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Smallpox: Clinical Features, Prevention, and Management

Roy Guharoy, Robert Panzik, John A Noviasky, Edward P Krenzelok, and Donald C Blair

OBJECTIVE: To describe a general overview of smallpox, clinical presentation, diagnosis, adverse events, and management of both pre- and postexposure vaccination.

DATA SOURCES: Literature was identified by search of MEDLINE (1966–June 2003) and *International Pharmaceutical Abstracts* (1966–May 2003) databases using the key terms smallpox, bioterrorism, biological warfare, and smallpox vaccine.

STUDY SELECTION AND DATA EXTRACTION: Articles identified from data sources were evaluated, and relevant information was included in this review.

DATA SYNTHESIS: Smallpox is spread by human-to-human contact with an infected host and therefore can be contagious. The mortality rate for smallpox is approximately 30%. While the disease was completely eradicated by 1980 with successful use of smallpox vaccine, concern has been raised that smallpox may emerge as a tool of bioterrorism. This concern, combined with the reality of current smallpox vaccination programs in the military and selected civilian populations, mandates a clear understanding of vaccination-related adverse events and contraindications by all healthcare professionals. The vaccine may cause moderate to severe adverse events such as eczema vaccinatum, progressive vaccinia, and generalized vaccinia.

CONCLUSIONS: The balance between the risks and benefits of mass vaccination in prevention of an epidemic is not clear. The Centers for Disease Control and Prevention has established a guideline for appropriate use of smallpox vaccine in the civilian population.

KEY WORDS: bioterrorism, immunization, smallpox.

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Throughout the history of mankind, infectious disease has been a limiting factor in our survival. Both viruses and virulent bacteria have ravaged entire populations on every continent throughout history. In some instances, various pathogen-related epidemics have resulted in profound mortality rates in towns, countries, and even continents. The Bubonic Plague, or Black Death, allegedly killed half of Europe's population in the 14th century. However, the impact of plague may pale in comparison to the societal impact of the dreaded variola virus, smallpox.

Smallpox has been a problematic infectious disease of mankind for thousands of years. It is believed that smallpox affected human existence in northeastern Africa 12 000 years ago.[1] Pockmarks have been identified on the mummies of the 18th and 20th Egyptian dynasties. In 1350 BC, Egyptians inadvertently infected Hittite populations during the Egyptian–Hittite war, resulting in a massive epidemic and claiming the lives of the king and his heir. During conquest of the New World, the variola-naïve Native American Indians suffered extensively from the inadvertent introduction of smallpox by the Spanish, English, and French.[1,2] The decimated Native American population resulted in decreased resistance to the European conquest of North America.

One of the first known examples of biological warfare involved the use of variola virus in 1763.[2] Although this premise is controversial, British forces in America are

Author information provided at the end of the text.

thought to have used the scabs from smallpox victims to contaminate blankets that were subsequently distributed to American Indians.[3] A massive smallpox epidemic resulted, allowing the English to easily invade new territories in the Ohio River Valley.[2]

Early in the history of this disease, it was recognized that persons previously infected with smallpox developed immunity to subsequent exposure. The Chinese first practiced immunization in the 17th century using ground-up scabs from persons previously infected.[1,4] Traders probably passed this art throughout the world, and knowledge of this practice arrived in Europe in the 18th century. In rural societies, knowledge of immunization against smallpox following infection with cowpox was common, and vaccination was practiced among groups of nobility. Immunization using the draining exudate from the pustules of persons infected with cowpox was introduced by Edward Jenner in 1788. This was then injected into disease-naïve persons to protect against smallpox. Unfortunately, Jenner's peers did not view many of his practices as being credible until 1799,[1,4] after which vaccination became a universally acceptable practice.

