF SMALLPOX

Before the successful eradication of smallpox, the disease was pandemic throughout the world. Smallpox existed in two principal forms: variola major and variola minor, the latter representing a much milder form of the disease. Until the end of the 19th century, variola major was the predominant form of the disease. Variola minor occurred first during the early 1900s in South Africa and in Florida. From there, it spread across the USA and further into South America and Europe (7). The case-fatality rates for typical variola major outbreaks were 20% or higher. Variola minor was rarely associated with case fatality rates of more than 1%, and rates were often lower.

Smallpox was typically transmitted from person to person via droplet nuclei or aerosols expelled from the oropharynx of infected persons. Transmission through direct person-to-person contact has also been described. In addition, contaminated clothing or bed linens have been implicated in the spread of the disease. However, there is no known animal or insect reservoir for smallpox (4, 7, 8). Historically, outbreaks of smallpox occurred in a fairly slow fashion, and the disease spread primarily among immediate contacts of the infected person, e.g., household members and health care workers. Large school outbreaks, for example, were not reported in the USA or Europe. This can be explained by the fact that smallpox virus is not transmitted until the appearance of the rash. By that time, many patients were already confined to bed rest. The patient was most infectious from the time of onset of the rash through the first week of the rash (7–10 days). As the scabs formed, infectivity rapidly decreased. Although scabs contained large amounts of viable virions, epidemiological and laboratory studies indicated that the infectivity of such material was low. It was assumed that virions were bound tightly to the fibrin matrix and could not be released in effective numbers (9).

Smallpox outbreaks had a typical seasonal appearance, with their highest incidence occurring during the winter and early spring. This observation was consistent with the fact that orthopoxviruses in aerosolized form are extremely sensitive to heat and humidity (10). The age distribution of infected persons during these outbreaks depended primarily on the degree of susceptibility to smallpox in the population. In most areas, including Europe and the USA, smallpox affected predominantly children, because adults were typically protected by immunity acquired via vaccination or previous smallpox infection. In rural areas, however, where the practice of vaccination was not as common as in the more populated cities, smallpox affected all ages equally, given the higher susceptibility of rural populations. If smallpox were to occur now, the disease would affect the entire population and all ages equally, because the vaccination immunity in the population has waned substantially after 1980 and the cessation of vaccination.

MICROBIOLOGY AND PATHOPHYSIOLOGY

Smallpox is a DNA virus and belongs to the genus of the orthopoxviridae (11). Orthopoxviruses belong to the family of Poxviridae, which is composed of several other poxviruses including parapoxvirus, capripoxvirus, suipoxvirus, and molluscipoxvirus. Only two species, variola virus (smallpox) and molluscum contagiosum virus, are specifically human viruses. However, several other species have also been known to occasionally affect humans. Four of the orthopoxviruses (smallpox, monkeypox, vaccinia, and cowpox) can cause significant infections in humans and produce cutaneous lesions, but only smallpox is readily transmitted from person to person.

Cowpox was known in Europe for many centuries as a disease of cattle, occurring as ulcers on the teats that caused similar ulcers

on the hands of milkmaids. A review of recent literature indicated that cows are an accidental and occasional host of cowpox virus and that cows, cats, and zoo animals are infected from a rodent reservoir host (12).

Vaccinia virus was the term used for the agent of vaccination as it was introduced by Edward Jenner. For some 100 years, this agent was used for vaccination against smallpox; it is now known as vaccinia virus. However, it is different from the original cowpox virus that Jenner used in his early vaccinations. The exact origin of vaccinia virus remains unknown. It is proposed that vaccinia virus could be the product of genetic recombination, a new species derived from cowpox or variola via serial passage. It is also possible that vaccinia is the living representative of another now-extinct orthopoxvirus (11).

Monkeypox is a zoonotic disease and is typically found in the rain forests of western and central Africa. It was first discovered as a disease of laboratory primates in Copenhagen, Denmark, in 1958, before it was recognized as a zoonosis in 1970. Since then, several human cases of monkeypox have been described in the medical literature. Those cases have been identified as a zoonotic disease among inhabitants of small villages in the tropical rain forests of Africa, where the transmission of the virions occurred between the rodent reservoir, monkeys, and the human population. However, during the past 5 years, human-to-human transmission of monkeypox has also been described (13). Vaccinia and cowpox seldom spread from person to person.

