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Smallpox as a Weapon for Bioterrorism

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1. INTRODUCTION

Smallpox, the only disease ever eradicated, is one of the six pathogens considered a serious threat for biological terrorism (Henderson *et al.*, 1999; Mahy, 2003; Whitley, 2003). Smallpox has several attributes that make it a potential threat. It can be grown in large amounts. It spreads via the respiratory route. It has a 30% mortality rate. The potential for an attack using smallpox motivated President Bush to call for phased vaccination of a substantial number of American health care and public health workers (Grabenstein and Winkenwerder, 2003; Stevenson and Stolberg, 2002). Following September 11, 2001, the United States rebuilt its supplies of vaccine and Vaccinia Immune Globulin (VIG), expanded the network of laboratories capable of testing for variola virus, and engaged in a broad education campaign to help health care workers and the general public understand the disease (Centers for Disease Control and Prevention, 2003a). This chapter summarizes the scientific and theoretical bases for use of smallpox as a bioweapon and options for preparation for defense against it.

2. VIROLOGY

Variola major, the virus that causes smallpox, is an orthopox. *Variola minor*, its less pathogenic cousin, has little theoretical expectation for use as a bioweapon. *V. major* is a large DNA virus (350 × 270 nm), with one of the most complex genomes of human viruses (180 kbp double-stranded DNA). The genome of several strains of *V. major* has been completely sequenced, but the functions of the genes have not all been elucidated (Moss, 2001).

Like most orthopox viruses, variola is host specific. Humans are the only natural hosts. Experimental infection of small numbers of monkeys with large intravenous doses of virus has been accomplished (LeDuc and Jahrling, 2001). The virus grows well on many tissue cultures and on the chorioallantoic membrane of embryonated chicken eggs. Vaccinia virus, a close cousin of variola, is routinely grown in many laboratories, and can be lyophilized to ensure stability to heat. The same techniques could be used with variola.

The genetics of vaccinia are well known, in part because vaccinia strains have been proposed as carrier viruses for genes from other agents, including HIV (Moss, 2001; Smith *et al.*, 2002). This work shows that the genes of orthopox viruses are amenable to deletions and additions. Researchers working with ectromelia (mousepox), another close cousin of variola, have created a very virulent strain, able to escape the protective effect of prior immunization with vaccinia (Born *et al.*, 2000; Jackson *et al.*, 2001). Recent research suggests that smallpox virus could be recreated by synthesizing long strands of DNA, thus enhancing its availability for bioterrorism. The viral genome has been deposited in public databases, making such work possible although time-consuming and highly technical (Wade, 2005).

Variola virus is fairly hardy in the environment if protected from heat and ultraviolet light. However, it is easy to kill with standard hospital disinfectants or ultraviolet light (Fenner *et al.*, 1988). There is little information about its ability to survive when aerosolized; by analogy to vaccinia virus, it probably could survive for an hour or more if not in direct sunlight (Harper, 1961; Thomas, 1974).

In summary, variola has several virologic attributes that make it attractive as a terrorist weapon. It is easy to grow. It can be lyophilized to protect it from heat. It can be aerosolized. Its genome is large and theoretically amendable to modification.

3. PATHOGENESIS

The pathogenesis of smallpox is believed to resemble that of mousepox (ectromelia), which was elucidated by Fenner and colleagues during the 1950s and 1960s. Subsequent work with rabbitpox and monkeypox, orthopoxes that also cause species-specific systemic disease, have refined our understanding of pathogenesis (Fenner *et al.*, 1988). Infection is via the respiratory route. During the first 4 or 5 days after infection, the virus multiplies in the epithelium of the upper respiratory tract. It is then released into the bloodstream in a primary (asymptomatic) viremia. This viremia is cleared by the reticuloendothelial system, where the virus again multiplies. About 8 or 9 days after the initial infection, the reticuloendothelial cells release a secondary viremia, which is probably cell-associated. This is a massive viremia that causes an intense and prostrating prodrome, with fever, myalgias, and other symptoms of a vigorous viremia. The secondary viremia is cleared toward the end of the prodrome, when the leukocyte-associated virus becomes localized in small blood vessels in the dermis and upper respiratory epithelium.

The skin lesions evolve in a stately and characteristic way (see section on “Clinical Disease”). The histopathology is characteristic. The lesions are full of virus. The fluid from vesicles and pustules and scabs is infectious, and virus can be isolated from scabs (Bremner and Henderson, 2002; Fenner *et al.*, 1988). The main source of natural infection is the secretions from the upper respiratory tract, where lesions quickly break down and excrete virus because the epithelium in the nose and throat lacks the firm keratinized layer that

seals in the virus in the lesions on the skin. Patients are therefore infectious from about 12–24 hours before the initial faint macular rash appears on the skin, and remain infectious throughout the course of the rash (Breman and Henderson, 2002; Dixon, 1962; Fenner *et al.*, 1988).

The clinical illness and fatality rate roughly parallel the density of the skin lesions. When lesions are sparse, cases are unlikely to die and probably are not efficient transmitters. However, their mobility may allow them to have enough social interaction to result in transmission. Vaccine-modified smallpox can be very mild and nonfatal, although if vaccination was more than 20 years prior to exposure, the fatality rate is not trivial and patients can still transmit the disease. As lesions become denser and confluent, the fatality rate increases, the amount of virus in the respiratory secretions increases, and patients are more infectious (Fenner *et al.*, 1988; Mack, 1972; Rao, 1972). Hemorrhagic smallpox has a fatality rate of nearly 100%, and patients are highly infectious. About 1–5% of unvaccinated patients with *V. major* get hemorrhagic smallpox, probably with disseminated intravascular coagulation (Bray and Buller, 2004; McKenzie *et al.*, 1965; Rao, 1972). They are usually very sick, usually unable to get out of bed and thus may not transmit efficiently. The clinical presentation (from mild to discrete to confluent to hemorrhagic) is a function of the host response, not the virus. The clinical types do not breed true, in that transmission from any patient can give rise to any of the clinical presentations, and the virus is the same.