Smallpox epidemics continued to affect the world's population until eradication of the disease in the late 20th century. In 1980, the World Health Organization (WHO) announced global smallpox eradication.[5] One of the last major smallpox epidemics in the US occurred in Boston between 1901 and 1903; there were 1596 reported cases and 270 deaths.[6] The last known natural infection of variola minor was documented in Somalia in 1977.[6] Unfortunately, a laboratory mistake in Birmingham, England, led to accidental infection of a 40-year-old woman in 1978.[1] After this incident, all variola stock in western nations were sent to Atlanta to be stored at the Centers for Disease Control and Prevention (CDC). Currently, the only other known stockpile of variola is stored in Novosibirsk, Russia.[4,7] The WHO ordered the destruction of all variola samples by June 1999, but this has yet to be completed by either the US or Russia.[8]

With the collapse of the Soviet Union, it is suspected that samples stored within those countries were purchased by rogue nations. Similarly, it is unknown whether all specimens were destroyed by countries other than the US and Russia following the Cold War.[4] Thus, the threat of bioterrorism with smallpox remains a possibility. Dispersal of smallpox by a terrorist organization would be devastating, especially considering that routine vaccination has not occurred in more than 30 years in the US.[4,9]

Virology

Variola is a member of the virus genus Orthopoxvirus and family Poxviridae and is characterized as a double-stranded DNA virus.[3,4,7,10] Viruses similar to variola include cowpox and monkeypox. The virus measures approximately $300 \times 250 \times 200$ nm and is characterized by a large, brick-shaped appearance on electron micrograph.[4] Variola replicates in the cytoplasm of an infected cell and invades the epithelium of the dermal layer. Variola only infects humans and cannot be acquired from another species.[11] Past outbreaks were more common during winter and early spring since the aerosolized variola survives longer in low humidity and low temperature environments.

Two forms of variola virus exist: minor and major.[12,13] Smallpox secondary to variola major is implicated in 90% of the cases. Variola minor may affect only 2% of unvaccinated persons, but may present in up to 25% of vaccinated hosts.[12,13]

Pathogenesis

Smallpox is a serious, contagious, and sometimes fatal infectious disease. Exposure to an infected individual by direct contact, body fluid contact, and aerosolized inhalation begins the pathogenesis of the disease process.[14] Manifestations of the disease usually appear within 7–17 days (average incubation 12 days) after exposure, beginning with high fever, myalgia, and headache. A maculopapular rash erupts, often beginning on the face and neck of the infected person. The lesions spread throughout the epidermis and appear simultaneously.[3,4] After 1–2 days, the rash papules become vesicular and pustular.[4] Vesicles appear round and firm with dermal involvement and measure 2–5 mm in diameter. Crusting and scabs appear 9–10 days after initial exposure.[3,4] Pitting scars are common following smallpox resolution. The disease can be spread by airborne droplets until the skin scabs fall off.[4] Some patients may experience a temperature spike 3–5 days following initiation of the prodrome, which may indicate secondary bacterial infection, a marker of increased mortality. In most cases, death secondary to smallpox is a result of toxemia, pneumonia, or bacteremia.

Mortality rates differ depending upon the strain of variola involved. Variola minor, more common among patients previously vaccinated for smallpox, has a mortality rate of approximately 1%.[3,7] On the other hand, variola major may be lethal in up to 30% of cases.[3,7] Much higher mortality rates are seen with hemorrhagic and malignant forms of variola, characterized by a shorter incubation period, severe prodromal illness, and petechiae, as well as cutaneous and mucosal hemorrhage.[3]

Morbidity following smallpox infection is common. Pockmarks are noticeable in up to 80% of smallpox survivors, and blindness from viral keratitis occurs in approximately 1% of affected patients.[4] The incidence of arthritis among smallpox survivors who were afflicted with the disease as a child is estimated at about 2%. Although very uncommon, encephalitis can occur in patients infected with smallpox, possibly resulting in retardation or death.[4]

Diagnosis

Confirmation of smallpox is problematic as it may be confused with chickenpox or other dermal conditions. Quick diagnosis is imperative to prevent spread of the disease to other persons and overall mortality. In order to sys-

tematically assess possible smallpox, the CDC has created a method for diagnosis based on major and minor criteria (Table 1).[15] The risk of smallpox infection is based upon characteristics that a patient exhibits during the prodrome.[3,15] Patients at high risk of having variola infection must meet all 3 major criteria. Moderate-risk individuals have a typical prodrome and must meet at least one of the major criteria or ≥4 minor criteria. Low-risk patients have ≥4 minor criteria with or without a febrile prodrome. Differential diagnosis should involve testing for varicella zoster virus and other viral infections that resemble smallpox manifestations.[3] Prior vaccination against chickenpox, round rather than oval lesions, and centrifugal rather than central distributions of rash and lesions on the patients' soles and palms suggest smallpox.[4] The rash of human monkeypox appears like smallpox clinically, but patient's with monkeypox often have lymphadenopathy. Coxsackievirus or measles virus can cause morbilliform rash on the face and can be confused with early smallpox.