All species of orthopoxviruses are morphologically indistinguishable. They are large, brick-shaped virions of complex structure with a diameter of about 200 nm (11). Replication occurs in the cytoplasm of host cells. The transcription is effected by a virion-associated DNA-dependent RNA polymerase. While in the cytoplasm, some of the virions acquire an envelope that contains several virus-specific polypeptides, including the hemagglutinin. Such newly transcribed and formed viruses are released from intact host cells as enveloped virions. Most virion particles, however, remain nonenveloped and are released by disruption of the host cells. Both enveloped and nonenveloped virus particles are infectious.

Variola and monkeypox cause a systemic disease with a generalized rash in humans and in experimental primate infections. Cowpox and vaccinia usually cause only a localized lesion at the site of introduction of the virus. Because smallpox is now extinct, I use the past tense in further describing it. Natural infection with variola virus occurred following transmission of infective aerosolized droplets on the oropharyngeal or respiratory mucosa. The infective dose was unknown but was and is believed to be only a few (<100) virions. Macrophages were among the early sites/cells of infection, and the virus migrated along the local lymphatic channels and multiplied in regional lymph nodes. Other sites of early viral replication were the spleen, bone marrow, and distant lymph nodes. This initial infection in the oropharynx and upper respiratory tract was essentially silent, and patients were asymptomatic.

Viremia was largely cell-associated, and the virions were localized in small vessels of the dermis. Infected macrophages migrated from these vessels into the epidermis, where they infected nearby cells of the basal layer. This resulted in necrosis and edema with splitting of the dermis. This was followed by migration of polymorphonuclear leukocytes into the lumen of the developing vesicles, which then became pustular. The outcome of the infection was either death or recovery with the elimination of the virus. Recovery was accompanied by lifelong immunity to reinfection with variola virus.

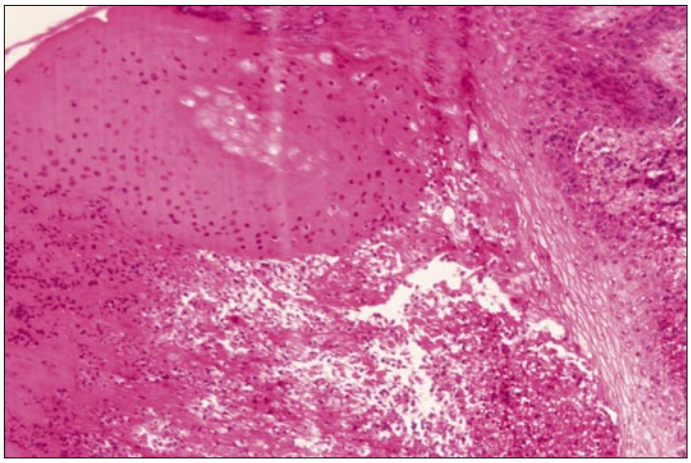

Figure 2. Histologic changes in human skin in a case of smallpox infection. Photo courtesy of the Centers for Disease Control and Prevention Public Health Image Library.

The foremost pathologic feature of smallpox was the rash. The earliest change in the development of the classic skin lesion was a dilatation of the capillaries in the papillae of the corium. This was accompanied by a swelling of the lining endothelium and infiltration by lymphocytes and histiocytes *(Figure 2)*. This stage was followed by signs that occurred in the epidermis. Those were characterized by enlargement and vacuolization of the cells in the middle epidermal layer. Cells of the malpighian layer proliferated, leading to a thickening of the entire epithelial layer. The process spread to the neighboring cells in the middle layer and was accompanied by profound edema, eventually leading to rupture of cell membranes and formation of a vesicle. Septa in these vesicles were formed by the remains of incompletely destroyed cells.

As this process continued to progress, polymorphonuclear leukocytes entered the vesicle from the dermis and produced a pustule with disappearance of the septa. Fluid from the pustule was then absorbed and the contents dried up. Epithelial cells from the sites of the cavity grew under the residual mass of the exudates, and a scab formed, consisting of degenerated epithelial cells, leukocytes, and debris. Pockmarks were caused by the destruction of sebaceous glands and formation of granulation tissue; they occurred all over the body but were most prominent on the face because of the large number of sebaceous glands located there. Lesions similar to those of the skin were found in the mucous membranes of the mouth, tongue, pharynx, larynx, and upper part of the esophagus. Damaged epithelial layers in these areas produced highly contagious oropharyngeal excretions, considering the absence of the impermeable keratin layer that is present in the skin. Other organs did not show specific lesions. However, small hemorrhages were often reported to occur in the heart and the liver. In the form of hemorrhagic smallpox, which accounted for a small percentage of all cases, hemorrhages occurred under the serosa in the pericardium, pleura, and peritoneum. Thus, typical bleeding sites were the lungs, kidneys, liver, bladder, uterus, and occasionally the bone marrow.