The immune response in smallpox includes both cell-mediated immunity and production of neutralizing antibodies. Both probably appear about 6 days after the onset of the rash (Fenner *et al.*, 1988). Immunity is essentially life-long in recovered patients, although very rare cases of second infections have been reported several decades after initial infections. The immune response in hemorrhagic smallpox is probably poor, contributing to the very bad outcome.

In summary, smallpox causes an acute illness with a devastating prodrome, with virus primarily transmitted via respiratory secretions. The fatality rate roughly parallels the density of the skin lesions and hence the intensity of the preceding viremia.

4. CLINICAL DISEASE

The clinical spectrum of variola major has been well described (Breman and Henderson, 2002; Dixon, 1962; Fenner *et al.*, 1988; Rao, 1972). The illness starts with a dramatic prodrome, with high fever and signs and symptoms indicative of massive viremia. The patient usually improves somewhat when the viremia is cleared, although the fever does not return to normal. As the fever decreases (about 2–4 days after the onset of the prodrome), the characteristic rash becomes evident. During the first day or two of the rash, it may be impossible to distinguish from measles or many other viral exanthems. On dark skin, the rash may not be apparent on the first day or two, being simply faint macules. If the mouth is carefully examined, an enanthem can be detected.

The lesions of smallpox have a predilection for the cooler parts of the body and are most dense on the face and peripheral extremities. Lesions are present on the palms and/or soles in the majority of cases.



Figure 5.1. Typical semiconfluent smallpox on the seventh or eighth day. Photo courtesy of CDC.

The individual lesions undergo a slow and predictable evolution. Excellent photographs can be found at the Centers for Disease Control and Prevention (CDC) website (Centers for Disease Control and Prevention, 2002a; World Health Organization, 2004). By about the 3rd day, the macules become papular, and the papules progress to fluid-filled vesicles by about the 5th day. These vesicles become large, hard, tense pustules by about the seventh or eighth day. Figure 5.1 is a typical patient with semiconfluent smallpox on about the 7th day of rash. The pustules are “in” the skin, not just “on” the skin. They are deep-seated and feel like dry garbanzo beans, usually nearly 1 cm in diameter.

About the 8th or 9th day, the lesions begin to dry up and umbilicate. By about 2 weeks after the onset of the rash, lesions are scabbing. About 3 weeks after onset, the scabs begin to separate, leaving pitted and depigmented scars.

The causes of death from smallpox are not well elucidated. Massive viral toxemia probably causes a sepsis cascade. Cardiovascular shock may be part of the agonal syndrome. In hemorrhagic cases, disseminated intravascular coagulation probably occurs. Antibacterial agents are not helpful. Loss of fluid and proteins from the exudative rash probably contribute to death. Modern medical care might reduce the fatality rate, but there is no way to prove that contention (Bray and Buller, 2004; Breman and Henderson, 2002; Fenner *et al.*, 1988; Koplan and Foster, 1979; Rao, 1972).

In summary, smallpox produces a serious and prostrating clinical disease. The characteristic pustular rash is easy to diagnose if smallpox is known to be circulating. There is no proven therapy. No data exist to show whether modern supportive care could reduce the death rate.

5. DIAGNOSIS

When smallpox is known to be circulating, the clinical presentation and characteristic rash make diagnosis fairly easy. Diagnosis can be difficult when smallpox is not high on the index of suspicion. Initial cases after a covert bioterrorist attack will probably be missed, at least until the 4th or 5th day of the rash. Transmission may have already taken place by this time. For that reason, but also as good clinical and public health practice, patients with undiagnosed rashes accompanied by fever should always be isolated until the diagnosis is established.

The CDC has produced a diagnostic algorithm based on experience with the differential diagnosis of suspect smallpox cases. This algorithm is [Figure 5.2](#) and can also be found at the CDC website (Centers for Disease Control and Prevention, [2002b](#); Seward *et al.*, [2004](#)). Most cases initially considered suspect smallpox turn out to be chickenpox, disseminated herpes simplex, secondary syphilis, or drug eruptions.

If this algorithm indicates that a patient is high risk to be smallpox, local and national public health authorities should be immediately notified by telephone, and laboratory specimens taken for polymerase chain reaction (PCR), electron photomicroscopy (EM), and viral culture. A network of laboratories around the United States can do real-time PCR on very short notice (Centers for Disease Control and Prevention, [2003b](#)). State health department laboratories are or know of the nearest one of these Laboratory Resource Network laboratories. Instructions for obtaining, handling, and shipping specimens can be found at the CDC website (Centers for Disease Control and Prevention, [2003b](#)).

Rapid diagnosis requires a sophisticated viral diagnostic laboratory. Rapid testing is best done using EM to identify actual virions and real-time PCR assays to detect viral DNA. These tests are highly sensitive if adequate specimens are provided to the laboratory (Kulesh *et al.*, [2004](#); Ropp *et al.*, [1995](#); Sofi *et al.*, [2003](#)). PCR is very specific, whereas most mammalian orthopoxviruses, including vaccinia and monkeypox, have the same brick-like viral structure and cannot be reliably differentiated from variola with EM. Public health action should be initiated by either a positive PCR or EM test, but confirmation by viral culture should also be attempted.