The use of electron microscopy greatly enhances confirmation of smallpox diagnosis, as does the use of polymerase chain reaction (PCR) technology. Using primer pairs, a specific diagnosis of variola infection can be made quickly in virtually all hospitals using commercially available PCR assay.[5] Methods of diagnosis using immunoglobulin M responses may increase the sensitivity and specificity of a diagnosis when using other diagnostic tools.[4]

A suspected case of smallpox is a public health and medical emergency and should be reported immediately to the local and/or state health department. Following notification, samples of pustules, skin lesions, vesicles, blood, and tonsillar swabs must be sent to the CDC for further investigation.[15]

Table 1. CDC Criteria for Smallpox Evaluation[15]

Major Criteria	Minor Criteria
Febrile prodrome occurs 1–4 days before rash onset (38.3 °C) and at least one	Centrifugal distribution greatest concentration of lesions on face and distal extremities
of the following: prostration, headache, backache, chills,	Lesions first appear on face, oral mucosa, or forearms
vomiting, or severe abdominal pain	Skin lesion progression over a course of days
Classic smallpox lesions deep-seated, firm/hard, round,	Lesions on palms of hands and/or soles of feet
well-circumscribed vesicles or	Patient appears toxic or moribund
pustules; as they evolve, lesions may become umbilicated or confluent	Slow rash evolution lesions evolved from macules to papules to pustules over days
Lesions in the same stage of development on any one part of the body (eg, face, arms), all the lesions are in the same stage of development (ie, all are vesicles or all are pustules)	(each stage lasts 1–2 days)

CDC = Centers for Disease Control and Prevention.

Treatment

Successful smallpox management involves isolation of the infected person(s), preferably in a negative-pressure room. Isolation of the infected person is critical during treatment and should last for at least 17 days.[3] Healthcare workers should wear appropriate airborne and contact precaution garments (disposable gloves, gowns, shoe covers, properly fitted masks) to prevent spread of this highly contagious disease.

There is no smallpox treatment approved by the Food and Drug Administration (FDA). Most of the medical care provided is supportive and, in patients with suspected secondary bacterial infection, broad-spectrum antibiotics with β-lactamase inhibition should be administered.[16] Cidofovir, approved for treatment of cytomegalovirus-induced retinitis, may be of use in the treatment and prevention of smallpox. In vitro, cidofovir has shown efficacy against various poxviruses including vaccinia, camelpox, and monkeypox.[17] In animals with cowpox, treatment with cidofovir decreased mortality by 60–100%.[18] Although the treatment is unproven, cidofovir may prove useful, especially in persons with contraindications to the vaccinia-derived vaccine. Ophthalmic keratitis may be treated with idoxuridine.[4]

Vaccination

Vaccination remains the primary method in reducing smallpox incidence in the case of a bioterrorism event. Vaccination has not been routine among American civilians since 1972, although the military continued to vaccinate until 1985.[1] Since vaccination is believed to offer protection for only 5–10 years to the majority of the population, virtually everyone in the US is susceptible to variola.[4,19,20] Vaccination using vaccinia is believed to create a cytotoxic T-cell and B-cell response, resulting in antibody formation.[4] Subsequent exposure to variola should result in minor or no response.

The recommended means of vaccination is to administer 15 needle pricks to the skin, usually in the deltoid region of the arm, in a circular motion using a bifurcated needle dipped into the vaccine.[11] If the vaccination is administered properly, a small amount of blood should appear at the vaccination site. If blood is not present, the procedure must be repeated. Following administration, the CDC recommends placing a semipermeable membrane bandage over the area vaccinated until the underlying skin has healed.[21] The bandage should be changed every 1–3 days. Also, at least one layer of clothing should cover the applied bandage.[21] A primary reaction, or erythema, at the vaccination site should occur by day 1.[15] If the primary reaction does not occur, the person should be revaccinated. Six to 8 days following successful vaccination, a grayish pustule 1–2 cm in diameter should appear. The pustule will spread peripherally, then crust 3–5 days later. A dark crust with local edema results and will last for approximately 3 weeks. The appearance of the palpable pustule for 6–8 days confirms successful vaccination. Revaccination should occur at least every 5 years in persons needing protection from smallpox.[4,19]