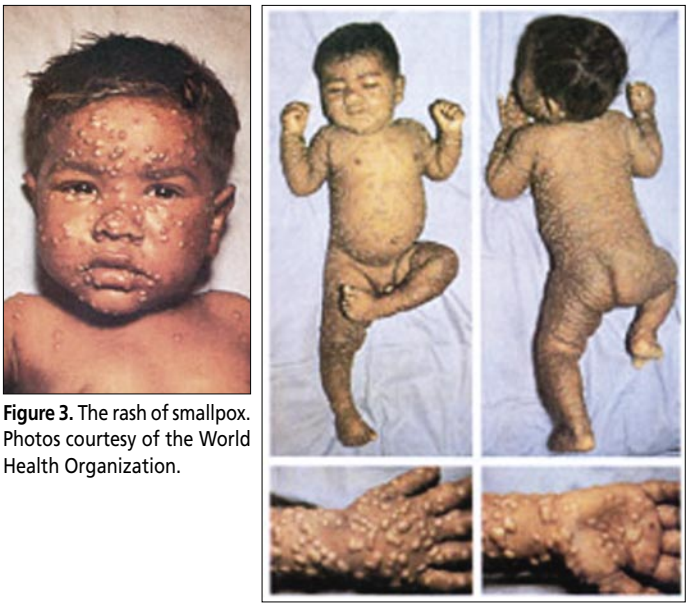

Figure 3. The rash of smallpox. Photos courtesy of the World Health Organization.

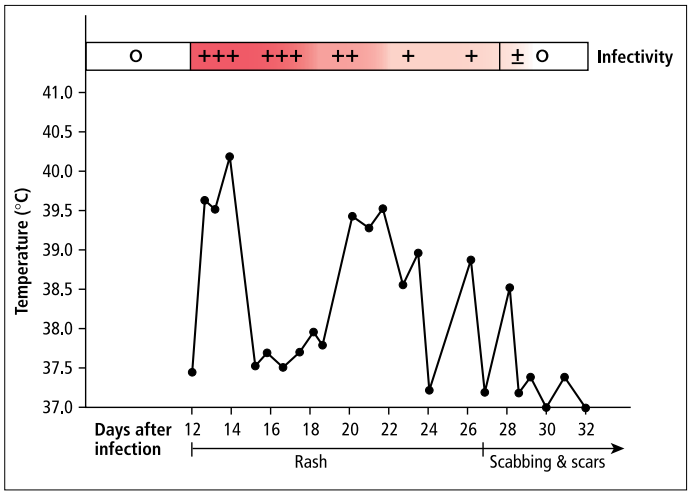

Figure 4. Typical temperature chart of a patient with smallpox, showing the approximate time of appearance and evolution of the rash in conjunction with the time of highest infectivity relative to the number of days after infection (4, 14).

Also characteristic of poxvirus infections were cytoplasmic inclusions. Two types of inclusions were reported. The A-type inclusions, also known as Downie bodies (cowpox), Marchal body (ectromelia), and Borrel body (fowlpox), occurred in only a few poxvirus infections. The B-type inclusions, also known as Guarnieri bodies, were the sites of viral replication. They were found in virtually all poxvirus infections. Guarnieri bodies were readily identified in smallpox lesions of the skin when sections of the skin biopsy were stained with hematoxylin and eosin. Guarnieri bodies were cytoplasmic, round to oval, faintly basophilic or acidophilic bodies, located in close proximity to the nucleus.

CLINICAL PRESENTATION AND DIAGNOSIS OF SMALLPOX

Shedding of the virus from an infected person and its transfer to a susceptible subject constituted the transmission of smallpox. In most cases, transmission was direct via infective droplets to the nasal, oral, or oropharyngeal mucosa or alveoli of the lung. Less commonly, the infection occurred indirectly as an airborne infection or via fomites. After transmission of the virus, the primary viral replication, often referred to as primary viremia, occurred at the site of infection. A secondary viremia developed around day 8 of the infection (4). This was followed by the sudden and abrupt onset of fever. During this phase, the virus was contained in leukocytes and was spread to the small vessels and capillaries of the dermis and mucosa, with subsequent infection of the adjacent epithelium.