Laboratory tests require adequate specimens. Copious specimens *MUST* be provided if smallpox is seriously suspected (i.e., if the clinical picture fits the “high-risk” category in the algorithm, or if intelligence or communications from terrorists suggests an attack). At least six lesions should be unroofed. The roof tissue and the pus should be placed in separate sterile vials. EM grids should be touched to the base of the opened lesions. Pus can be dried directly onto plastic slides. Punch biopsies of several lesions should be taken, with half put into formalin fixative and half sent unfixed. Shipping and handling of specimens are important; guidance should be sought from CDC (Centers for Disease Control and Prevention, [2003b](#)).

Efforts are currently underway to detect smallpox virus in the environment, including in air distribution systems in large buildings. These involve filtration of large volumes of air and testing the material from the filters with PCR (NBC10 News, [2003](#)). These techniques are conceptually encouraging, but have unknown sensitivity and specificity.

In summary, clinical diagnosis is easy when smallpox is suspected and the rash is fully developed. Sophisticated laboratory tests are available to diagnose suspect cases

EVALUATING PATIENTS FOR SMALLPOX

ACUTE, GENERALIZED VESICULAR OR PUSTULAR RASH ILLNESS PROTOCOL

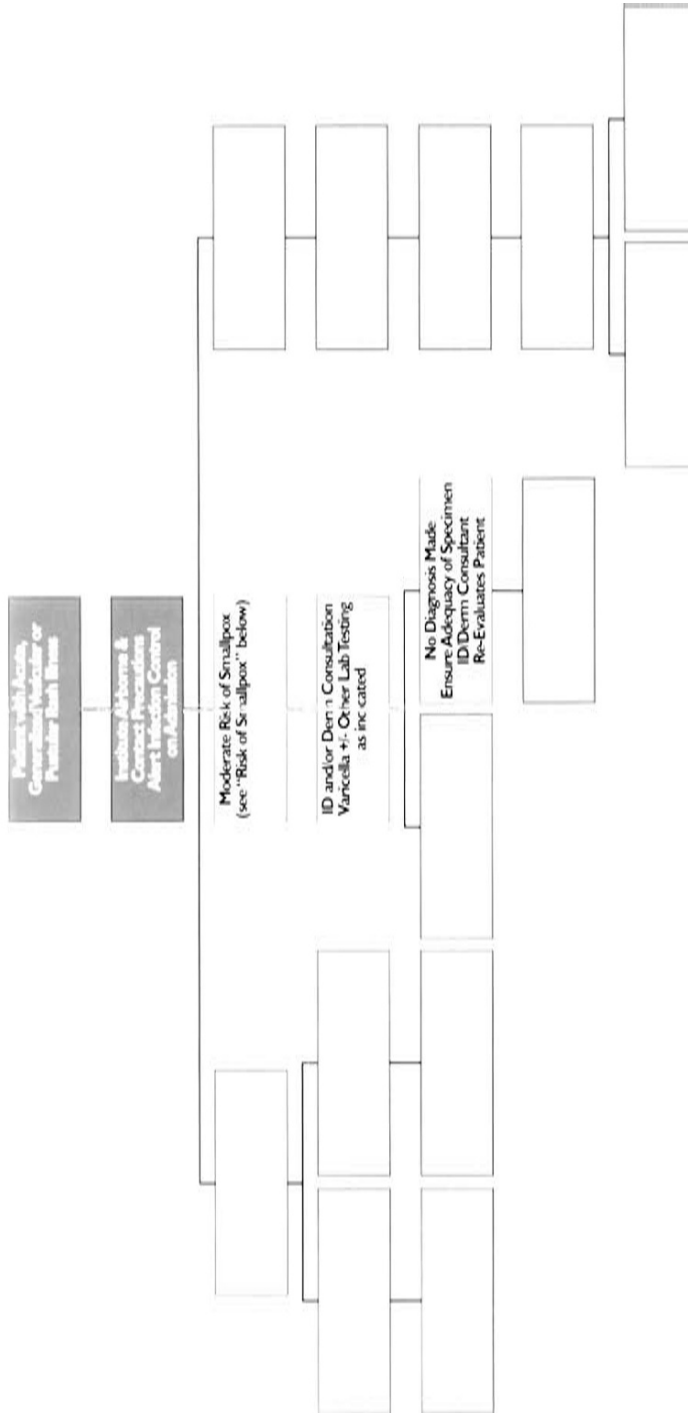


Figure 5.2. Diagnostic algorithm for rash illness. Courtesy of CDC.

rapidly and accurately. Laboratory specimens must be adequate in volume, and carefully handled. Suspect smallpox is a public health emergency and proper public health authorities must be immediately informed.

6. EPIDEMIOLOGY

There is no nonhuman host for smallpox, and there are no subclinical carriers. Once patients have recovered, they are immune and cannot transmit the infection (Fenner *et al.*, 1988). Since there have been no cases since 1977, any new cases must be the result of bioterrorism, or a highly unlikely escape from one of the two official laboratories.

The epidemiology of naturally occurring smallpox has been well studied. The work of Downie *et al.* (1965), Rao *et al.* (1968), Heiner *et al.* (1971), Mack (1972), Mukherjee *et al.* (1974), Sommer and Foster (1974), and the recent demographic analysis by Gani and Leach (2001) provides a good picture of the occurrence and spread of the disease. Smallpox does not ordinarily spread rapidly. Transmission requires prolonged face-to-face contact, such as that which occurs among family members or caregivers. Transmission is most efficient when the index patient is less than 6 feet from the recipient, so that the large-droplet respiratory secretions can be inhaled (Downie *et al.*, 1965; Mack, 1972; Sarkar *et al.*, 1973). Since virus is not secreted from the respiratory tract until the end of the prodrome, patients are usually bedridden when they become infectious and usually do not transmit the disease widely.