The Advisory Committee on Immunization Practices (ACIP) and the Health-care Infection Control Practices Advisory Committee (HICPAC) have issued the following exclusion criteria for smallpox vaccination, unless the patient is directly exposed to the virus or at great high risk of exposure to smallpox virus: history or presence of atopic dermatitis or eczema; acute, active, or exfoliative skin conditions; pregnant and breast-feeding women; immunocompromised patients (eg, HIV, AIDS, leukemia, lymphoma, immunosuppressive drugs); serious allergy to any component of the vaccine; and children <1 year old.[22,23]

Adverse Reactions

Unfortunately, vaccination of persons using vaccinia is not benign. In 1984, an HIV-infected military trainee developed severe generalized vaccinia covering the vast majority of his body, necessitating the need for treatment with vaccinia immune globulin.[24] Indeed, adverse reactions, as well as rarity of disease, played a role in the discontinuation of routine smallpox vaccination in the US in 1972.[25-31] Severe adverse reactions are rare, but without active disease, the risk seemingly outweighs the benefit. Another reason for reluctance for mass vaccination is the contagious nature of vaccinia.[16,32] Since vaccination has not been routinely offered in the US in 30 years, most information on incidence and severity of vaccination adverse reactions is retrospective in nature (Table 2).[26-31,33,34]

Most adverse reactions occurring from administration of smallpox vaccine are relatively mild. Examples include headache, myalgias, rash, chills, and fever (Figure 1).[15] More serious adverse effects associated with smallpox vaccination include secondary bacterial infections, vaccinia necrosum, eczema vaccinatum, generalized vaccinia, erythema multiforme, accidental inoculation, and encephalitis.[25-31] Secondary bacterial infections following vaccinia administration are rare.[25] Vaccinia necrosum has been defined as dermal involvement that appears malignant, evolving from the vaccination site and progressing to other areas of the body.[25-27,29-31] It has also been termed "progressive vaccinia" (Figure 2). Eczema vaccinatum is a generalized spreading of lesions throughout other areas of the body when the patient has an active or past history of eczema. Generalized vaccinia is the spread of lesions from the vaccination site to other areas of the body in persons without eczema or a past history of eczema (Figure 2). Erythema multiforme is a maculopapular rash developing shortly after vaccination in a person without risk factors for adverse events.[31] This condition manifests 7–10 days following vaccination and usually clears within 3–5 days.[25] Accidental infection accounts for 50% of all complications following primary and revaccination.[15] It is defined as unintentional delivery of vaccinia to other areas of the body, particularly the eyes, nose, genitalia, rectum, and mouth.[25-27, 29-31] Encephalitis occurs only with use of primary vaccines and is influenced by the strain of virus used for vaccination.[15] The reported incidents were lower with the New York City Board of Health (NYCBOH) strain used in the US than with the strains used in Europe. The most common serious adverse reactions involving children are generalized vaccinia and eczema vaccinatum.[26] The incidence of these reactions decreases with increasing age. Incidences of accidental infection, vaccinia necrosum, and encephalopathy remain unchanged throughout childhood and adulthood.[29] Mortality rates secondary to vaccinia are estimated at approximately 1:2 000 000.[27-32,35]

Table 2. Comparison of Smallpox Vaccine Adverse Events—1960s vs 2003

Study	Patients Vaccinated (N)	Adverse Events Reported	
		N	%
Events reported in the 1960s			
1963 National survey[26]	14 014 000	433	0.003
1963: 4 States survey[29]	668 000	435	0.065
1968 National survey[28]	14 168 000	572	0.004
1968: 10 States survey[30]	1 648 000	968	0.058
1968 Kentucky survey[27]	241 000	109	0.045
1968 Maryland survey[31]	275 000	105	0.038
TOTAL	31 014 000	2622	0.008
Events reported in 2003			
civilian population[33]	38 257	127	0.331
military population[34]	450 293	144	0.032
TOTAL	488 550	271	0.055