At the end of this 12- to 14-day incubation period, the patient typically presented with high fever, malaise, and prostration with headache. In some cases, delirium and severe abdominal pain were also reported. Around day 14, a maculopapular rash appeared on the mucosa of the mouth and pharynx, as well as the face and the forearms *(Figure 3)*. It then spread to the trunk and legs. The characteristic smallpox rash had a centrifugal appearance and was most prominent on the face and the extremities, including the palms and soles. The smallpox lesions typically appeared during a 1- to 2-day period and were generally in the same state of development at any given part of the body. Patients with smallpox were most infectious during the first week of the rash. Once the scabs had separated, patients were no longer infectious *(Figure 4)*. Except for the skin and the mucous membranes, other organ systems were rarely involved in patients with the typical (ordinary) form of smallpox.

Complications of smallpox infections were secondary bacterial infections, meningitis, and encephalitis; however, those were rather uncommon. Another complication that was more frequently reported was blindness, usually seen in cases of severe malnutrition and concomitant bacterial infection. Deaths from smallpox usually occurred during the second week of the disease and most often resulted from profound hypotension and severe toxemia associated with circulating immune complexes and soluble variola antigens (11, 14).

In addition to this "*ordinary-type*" smallpox, three other clinical forms of the disease were recognized (4, 11). The rare *hemorrhagic-type* smallpox was associated with petechiae in the skin and bleeding from the conjunctiva and mucous membranes. This form was associated with very severe toxemia and high mortality rates, often in early stages of disease development. The *flat-type* smallpox was characterized by severe toxemia and delayed onset and slow development of skin lesions. Most of these cases were fatal. The *modified-type* smallpox was often seen in patients who had been previously vaccinated. Skin lesions in these cases usually evolved quickly and were more variable in their appearance. Very few of these cases were fatal.

A disease that can still be confused with smallpox is varicella (chickenpox). Chickenpox is caused by the varicella-zoster virus, a DNA virus that belongs to the family of Herpesviridae. Similar to smallpox, chickenpox is transmitted via respiratory secretions or contact with skin lesions (15). Chickenpox presents with an abrupt onset of a pruritic rash, low-grade fever, and malaise. New lesions appear in crops every few days and are seen in different stages of maturation. The distribution of varicella lesions is centripetal with a greater concentration on the trunk. Palms and soles are almost never involved. The clinical course and the characteristic appearance of the skin lesions aid in the ability to distinguish one from another.

When smallpox was endemic, the diagnosis was easily made based on the appearance and distribution of the rash. Clinically,

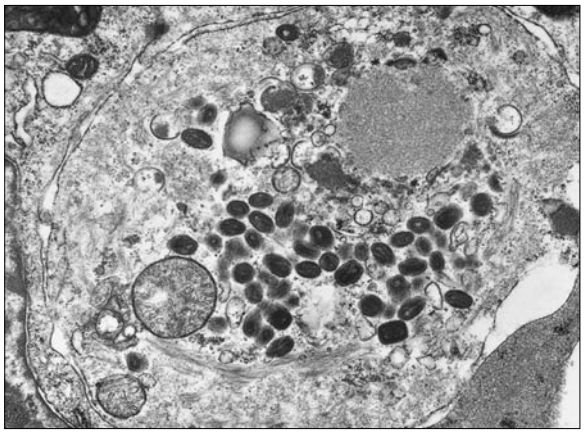

Figure 5. Transmission electron micrograph of a tissue section containing variola virus. Photo from Fred Murphy and Sylvia Whitfield, Centers for Disease Control and Prevention, courtesy of the Public Health Image Library.

human monkeypox cannot be differentiated from smallpox. Cowpox and vaccinia are at this point only of historical importance. The ordinary-type variola as well as variola minor can be confused with chickenpox as stated above. More rarely, on the first examination of a case, erythema multiforme and secondary syphilis might cause difficulties in diagnosis. In the past, problems with diagnosis occurred when the infection was imported into nonendemic countries. Cases of hemorrhagic smallpox were often confused with meningococcal septicemia or acute leukemia. Hemorrhagic and malignant smallpox presented in such ways that smallpox was rarely suspected until more typical cases were identified. When the diagnosis was made, the smallpox outbreak was usually in progress (4).