Smallpox has been documented to spread from bedding containing pus and scabs, and from dead bodies (Dixon, 1962; Fenner *et al.*, 1988; Hopkins *et al.*, 1971). Modern hospital systems for handling infectious wastes and cremation of bodies should eliminate such transmission (Centers for Disease Control and Prevention, 2003c).

Under natural conditions, smallpox is a highly seasonal disease. Transmission is most efficient in cool dry seasons, possibly because respiratory droplets evaporate quickly in dry conditions – creating small droplets that remain suspended in the air. Although the vast majority of smallpox is acquired by prolonged face-to-face contact, a well-documented outbreak proves that true aerosolization does occur. A patient whose smallpox had not been diagnosed was hospitalized in Meschede, Germany, in 1972. He was coughing vigorously, which probably contributed to creating an aerosol. Patients and visitors on a floor above his room became infected with smallpox (Wehrle *et al.*, 1970). Modern hospital infection control practices should keep such transmission from occurring in hospitals, but the outbreak proves that aerosols can be dangerous.

6.1. Surveillance and Containment Strategy

These epidemiological observations led the World Health Organization in 1968 to switch tactics from mass vaccination to the “surveillance and containment” method. This method is also sometimes called “ring vaccination”. C.W. Dixon describes, in his once-definitive textbook on smallpox (1962), how he used “expanding ring” vaccination to control a smallpox epidemic in North Africa after World War II. Vaccine supplies and workers were in short supply, so mass vaccination was impractical. The identification of patients and vaccination of their

contacts was his first priority. The next was vaccinating people living in tents surrounding the infected family. Finally, an entire infected village was vaccinated if time and vaccine supply permitted (Dixon, 1948). This concept formed the basis of the surveillance and containment method, after Foege and his colleagues made similar observations about the ease of controlling smallpox by vaccinating close contacts in West Africa in 1967–1968 (Foege *et al.*, 1971; Foege *et al.*, 1975). Surveillance and containment methods work well, even in large and geographically extensive outbreaks, such as that which occurred among several tens of millions of people in the Ganges floodplain in 1974 (Fenner *et al.*, 1988). It is the method that eradicated smallpox when 150 years of mass vaccination failed.

Surveillance and containment consists of five steps. The first step is to identify and report cases. The diagnostic algorithm developed by CDC (Figure 5.2), and the widespread availability of PCR lab tests expedite this process. The second step is to isolate the patient(s). The profound illness and fear of transmission make isolation readily acceptable to the patients and the public. Legal authority exists for isolation if necessary (Centers for Disease Control and Prevention, 2002c). The third step is to identify contacts, the persons who might have had prolonged face-to-face interactions with the patients during the time they were clearly ill. Often patients themselves are dead or moribund and cannot be interviewed. Their family members should be considered contacts, and one or more of them can usually provide information about other possible contacts. Contacts are usually easy to find; they want to be vaccinated and will seek health officials once the patient has been diagnosed.

The fourth step is to vaccinate the contacts. Vaccination prevents smallpox from developing if performed within 3 or 4 days of exposure (Massoudi *et al.*, 2003, Kennedy *et al.*, 2004). The copious supply of bifurcated needles and lyophilized vaccine now available means that vaccination can be rapid and efficient. The rate-limiting factor will be the paperwork demanded by modern medicolegal systems. The contacts are placed under fever surveillance, with temperatures taken twice a day. If they become febrile, and therefore possibly prodromal, they are immediately isolated before they become capable of transmitting the virus.

The fifth step is to vaccinate people who have been or might be associates of one of the first-ring contacts, particularly if the process is not initiated until several days after the index patient(s) became infectious. There is ample time to vaccinate these “second-ring” contacts, because they have not yet been exposed to actual illness. Most new cases detected after initiation of containment activities will be known contacts vaccinated in the incubation period and can be promptly isolated. In the unlikely event that a case develops in a missed contact, the containment process is promptly restarted.

In summary, under natural conditions, smallpox does not spread rapidly. Transmission is by prolonged face-to-face contact. True aerosol spread can occur, but is rare. Surveillance and containment tactics should quickly control outbreaks, even large ones resulting from widespread bioterrorist activity.

7. PATIENT MANAGEMENT AND INFECTION CONTROL

Patients suspected of having smallpox must be immediately isolated under full contact and airborne precautions (Centers for Disease Control and Prevention, 2003d). Suspect smallpox is a public health emergency, and public health authorities should be immediately

notified. Smallpox outbreaks in Europe and the United States had a high degree of nosocomial transmission (Mack, 1972; Mack, 2003). If the diagnosis is suspected, modern infection control procedures and effective isolation should virtually eliminate nosocomial transmission. Early in a bioterrorist attack, if smallpox is not high on most clinicians' index of suspicion, cases may be missed and transmit the disease before being effectively isolated. Most hospitals have procedures to isolate patients with fever and an undiagnosed rash to reduce nosocomial transmission of measles and chickenpox, but these procedures may be difficult to implement in a large, busy city emergency ward.

Only recently vaccinated personnel should be allowed to attend patients. If the health facility does not have such personnel prevaccinated and designated as clinical team members, anyone entering the room must be vaccinated with fresh vaccine and vigorous technique, and should also wear a properly fitting N-95 respirator. Personnel should be vaccinated even if they claim to have had a recent successful vaccination; if they are immune, such vaccination carries no risk, and it will eliminate the possibility of an error in the vaccination history.

Supportive care is the basis of the clinical management of smallpox (Bremer and Henderson, 2002; Fenner *et al.*, 1988). Adequate food and fluids must be provided in a clean environment. If patients are obtunded, intravenous hydration with monitoring of electrolytes is important, although intravenous access may be difficult through the edematous and pock-laden skin.