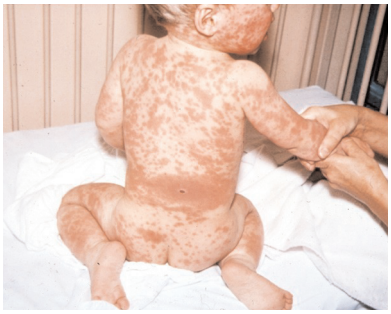

Figure 1. Example of nonspecific rash in an infant aged 14 months with a vaccination site on the small of his back. He has extensive erythematous patches over his entire body, except for relative sparing of the soles of the feet. Reproduced with permission of J Michael Lane MD and Christine G Casey MD.

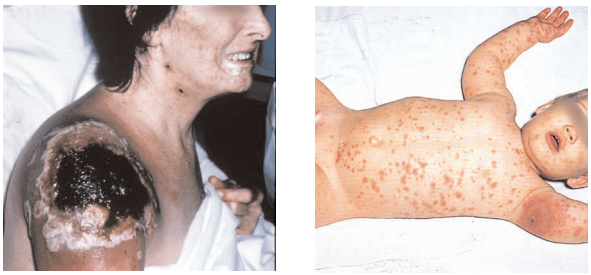

Figure 2. Progressive vaccinia in a woman, aged 62 years, with chronic lymphocytic leukemia (left). Note the distant lesions on her face, neck, and chest and the progression of vaccination site. Generalized vaccinia with a substantial erythematous base in an infant (right). Reproduced with permission of J Michael Lane MD and Christine G Casey MD.

Unfortunately, these results cannot be extrapolated to a contemporary mass vaccination initiative. In fact, adverse reactions, including those causing serious morbidity and mortality, could have much higher incidences in populations that were not identified or as prevalent at the time of the original studies. For example, patients infected with HIV, and those on chronic steroid therapy, chemotherapy, and radiation therapy, would be at higher risk for adverse reactions. In addition, the older data consider persons who were revaccinated using vaccinia, which carries a much lower chance of adverse drug reactions.[25-31]

Although a death certificate study of vaccinia-associated deaths in the US conducted during 1959–1966 and 1968 did not identify any deaths associated with cardiac complication,[36] they have been reported in Australia and Europe and appear to be associated with myocarditis.[35,37-39] Data from the current US smallpox vaccination program are consistent with a causal association between vaccination and myopericarditis, although this association has not been proven.[40]

Adverse Reactions from Current Vaccination Program

The CDC, the FDA, and state health departments are conducting surveillance for vaccine-associated adverse events among the civilian population. From January 24 to August 8, 2003, the vaccine was administered to 38 257 civilian healthcare and public health workers as part of an effort to prepare the US for a possible terrorist attack using smallpox.[33] Active surveillance is being conducted for adverse events and for vaccinia transmission. As of August 8, 2003, 127 cases of serious adverse events had been reported among civilians since the beginning of the smallpox vaccination program.[33] This includes 3 cases of generalized vaccinia, 21 cases of inadvertent nonocular inoculation, 3 cases of ocular vaccinia, one case of encephalitis, and 22 cases of myocarditis/myopericarditis (ie, chest pain, electrocardiogram changes).[22,33,40,41] There were 2 ischemic cardiac deaths that occurred in civilian vaccinees aged 55 and 57 years.[33,41]

As of May 28, 2003, a total of 36 cases of mild generalized vaccinia, one case of erythema multiforme, 48 cases of self-inadvertent inoculation, 21 cases of contact vaccinia, one case of encephalitis, and 37 cases of myopericarditis have been identified among approximately 450 293 vaccinees (70.5% primary, 29.5% revaccinees) in the military smallpox vaccination program.[34] Thirty-six of 37 patients with myopericarditis had elevated cardiac enzyme levels. No vaccination-related fatalities occurred. There was one case of ischemic cardiac death in a 55-year-old person with a history of smoking and hyperlipidemia.[34,41] He developed a myocardial infarction and was found unresponsive in a vehicle 5 days after receiving smallpox vaccine and 2 other inactivated vaccines. Resuscitation was attempted, but the patient died the next day. Autopsy showed acute thrombosis of the right anterior descending coronary artery, 3-vessel coronary artery disease with 75–80% occlusion, left ventricular hypertrophy, and cardiomegaly.[34] It is interesting to note that the reported adverse event rates in the military population were largely below those reported in the 1960s and 1970s. However, factors such as differences in age, prior vaccination, population immunity, and underreporting may affect the rate.[34]