Laboratory confirmation of the diagnosis in a smallpox outbreak is important. The specimen should be collected by someone who has been recently vaccinated. Personal protection with gloves and face mask is imperative. Either pustular fluid or scabs can serve as specimens for laboratory evaluation (2). The specimen should be placed in an evacuated tube and sealed with adhesive tape. This specimen collection tube should then be placed in a second durable, water-tight container. State and local health department laboratories must be notified immediately regarding the shipment of the specimen. Laboratory examination of the specimen requires high-containment (BSL-4) facilities and should be performed only in designated laboratories with the appropriate training and equipment (14).

The best method for diagnosis of smallpox is identification of species-specific DNA sequences. Other laboratory methods for diagnosis include electron microscopy *(Figure 5)*, immunohistochemistry, various polymerase chain reaction (PCR) technologies, and serologies (16) *(Table 2)*. Electron microscopy of vesicular or pustular fluid is a suitable and rapid method for confirmation of smallpox infection. However, the definitive diagnosis and identification of species of orthopoxvirus rests on viral culture and characterization of the virus by various biologic assays, including PCR and restriction fragment-length polymorphisms (17). PCR is a relatively simple, rapid, and accurate method for detection and differential diagnosis of several different orthopoxvirus infections.

Table 2. Laboratory techniques for confirmation of smallpox (orthopoxvirus) diagnosis*

Virus culture
Immunohistochemistry
Electron microscopy
Various polymerase chain reaction techniques
– Essential conserved genes *(E9L, A25R)*—difficult to discriminate among species of orthopoxviruses
– Nonessential, variable genes *(HA, HTI, crmB)*—species specific
Serology
– Antigen detection (immunofluorescent assay, enzyme immunoassay, antigen capture)
– Neutralization antibodies
– Immunoglobulin M capture
– Immunoglobulin G enzyme-linked immunosorbent assay

*From reference 16. Reproduced with permission of Russell Regnery, PhD, National Center for Infectious Diseases, Centers for Disease Control and Prevention.

TREATMENT AND PROPHYLAXIS

The concept of care for patients with smallpox infections has to consider not only postexposure therapy but also postexposure infection control measures and preexposure preventive measures.

Before 1972, smallpox vaccination was recommended for all children in Europe and the USA at age 1 year (14). Most countries and most US states also required that the child be revaccinated before school entry. Special recommendations existed for military personnel and for tourists planning to visit certain foreign countries. Routine vaccinations in the USA were stopped in 1972, and since then few persons younger than 30 years have been vaccinated. The duration of protective immunity from previous vaccinations was historically based on the experience of naturally exposed susceptible persons. However, this has never been satisfactorily evaluated. Therefore, the world population is now considered an immunologically naive, nonprotected population, highly susceptible to smallpox, should the disease be reintroduced.

Worldwide only a small supply of smallpox vaccine is available. Most of this supply is under the control of the CDC; additional doses of vaccine are available at the WHO. The USA is currently increasing the number of doses of smallpox vaccine. Until recently, only 15.4 million doses of smallpox vaccine (Dryvax, produced 20 years ago by Wyeth Laboratories) were available (18). In addition, Aventis Pasteur (Paris, France) donated a supply of 80 million doses of smallpox vaccine (Wetvax or APSV) to the US government (19). Wetvax is a different formulation of the vaccinia smallpox vaccine and was in storage for 40 years. It is now being investigated by the National Institute for Allergy and Infectious Diseases for efficacy and safety and use in adults who have never received the smallpox vaccine.

Efforts to develop and produce a new vaccine are now focused on a live cell culture–derived smallpox vaccine. In 2001, it was estimated that the development and licensure of such a vaccine as well as development of a production facility would require a minimum of 36 months (14). Since only a limited amount of vaccine is available, the Advisory Committee on Immunization