Smallpox is disfiguring. Older texts suggested removing mirrors from patients' rooms (Dixon, 1962).

There is controversy about the optimal locus for medical care for smallpox patients. There is an ethical imperative to provide the best care possible, but modern hospitals have many immunosuppressed patients (HIV, cancer therapy, transplants, etc.) who would do poorly if they contracted smallpox or had to be vaccinated. Facilities with good isolation possibilities – such as motels, older tuberculosis, mental, or Veterans Administration hospitals, or mobile hospitals, such as those available from the Federal Emergency Management Authority or the military – might make adequate smallpox hospitals. Medical care can be brought to such facilities, and isolation of the entire facility may be possible. (Centers for Disease Control and Prevention, 2003d)

Dead bodies, bedding, and wastes are potentially infectious (Fenner *et al.*, 1988; Hopkins *et al.*, 1971). Bodies of patients dying from smallpox should be cremated. Modern handling of infectious bedding and wastes will kill the variola virus. Rooms where patients have been cared for should be disinfected with any standard hospital disinfectant. Personnel handling bodies, linen, or wastes must be vaccinated.

In summary, careful consideration should be given to the locus of medical care during an outbreak because smallpox is transmissible nosocomially. Scrupulous adherence to infection control guidelines must be maintained, including judicious disposal of medical wastes and dead bodies. Only recently vaccinated personnel should provide care to patients.

8. POTENTIAL AS A BIOWEAPON

No historical evidence exists that smallpox was an effective bioweapon. Over several centuries of colonial settlement in North and South America, anecdotes, diaries, and public letters expressed intent to use smallpox against indigenous people. Much like the current

discussions about the potential use of smallpox as a weapon, what has been written into historical texts and some medical journals may have been fueled more by fear than plausibility.

The correspondence between the British General Jeffery Amherst and his colonels about infecting hostile Indians with smallpox is prolifically referenced in recent journals. The general made this suggestion in July 1763, as strategy against tribes near Fort Pitt, Pennsylvania, involved in Pontiac's Rebellion: "Could it not be contrived to send a small pox among the disaffected tribes of Indians?" A week later, his colonel replied in the only mention of it ever made again: "I will try to inoculate the ___ with Some Blankets that may fall in their Hands, and take care not to get the disease myself" (Knollenberg, 1954). Several weeks before that communication William Trent, an Indian trader at Fort Pitt, suspicious of two Delaware Indian visitors, wrote in his personal journal, "We gave them two Blankets and a Handkerchief out of the Small Pox Hospital. I hope it will have the desired effect." Intent is clear, but the epidemiological record shows that smallpox was raging among the tribes the previous spring, weeks before these documents were written (Knollenberg, 1954). More reasonably, the seasonal nature of smallpox caused subsequent outbreaks rather than blankets. The disease, particularly devastating to American-Indians, had been endemic among them for over a century.

During the American Revolution, George Washington may have believed that British soldiers infected fleeing citizens by using variolation, despite the fact that variolation was a procedure normally used to prevent smallpox. In an 1811 record, a council of Indian chiefs faced a Pacific Fur Company trader, who called himself "the smallpox chief," and threatened to uncork a bottle of the virus if the council decided to attack; fear of smallpox may have averted war. Oral history relates the use of scabs in blankets, linen, clothing, and virus-contaminated tobacco, spanning activities throughout North America and Brazil (Knollenberg, 1954; Wheelis, 1999).

Smallpox virus currently exists legally in only two laboratories: the CDC in Atlanta and at the State Research Center for Virology and Biotechnology in the Novosibirsk region of Russia. Possession of smallpox virus in any place other than these two laboratories is illegal by international convention.

A former Deputy Director of the Soviet Union's bioweapons program has written that, during the cold war, their laboratories produced smallpox in large amounts, and made efforts to adapt it for loading into intercontinental missiles (Alibek, 1999). Scientists defecting from the former Soviet Union, or leaving Russia seeking work in other nations, may have illegally carried stocks of the virus to "rogue" nations (Alibek, 1999; Gellman, 2002; Mangold *et al.*, 1998; Warrick, 2002). There is no publicly accessible proof that such defectors actually transported smallpox out of Russia, but no way of disproving that they did. Allegations have been made that Iraq, Iran, North Korea, and France may have stocks of the virus; these allegations have neither been proved nor disproved (Gellman, 2002; Johnson *et al.*, 2003). During the middle of 2003, a team of top American scientists found no physical or anecdotal evidence to suggest that Iraq was producing smallpox or had stocks in its possession. (Linzer, 2003).

Smallpox can be grown in large quantities and lyophilized for stability. Large amounts can be stored in relatively small containers. The virus would be relatively stable in an aerosol if protected from heat and ultraviolet light (Harper, 1961). The infectious dose may be fairly small (Fenner *et al.*, 1988). An outbreak of 10 cases occurred in Aralsk, Kaza-

khstan, in 1971 and was kept secret by the Soviets. The index case was allegedly on a boat on the Aral Sea when she was apparently infected (Enserink, 2002; Zelicoff, 2003). A recent claim suggests that an aerosol released from a bioweapons installation on an island in the Aral Sea infected her while the boat passed close to the island. The fact that only one of several workers on the boat was infected makes this distant mode of infection improbable. The subsequent additional cases, experiencing close face-to-face contact, were consistent with natural spread of the disease (Henderson, 2003).