Based on the cardiac adverse events reported in both civilian and military populations, as a precautionary measure, the CDC recommends that persons with cardiac disease with or without symptoms (eg, previous myocardial infarction, congestive heart failure, angina, or cardiomyopathy) be excluded from vaccination during the current smallpox preparedness program.[33,42,43] The Department of Defense is now following the CDC's updated recommendations to exclude high risk patients.[42] Meanwhile, people directly exposed to the smallpox virus will be vaccinated unless the risk exceeds the benefit.[43]

Vaccinia can be spread to other individuals. Unlike smallpox, vaccinia is not spread through aerosolized or small-droplet forms, but rather by direct contact with infected material. Deaths have been reported from contagious spread of vaccinia.[16,31] In fact, 12 of 68 deaths occurring from vaccinia were the result of secondary vaccinia infection in previously unvaccinated persons.[16] Adequate site care and frequent handwashing following vaccination will prevent transmission to other persons.[15]

Treatment of adverse reactions secondary to vaccinia administration is dependent upon severity. For example, a mild case of generalized vaccinia in a relatively healthy adult does not require emergency actions. On the other hand, encephalitis may require aggressive intensive care. Patients with severe adverse reactions should be isolated to prevent further environmental harm,[16] such as secondary bacterial infections of the skin and lungs, that could easily occur due to immunocompromised state. Vaccinia immune globulin (VIG), cidofovir, and topical ophthalmic drugs are the therapies used to treat adverse events. VIG should be administered in cases of adverse reactions that are life threatening and may be indicated for eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and inadvertent inoculation of the eye or eyelid without vaccinial keratitis.[15,16] VIG is not indicated for treatment of post-vaccination encephalitis. Mild adverse events such as local pain, erythema, and swelling at the injection site have been reported with VIG use. Rare severe adverse events include hypotension, anaphylaxis, renal dysfunction, and aseptic meningitis syndrome with VIG use.[16]

Bioterrorism Management

Bioterrorism is defined as "the use of microorganisms to kill or harm an enemy or a population of people, food, or livestock by whatever means necessary to demoralize, intimidate, or conquer.[11,44] Unfortunately, the world today is extremely volatile, and bioterrorism involving variola release should be considered. In the event of a biological attack on a city the size of New York, it has been hypothesized that 110 000 deaths could occur within one year.[9]

With that in mind, the CDC has established guidelines for medical personnel and medical facilities to follow in the event of attack using variola. Indeed, a high level of preparedness is crucial in limiting infection to healthcare personnel and patients within a hospital who may be exposed to smallpox.[45,46] Moreover, the US government released a limited supply of vaccinia for use in a prevaccination program involving 450 000 medical personnel.[47]

In the case of suspected bioterrorism involving smallpox, diagnosis and containment (quarantine) of infectious persons are critical to preventing contagious spread and resulting epidemic.[48-50] The CDC recommends immediate isolation of a suspect case, vaccination, and tracing of other persons who came within 6.5 feet of the infected individual.[15,51] Patients should remain in isolation until all scabs have broken off the epidermal layer.[44] Any person in contact with an infected patient must be evaluated and monitored for fever. Any new fever >38 °C within 17 days following exposure should be considered a possible new case of smallpox.

If a documented outbreak of variola occurs, priority-groups should be identified.[15,21] These groups include close contacts, household members of the infected person, medical personnel treating the infected person, laboratory personnel, and many others.[15] One hundred twenty million (42%) members of the US population were born after 1972 and have never been vaccinated.[52] The other 162 million have not been vaccinated for at least 30 years. A policy on mass vaccination might cost between 125 and 500 lives. In June 2002, HICPAC and ACIP recommended that, for the first stage of a pre-event smallpox vaccination program, each acute care institution should identify a group of healthcare workers (respiratory therapists, radiology technicians, medical subspecialists, emergency department, intensive care unit, general medical, housekeeping, security, primary care house staff).[21-23] More recently, in December 2002, President Bush announced the volunteer National Smallpox Immunization Plan (NSIP) to immunize 500 000 healthcare workers who would serve as first responders in the event of mass exposure to smallpox, and the program was implemented in January 2003.[23]

In the US, vaccine is made by using the NYCBOH strain of vaccinia grown on the skin of cows.[52] New vaccine is currently under development using the same NYCBOH strain on cell cultures (vero cells, human MRC5 cells). It is expected to be approved by the FDA in 2004.