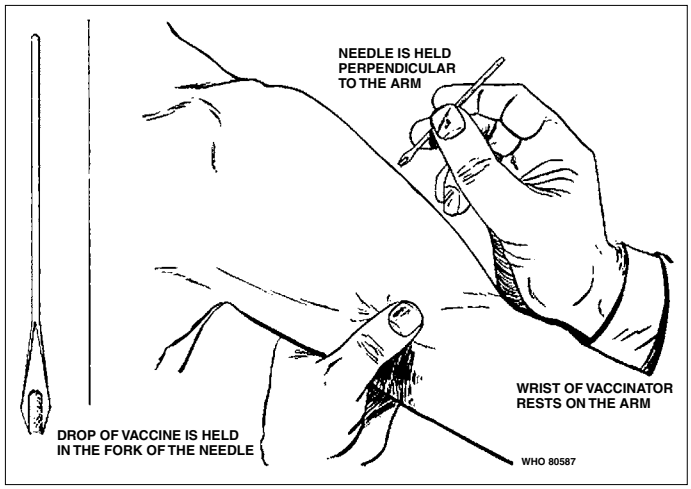

Figure 6. Multipuncture vaccination by birfurcated needle. Image courtesy of the World Health Organization.

Practices recommended in 2001 that a preventive vaccination program be initiated to protect the first-line responders, i.e., emergency and key health care personnel and law enforcement personnel. Such newly vaccinated persons also should receive a booster dose every 10 years, as recommended by the committee. Currently, widespread vaccination is recommended only under epidemic circumstances, in the event of a laboratory accident or an act of bioterrorism (20).

Most known immunizations are administered by injection either intramuscularly or subcutaneously. In contrast, the smallpox vaccine is administered intradermally on the area of the deltoid muscle or the posterior aspect of the arm over the triceps muscle, using a bifurcated needle *(Figure 6)*. Advantages and disadvantages of using other vaccination sites have not been conclusively evaluated. Cleaning the vaccination site with alcohol or other chemical agents is not necessary and is actually discouraged. If the area is cleaned with such agents, it is necessary to let it dry completely to prevent vaccine inactivation. A droplet of the reconstituted vaccine is held between the tines of the needle. The vaccine maintains its position on the tines because of its high viscosity and capillary forces. The needle is held perpendicular to the skin, and 3 strokes with the needle are then made within an area of 5 mm in diameter. Fifteen strokes are recommended in cases of revaccination. This action should be vigorous enough to cause minor bleeding at the vaccination site within 25 seconds after the procedure. The site should then be covered with a loose, nonocclusive bandage to prevent autoinoculation (14).

Within 3 to 7 days after vaccination, a hard, pocklike vesicle should form, indicating successful vaccination. Formation of the vesicle may be accompanied by several "adverse effects" that are often transient (21). Most of these effects occur within the first 7 days after vaccination and include redness and pain at the vaccination site, fever, headache, fatigue, muscle aches, chills, nausea, and rash distal to the vaccination site. However, before cessation of the vaccination program in 1972, some more serious adverse events had been reported. Those included vaccinial encephalitis, progressive vaccinia, eczema vaccinatum, and death *(Table 3)*. Vaccinia immune globulin (VIG) is the only treatment option for complications of vaccinia vaccination, but it is generally not used for the treatment of smallpox (18). VIG is derived from plasma of patients who have been vaccinated with vaccinia virus. VIG can be used to treat autoinoculation of the eye, eczema vaccinatum, generalized vaccinia, and progressive vaccinia. In cases of vaccinial encephalitis, it has shown little or no efficacy. Since the CDC's supply of VIG is limited, its use should be limited to cases of serious adverse events to vaccination.

Table 3. Rates of adverse reactions to the smallpox vaccine*

Adverse event	Rate per million vaccinees
Encephalitis	2.4–12.3
Progressive vaccinia	0.9–1.7
Eczema vaccinatum	10.4–41.5
Death	0.6–1.1
Generalized vaccinia	17.7–241.5
Autoinoculation	25.4–532.0
Erythema multiforme	131.3–164.6

*Data from the Centers for Disease Control and Prevention (http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp; accessed September 30, 2004).

Consensus recommendations for special risk groups have been established by the Working Group on Civilian Biodefense and the CDC (14). Five groups of persons have been identified to be at high risk of complications from smallpox vaccine: 1) persons with eczema; 2) patients with leukemia, lymphoma, or other generalized malignancy who are receiving therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids; 3) patients with HIV infection; 4) patients with hereditary immune deficiency disorders; and 5) pregnant women. At the present time, administration of smallpox vaccine is contraindicated in these persons. If persons with contraindications have close contact with a smallpox patient or the individual is at high risk for occupational reasons, VIG should be given simultaneously with vaccination. This should not alter the efficacy of the vaccination. If VIG is not available, the vaccine should still be administered, considering the far higher risk of an adverse outcome from smallpox infection compared with vaccination.