“Dark Winter,” a widely publicized political exercise intended to educate public health and government leaders about biological terrorism, used smallpox in its script (O’Toole and Inglesby, 2001). The narrative exaggerated transmission rates, and many leaders and media took the fictitious results literally. BBC Television followed with a docudrama, “Smallpox 2002,” in which a crazed terrorist infected himself and spread smallpox through casual and biologically impossible contact (BBC2 England, 2002). The epidemiology of smallpox renders these fictitious accounts highly improbable. Such zeal to alert us to general biosecurity issues obscures many specific aspects of an attack using smallpox.

While no official statements identify specific modes of spread that terrorists might choose, unofficial speculations abound. A fear-inducing hoax, or virus sprayed into a building’s air circulation system, or the use of nebulizers to infect thousands at a large airport, are all realistic scenarios (Bozzette *et al.*, 2003). The concept of a volunteer suicidal terrorist who walks around a busy mall, or a big city subway, is unrealistic because smallpox renders people so sick that they are rarely mobile, and they are so visibly sick that they would be avoided by the general public (Piller, 2002). Given the respiratory portal of entry of the virus, a spray or aerosol may be the likely method of introduction.

A large aerosol spray from a light airplane, such as a crop duster outfitted to release lyophilized smallpox virus over a public event such as a political rally or sports competition, is technically feasible. The Federal Aviation Administration, or any developed country’s aviation security system, would quickly impound such an unauthorized airplane. If smallpox virus is found, the containment efforts, beginning with a public announcement that attendees of the relevant event should get vaccinated, would abort the attack.

If smallpox virus is introduced into the air circulation of a large building, large numbers of respiratory infections could take place. Several large cities are currently using air filtration systems and doing daily laboratory tests for smallpox, anthrax, and other biohazards. The U.S. government’s “Biowatch” program deploys devices to sample air throughout 31 cities and operates in open air, but not closed arenas (NBC10 News, 2003). The sensitivity and specificity of these tests in realistic situations have not been determined, but they are theoretically very sensitive because they use real-time PCR.

Some terrorist groups are associated with the illegal drug trade (Hastert, 2002). Cocaine is sniffed into the upper respiratory tract, so contamination of cocaine with smallpox virus could seed the infection in a widespread population. Many drug users do not readily access the health care system when they are ill and might not be quickly diagnosed, and thus transmit the virus.

Terrorists might spray virus in an airport bus outside the target nation, and infect passengers bound for widespread destinations within that nation. Multiple simultaneous cases would thus occur in many cities, with resultant panic.

Large numbers of smallpox cases are not necessary for an effective bioterrorist attack. A small number of cases could generate public panic. Terrorists could put a solution of smallpox virus into hand-held atomizers, and station volunteers outside of such places as entertainment theme parks, military installations, and critical industries. The virus could be sprayed directly into the faces of persons leaving such facilities, under the guise of marketing a new perfume, etc. Half a dozen cases, with obvious connections to well-known institutions, could invoke panic and social disruption, such as that which followed the 17 anthrax cases in the United States in 2001.

Terrorists with access to a modern virus laboratory might genetically modify smallpox in ways similar to the published manipulations of ectromelia (Jackson *et al.*, 2001; Roos, 2003). Such a strain could not be tested for pathogenicity because there is no animal model for human infection. Genetically altered strains might pose problems of transmission; alteration of pathogenicity might have unknown effects on the transmissibility of the virus. Experienced intelligence observers feel that terrorists would avoid creating a strain with enhanced virulence. Such strains could devastate developing countries with poor public health systems, and a widespread outbreak would quickly spread to such countries (Johnson *et al.*, 2003). Natural smallpox could similarly boomerang. Terrorists with the ability to manufacture it would realize that an effective attack might cause widespread disease in nations harboring their colleagues. Many such nations have poor public health systems and little vaccine, and would be more devastated than the nation initially attacked (Johnson *et al.*, 2003; Oxford, 2003).

In summary, smallpox virus may exist in “rogue” nations. Scenarios involving aerosol spread of smallpox are technically feasible, but have limitations. Even small numbers of cases might suffice to create considerable panic.

9. PREVENTION

The most important aspect of prevention of a bioterrorist attack using smallpox is reliable intelligence. The location of the virus and the abilities and intent of its possessors drive preventive efforts. Allegations that Iran has weaponized smallpox must be viewed through our knowledge that these allegations have been made by an Iranian opposition group (Warwick, 2002). The claims that France, Iraq, North Korea, and Yemen have the virus await firm data (Gellman, 2002). Unproven statements in an internationally politicized climate must be weighed with evidence-based intelligence. Reliable intelligence, the key factor, is an unknown.

Public health efforts, and the extensive publicity about them, have direct preventive value for averting an attack or a resulting major epidemic of smallpox, and can be emulated in many nations. The announced British strategy is to stockpile vaccine and train a cohort of health workers who can identify and isolate smallpox cases and start surveillance and containment activities (Oxford, 2003). In the months after September 11, 2001, the United States increased its vaccine supply from 15 million doses to about 340 million doses. The supply of VIG increased more than 10-fold. The number of laboratories capable of doing real-time PCR for orthopoxviruses increased from two to at least 50. Courses for clinicians, public health officials, and others have been widely held. Several new websites have been created to assist professionals with the diagnosis and management of smallpox, and acquaint them with all aspects of vaccination. Posters and training materials have been widely

distributed. Nearly 40,000 front-line medical personnel have been vaccinated (Centers for Disease Control and Prevention, 2003f).

In the absence of solid information about the risk of a bioterrorist attack using smallpox, nations face a policy dilemma. If vaccination carried no risk, there would be no dilemma; widespread vaccination would be reinstated. However, vaccinia is a pathogenic live virus. Vaccination carries well-known risks, particularly in populations that are largely naive to the virus, and in which large numbers of persons are immunosuppressed by HIV, posttransplant therapy, cancer chemotherapy, and steroid medication (Lane and Goldstein, 2003).