Currently, about 70 million doses of smallpox vaccine are available.[52] Initially, this raised concern that not enough vaccine existed for the masses. Meanwhile, a study measuring clinical response of vaccinia vaccination in undiluted and 1:10 geometric dilution found that serial dilution had no effect upon the immunologic response and efficacy of the vaccine.[51,53] This procedure increases available vaccine tenfold. Until a bioterrorist outbreak occurs, limited vaccination of essential medical personnel will be the only drain on current stores of the vaccine. This will expose a minimum number of people to the dangers of the vaccine while protecting those who would most likely become infected.[19] However, diluted vaccines have not been licensed and must be administered under an Investigational New Drug protocol.

In the event of a need for mass vaccination, factors such as thorough staff training, patient screening, patient education, and attention to bandaging are crucial tools for successful implementation with fewer adverse events.

Summary

Because of the active role the US plays in world politics, we have become increasingly vulnerable to bioterrorism attacks. Unfortunately, there is a possibility that variola exists outside of government-controlled stocks. Recently, some experts have discussed the need for mass vaccination to prevent an epidemic in the case of smallpox release. However, balance between the risks and benefits of mass vaccination are not clear since the number of deaths in the 21st century would be considerably higher than the numbers in the late 1960s because of the significant increase in the number of severely immunodeficient patients in our society.

It seems appropriate to vaccinate the first responders who might be involved in caring for patients with suspected smallpox and their contacts since no current creditable threat exists. Most importantly, well-organized team efforts between area hospitals are critical for optimal utilization of available resources and would strengthen the level of preparedness. The current first-response strategy would help build the vaccine supplies, develop laboratory expertise, and train first-response clinicians.

Healthcare providers needing assistance in evaluating a vaccinee with a serious adverse event should contact their state health department or CDC's Clinician Information Line (877/554-4625). The information line is staffed 24 hours a day, 7 days a week for assistance with smallpox adverse event reporting.

Roy Guharoy PharmD FCP FCCP FASHP, Director of Pharmacy Services and Associate Professor of Medicine, Associate Chief, Section of Clinical Pharmacology, SUNY—Upstate Medical University, Syracuse, NY

Robert Panzik PharmD, Staff Pharmacist, RiteAid, Shamokin, PA

John A Noviasky PharmD, Clinical Coordinator, St. Elizabeth Medical Center, Utica, NY

Edward P Krenzelok PharmD FAACT ABAT, Director, Pittsburgh Poison Center; Professor of Medicine and Pharmacy, University of Pittsburgh, Pittsburgh, PA

Donald C Blair MD, Chief of Infectious Diseases, Professor of Medicine, SUNY—Upstate Medical University

Reprints: Roy Guharoy PharmD FCP FCCP FASHP, Room 119, University Hospital, 750 E. Adams St., Syracuse, NY 13210-2375, fax 315/464-4221, GuharoyR@Upstate.edu

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References

1. Barquet N, Domingo P. Smallpox: the triumph over the most terrible of the ministers of death. Ann Intern Med 1997;127:635-42.
2. Patterson KB, Runge T. Smallpox and the Native American. Am J Med Sci 2002;323:216-22.