In the situation of a clandestine release of smallpox, even if only 50 to 100 people were infected at first, the disease would rapidly spread in a now highly susceptible population, expanding by a factor of 10 to 20 times with each generation of cases (4, 22). As soon as the diagnosis of smallpox is established, all individuals in whom the disease is suspected should be isolated immediately. Close contacts such as household members should be vaccinated and placed under surveillance for disease symptoms.

Smallpox transmission within hospitals has long been recognized as a serious problem (22). For more than 200 years, smallpox patients were cared for in specialized hospitals to minimize the spread of the disease. In the setting of a limited outbreak with few cases, patients could be admitted to hospitals and confined to rooms under negative pressure and equipped with high-efficiency particulate air filtration. Since smallpox in aerosolized form can be easily disseminated and poses a serious threat in hospitals and public places, different guidelines exist for large smallpox outbreaks, and patients should then be isolated in their homes or other nonhospital facilities. According to the recommendations of the Advisory Committee on Immunization Practices and the

Working Group on Civilian Biodefense, home care seems to be a reasonable approach, since little can be done for the patient other than to offer supportive care. In addition, antibiotics may be indicated for treatment of occasional secondary bacterial infections.

No antiviral substances have the proven potential to be effective in the treatment of human smallpox infection. Therefore, the strategy for control of a smallpox outbreak centers on surveillance and containment. This strategy was instrumental in the global eradication of smallpox in the past century. An assessment algorithm devised by the CDC can help in identifying smallpox in a febrile patient with a rash. This algorithm can be obtained from state health departments or online from the CDC (23). Identification and surveillance of the individual's close contacts are the center of every proposed strategy of disease containment. Priority within the rings of contact will be determined by interviews with the patients and their contacts. Surveillance and vaccination should begin as soon as those contacts are identified. Vaccination within 4 days after exposure is currently considered effective in preventing infection or the severe form of infection. Vaccinated contacts are not considered infective and do not have to be isolated. However, it is currently recommended that they stay within 20 miles of their home.

In addition to hospital infection control and the containment of identified cases, decontamination of the environment after an attack with aerosolized smallpox is an important factor to control the spread of the disease. If vaccinia virus is released as aerosol and not exposed to ultraviolet light, it may persist for as long as 24 hours or somewhat longer under favorable conditions (10). It is believed that variola virus would exhibit similar properties. However, by the time the first cases of smallpox become clinically evident, no viable smallpox virus would be present in the environment. Virus identified in scabs appears to be more durable, and survival of up to 8 weeks depending on temperature conditions has been observed. Therefore, special focus should be given to the close environment of patients. The occurrence of smallpox infections among personnel who handled laundry from infected patients is well documented (22). It is believed that virus remains viable for much longer periods, requiring special precautions and procedures for handling such material from infected patients.

A more detailed discussion of all aspects of preexposure and postexposure infection control would be beyond the scope of this article. In addition, in recent years, much focus has been given to research and development of new vaccines, immunotherapy, and drugs. Additional information on new recommendations for disease surveillance and containment, as well as recent pharmaceutical developments, is available on the websites of the CDC and the National Institutes of Health.

CONCLUSIONS

Although smallpox was eradicated in 1980, it remains a potential agent of biowarfare and bioterrorism. It is considered a category A organism, which is easy to disseminate and transmit from person to person. Furthermore, smallpox has the potential to result in high mortality rates with a major public health impact, eventually causing public panic and social disruption. Given the enormous efforts made to eradicate the disease, the deliberate release of smallpox as a biological weapon would be an international crime of unprecedented proportions. Unfortunately, the possibility of releasing smallpox in aerosolized form is now a reality and the potential for a catastrophic scenario is great, and effective control measures must be implemented.

Many models have been developed for emergency response. However, all leave many uncertainties, and no model can be truly predictive in the context of smallpox outbreak planning. But it is clear from reviewing different scenarios that early detection, isolation of infected individuals, surveillance of contacts, and a focused, selective vaccination program are the essential items of an effective control program.

The efficacy of such a program, however, depends on the level of education, both in the public as well as in the medical community. Education of health care professionals should permit early detection of infected individuals and allow for prompt initiation of adequate first steps to contain the approaching epidemic. Advanced planning for isolation of infected individuals, both in their homes as well as in hospitals, will be critical to prevent the outbreak from further expansion. Finally, the success in conquering the threat of a reemerging smallpox epidemic will rest on the availability of adequate supplies of vaccine and other medications necessary for treatment. To ensure an effective and relatively inexpensive safeguard for such a tragedy, it is necessary to provide an adequate stockpile of vaccine. However, proper education of the medical community as well as the public remains an essential cornerstone of such preventive efforts.