The potentially fatal complications of vaccination have recently been reviewed (Centers for Disease Control and Prevention, 2003e; Fulginiti *et al.*, 2003; Lane and Goldstein, 2003). Postvaccinial encephalitis occurs about four or five times per million vaccinees, but carries a 25% fatality rate. Progressive vaccinia is rare, but in our highly immunosuppressed population could be more common than in the past. It may be fatal in 20% or more of cases. Eczema vaccinatum is more common, and the background prevalence of eczema (atopic dermatitis) is about three times higher today than in the 1960s when studies of the frequency of eczema vaccinatum were performed. It has a fatality rate of about 1%. Figure 5.3 is the face of an eczematous woman who acquired vaccinia from her child. Recently, myocarditis has been found to occur about once in every 18,000 vaccinees (Arness *et al.*, 2004; Eckart *et al.*, 2004; Halsell *et al.*, 2003). Postvaccinial myocarditis has an unknown fatality rate, but deaths have been reported in the past (Dalgaard, 1957; Ferry, 1977; Finlay-Jones, 1964). In addition to these serious complications, a number of vaccinees suffer from “robust” major reactions, with fever, pain, and inflammation at the site; about 1% develop inconsequential, but sometimes, unsightly rashes (Frey *et al.*, 2002; Grabenstein and Winkenwerder, 2003).

Vaccinia is transmissible by direct contact. Transmission is rare and generally only to very close contacts such as family members sharing a bed (Grabenstein and Winkenwerder, 2003; Neff *et al.*, 2002). The presence of immunosuppressed patients on the wards of major hospitals has kept many medical personnel from accepting vaccination. Careful management of the vaccination site and scrupulous hand hygiene can minimize transmission (Lane and Fulginiti, 2003).

Vaccination is not the only means of preventing smallpox. Rigorous isolation of patients coupled with quarantine of contacts until their incubation period is over will prevent transmission (Bozzette *et al.*, 2003; Eichner, 2003; Eubank *et al.*, 2004; Mack, 2003; Meltzer *et al.*, 2001). The prolonged incubation period (12 days) provides time to allow public health action and education of the population once initial cases are recognized.

9.1 Vaccination Policy

In the absence of circulating smallpox, but the presence of a theoretical threat of a bioterrorist attack, there are several options for the use of smallpox vaccine. In 1980, the United States government’s Advisory Committee on Immunization Practices (ACIP) recommended that vaccinia be reserved for laboratory personnel who work with orthopoxviruses capable of infecting humans (e.g., variola, vaccinia, and monkeypox) (Centers for Disease Control and Prevention, 1980). These guidelines were expanded to include animal handlers working with animals infected with orthopoxviruses.

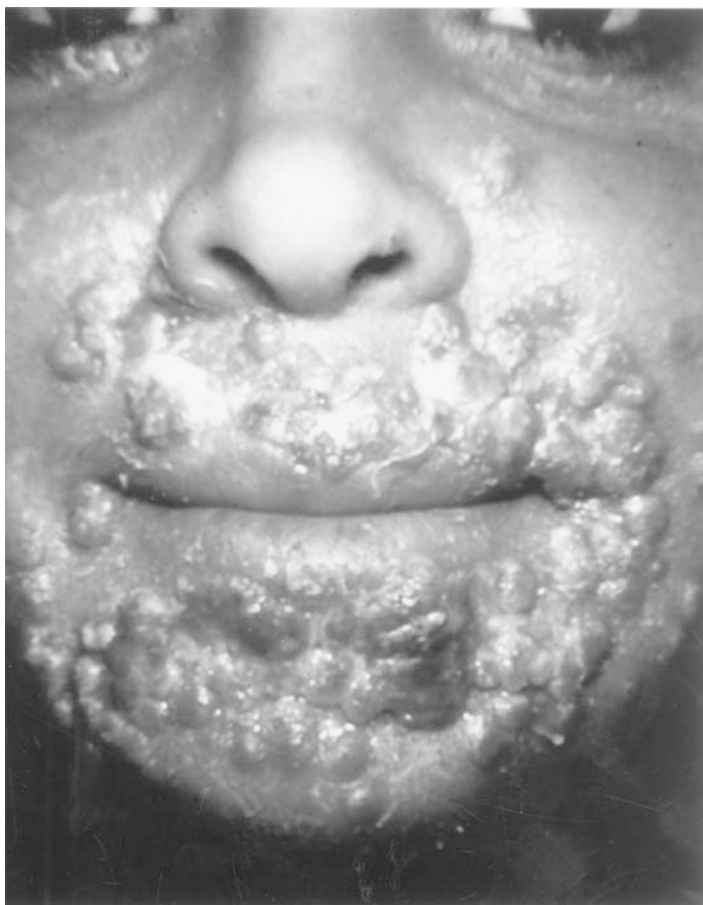


Figure 5.3. Woman with eczema vaccinatum. Photo courtesy of CDC.

After September 11, 2001, when smallpox vaccine in the United States was limited to 15 million doses, the ACIP formed a Smallpox Working Group, which held public hearings and studied scientific data and political opinions. Many public health and academic officials suggested that vaccine be made available to limited numbers of workers who would form response teams in the event of a terrorist attack. In June 2002, the ACIP recommended that vaccine be made available to selected state and local officials with responsibility for protection of public health (Centers for Disease Control and Prevention 2002d). This was consistent with CDC's plan for containment of a smallpox attack and coincided with proof that the 15 million doses of vaccine could be diluted 1:5 (Centers for Disease Control and Prevention, 2002d; Frey *et al.*, 2002), that additional vaccine was on hand, and that production of new vaccine was well under way.

Vaccine supplies are now more than adequate to immunize the entire U.S. population, and suggestions have been made to resume vaccination more widely (Bicknell, 2002; DeRugy and Pena, 2002). Public announcements suggested vaccinating considerable

numbers of health care workers, particularly in big city emergency wards and other areas where initially undiagnosed smallpox cases might seek medical care. Many states sought to revaccinate predominantly older workers who had a past history of vaccination, because the residual immunity in such revaccinees is not trivial, and they are less likely to experience adverse events after vaccination (Hammarlund *et al.*, 2003). The number of health care workers in big city hospitals is large, and they turn over rapidly. Many health care workers vaccinated under such a policy are in frequent contact with patients with HIV, status postorgan transplants, atopic dermatitis, etc. Given the recent data (Frey *et al.*, 2002) that adults given primary vaccination frequently need to take one or more days off work because of fever and malaise, many hospitals expressed concern about the effects of widespread vaccination (Connolly, 2003; Gettleman, 2002). Other “first responders” – including policemen, firemen, ambulance workers, and other emergency medical personnel – should be considered for preevent vaccination (Bush, 2002; Centers for Disease Control and Prevention, 2003g; Stevenson and Altman, 2002). In part reflecting these concerns, in August 2003 the Institute of Medicine recommended shifting emphasis away from vaccinations to focus on measures to improve coordination and quicken response time to any public health threat (Olson, 2003).

Several writers suggest that individuals have the right to decide for themselves about the risks and benefits of vaccination, particularly given the current copious vaccine supply (Bicknell, 2002; DeRugy and Pena, 2002). The morbidity and mortality from vaccinia, the problems of screening potential vaccinees and their household members for contraindications, and the efficacy of surveillance and containment methods for controlling smallpox outbreaks, argue against such a policy (Bozzette *et al.*, 2003; Eichner, 2003; Eubank *et al.*, 2004; Lane and Goldstein, 2003; Meltzer *et al.*, 2001).

The United States stopped routine vaccination in 1972. It could be resumed if the threat of smallpox becomes considerable. Only in a scenario where smallpox becomes widespread would it be wise to resume mass vaccination. Such a scenario would inevitably include inadvertent exportation of the disease to other nations, including those with poor fiscal and public health resources and no vaccine. Such resumption of endemicity of smallpox would be a human tragedy of untold proportions. Thus, developed nations must stockpile vaccine and maintain preventive public health efforts for rapid containment of terrorist-induced outbreaks.

In summary, intelligence about the existence of smallpox in the hands of terrorist groups, and their intent for its use, is the best means of preventing an attack. Readiness to control an outbreak resulting from an attack entails a high index of suspicion among clinicians, a good network of diagnostic laboratory capabilities, and a plan for use of surveillance and isolation techniques to quickly contain outbreaks. Vaccination policies need periodic review, because the risks and benefits of vaccination of various medical and law enforcement groups are controversial. Resumption of widespread vaccination is dangerous and unnecessary.

10. FUTURE DIRECTIONS

The United States has rebuilt its vaccine supply, trained diagnostic laboratories, enhanced the availability of clinical and epidemiologic information, and completed a detailed plan for handling a smallpox attack. What should be done to reduce the threat of

smallpox further? There are scientific and political efforts currently underway to prepare for an outbreak, to reduce its likelihood, and to enhance the safety of vaccines.

The intelligence community and the new Department of Homeland Security have increased the antiterrorism budget and the amount of attention paid to possible bioterrorist threats. Presumably much of this work is classified, but rumors of nations that may still have (illegal) stocks of variola virus are under investigation.

Rapid detection of variola virus in the environment would be useful. Air filtration systems are being improved so that huge volumes of air inside large buildings, such as commercial or government offices, can be routinely and rapidly filtered. The filters are then tested by PCR for the presence of variola virus DNA (Fackelmann, 2003; NBC10News, 2003). The sensitivity and specificity of such systems cannot be calculated, because no real smallpox has been found or can be injected into these systems. Given the high sensitivity of PCR, they should be good at detecting variola.

A test that could find virus in the throats of patients early in the prodrome could help identify patients who need immediate isolation in the event of an outbreak. Such tests have been developed, again using PCR techniques, and are being explored using material taken from experimentally infected monkeys (Jahrling *et al.*, 2004).

Antiviral compounds, particularly ones derived from cidofovir and its analogues, are being investigated. A nontoxic antiviral with good activity against variola, or indeed against the serious complications of vaccinia, would change the risk-benefit calculations for both pre- and postevent vaccination programs. Compounds that are more soluble and thus more bioavailable than cidofovir are currently being screened for activity against variola (Bray and Roy, 2004; Langbein, 2003; Nyets and DeClercq, 2003; Smeets and Sidwell, 2003).

A vaccine that provides protection against variola but is less pathogenic than vaccinia would be useful. Several candidate strains derived from vaccinia are being actively investigated. Modified Vaccinia Ankara, NYVAC, and LC 16m8 are prominent among these attenuated strains (Bonnilla-Guerrero and Poland, 2003; Drexler *et al.*, 2003; Earl *et al.*, 2004; Henderson, Borio, and Lane, 2003; Lane and Goldstein, 2003; McCurdy *et al.*, 2004).

Ultimately, the United States, Russia, and the World Health Organization will have to decide whether retaining the existing legal stocks of variola virus is worthwhile. As long as the virus exists in any laboratory, terrorist groups may claim that one motivation for retaining the virus is its potential as a bioweapon. If the stocks are destroyed, this argument no longer exists. International cooperation under the aegis of the World Health Organization is needed to affirm the illegality of biowarfare using variola, and maximize efforts to find and destroy illegal stockpiles (Breman *et al.*, 2003).

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