1. Riedel S. Biological warfare and bioterrorism: a historical review. *BUMC Proceedings* 2004;17:400–406.
2. Barquet N, Domingo P. Smallpox: the triumph over the most terrible of the ministers of death. *Ann Intern Med* 1997;127(8 Pt 1):635–642.
3. Riedel S. Edward Jenner and the history of smallpox and vaccination. *BUMC Proceedings* 2005;18:21–25.
4. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and Its Eradication*. Geneva: World Health Organization, 1988.
5. Institute of Medicine. *Assessment of Future Scientific Need for Live Variola Virus*. Washington, DC: National Academy Press, 1999.
6. Eitzen EM Jr, Takafuji ET. Historical overview of biological warfare. In Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. Washington, DC: Office of the Surgeon General, Borden Institute, Walter Reed Army Medical Center, 1997:415–423. Available at http://www.bordeninstitute.army.mil/cwbw/default_index.htm; accessed August 31, 2004.
7. Chapin CV. Variation in the type of infectious diseases as shown by the history of smallpox in the United States, 1895–1912. *J Infect Dis* 1913;13:171–196.
8. Anders W, Sosch J. Die Pockenausbrueche 1961/62 in Nordrhein-Westfalen. *Bundesgesundheitsblatt* 1962;17:265–269.
9. Rao AR. *Infected Inanimate Objects (Fomites) and Their Role in Transmission of Smallpox* [WHO/SE/72.40]. Geneva: World Health Organization, 1972.
10. Harper GJ. Airborne micro-organisms: survival test with four viruses. *J Hyg* 1961;59:479–486.
11. Fenner F. Poxviruses. In Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE, eds. *Fields Virology*, 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1996.
12. Bennet M, Gaskell CJ, Baxby D, Gaskell RM, Kelly DF, Naidoo J. Feline cowpox virus infection. A review. *J Small Anim Pract* 1990;14:167–173.
13. Breman JG, Henderson DA. Poxvirus dilemmas—monkeypox, smallpox, and biologic terrorism. *N Engl J Med* 1998;339:556–559.
14. Henderson DA, Inglesby TV, Bartlett JG, Ascher MS, Eitzen E, Jahrling PB, Hauer J, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl T, Russell PK, Tonat K; Working Group on Civilian Biodefense. Smallpox as a biological weapon: medical and public health management. *JAMA* 1999;281:2127–2137.

15. McCrary ML, Severson J, Tyring SK. Varicella zoster virus. *J Am Acad Dermatol* 1999;41:1–16.
16. Regnery R. Virology and diagnosis of smallpox [webcast and slides]. Presented at International Conference on Emerging Infectious Diseases, March 25, 2002. Available at http://www.cdc.gov/iceid/webcast/smallpox_response.htm; accessed September 23, 2004.
17. Ropp SL, Jin Q, Knight JC, Massung RF, Esposito JJ. PCR strategy for identification and differentiation of smallpox and other orthopoxviruses. *J Clin Microbiol* 1995;33:2069–2076.
18. Centers for Disease Control and Prevention. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *MMWR Morb Mortal Wkly Rep* 2001;50(RR-10):1–24.
19. National Institutes of Health. NIAID's vaccine and treatment evaluation units [fact sheet]. Available at http://www.niaid.nih.gov/factsheets/vteu.htm; accessed September 29, 2004.
20. Centers for Disease Control and Prevention. Emergency preparedness and response. Available at http://www.bt.cdc.gov/index.asp; accessed September 24, 2004.
21. Centers for Disease Control and Prevention. Generalized vesicular or pustular rash illness protocol. Available at http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/annex/annex-4-rash-color.pdf; accessed September 28, 2004.
22. Wehrle PF, Posch J, Richter KH, Henderson DA. An airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. *Bull World Health Organ* 1970;43:669–679.
23. Centers for Disease Control and Prevention. Guide B, part 1 of 2: Vaccination guidelines for state and local health agencies. In *Interim Smallpox Response Plan and Guidelines*. Available at http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-b-part1of3.pdf; accessed September 28, 2004.