3. Bronze MS, Huycke MM, Machado LJ, Voskuhl G, Greenfield RA. Viral agents as biological weapons and agents of bioterrorism. Am J Med Sci 2002;323:316-25.
4. Breman JG, Henderson DA. Current concepts: diagnosis & management of smallpox. N Engl J Med 2002;346:1300-8.
5. 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;33:2069-76.
6. Albert MR, Ostheimer KG, Liewehr DJ, Steinberg S, Breman J. Smallpox manifestations and survival during the Boston epidemic of 1901 to 1903. Ann Intern Med 2002;137:993-1000.
7. Varkey P, Poland GA, Cockerill FR, Smith TF, Hagen PT. Confronting bioterrorism: physicians on the front line. Mayo Clin Proc 2002;77:661-72.
8. Radetsky M. Smallpox: a history of its rise and fall. Pediatr Infect Dis 1999;18:85-93.
9. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: the case for mass vaccination. Proc Natl Acad Sci 2002;99:10935-40.
10. Esposito JJ, Knight JC. Orthopoxvirus DNA: a comparison of restriction profiles and maps. Virology 1985;143:230-51.
11. Sibley CL. Smallpox vaccination revisited. Am J Nursing 2002;102(9): 26-32.
12. Rao AR. Smallpox. Bombay, India: Kothari Book Depot, 1972.
13. Dixon CW. Smallpox. London: J & A Churchill, 1962.
14. Hope Simpson RE. Infectiousness of communicable diseases in the household (measles, chickenpox, and mumps). Lancet 1952;2:549-54.
15. Centers for Disease Control and Prevention. Interim smallpox response plan and guidelines. www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/index.asp (accessed 2003 Mar 1).
16. Sepkowitz KA. Current concepts: how contagious is vaccinia? N Engl J Med 2003;348:439-46.
17. Clercq ED. Cidofovir in the treatment of poxvirus infections. Antiviral Res 2002;55:1-13.
18. Bray M, Martinez M, Smee DF, Kefauver D, Thompson E, Huggins JW. Cidofovir protects mice against lethal aerosol or intranasal cowpox virus challenge. J Infect Dis 2000;181:10-9.
19. Baltimore RS, McMillan JA. Smallpox and the smallpox vaccine controversy. Pediatr Infect Dis 2002;21:789-90.
20. Arita L. Duration of immunity after smallpox vaccination: a study on vaccination policy against smallpox bioterrorism in Japan. Jpn J Infect Dis 2002;55:112:116.
21. Wharton M, Strikas RA, Harpaz R, Rotz L, Schwartz B, Casey CG, et al. Recommendations for using smallpox vaccine in a pre-event vaccination program. MMWR Dispatch 2003;52(Feb 26):1-16.
22. Update: adverse events following civilian smallpox vaccination—United States 2003. MMWR Weekly 2003;52:475-7. www.cdc.gov/mmwr/preview/mmwrhtml/mm5220a5.htm (accessed 2003 Jun 2).
23. Babinchak TJ. Smallpox vaccine. P&T 2003;28:457-9.
24. Redfield RR, Wright DC, James WD, Jones TS, Brown C, Burke DS. Disseminated vaccinia in a military recruit with human immunodeficiency virus (HIV) disease. N Engl J Med 1987;316:673-6.
25. Brown EH. Complications of smallpox vaccination. Postgrad Med 1965;41:634-5.
26. Neff JM, Lane M, Pert JH, Moore R, Millar JD, Henderson DA. Complications of smallpox vaccination: national survey in the United States, 1963. N Engl J Med 1967;276:125-32.
27. Nitzkin JL, Anderson L, Skaggs JW, Hernandez C. Complications of smallpox vaccination in Kentucky in 1968: results of a statewide survey. J Kentucky Med Assoc 1971;69:184-90.
28. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: National Surveillance in the United States. N Engl J Med 1969;281:1201-8.
29. Neff JM, Levine RH, Lane M, Moore R, Millar JD, Henderson DA. Complications of smallpox vaccination in the United States 1963 II: results obtained by four statewide surveys. Pediatrics 1967;39:916-23.
30. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination in the United States: national surveillance in the United States. N Engl J Med 1969;281:1201-8.
31. Mellin H, Neff JM, Garber H, Lane JM. Complications of smallpox vaccination: Maryland. Hopkins Med J 1968;126:160-8.
32. Neff JM, Lane JM, Fulginiti VA, Henderson DA. Contact vaccinia—transmission of vaccinia from smallpox vaccination. JAMA 2002;288:1901-5.
33. Update: adverse events following civilian smallpox vaccination—United States 2003. MMWR Weekly August 29, 2003;52:819-20. www.cdc.gov/mmwr/preview/mmwrhtml/mm5234a4.htm (accessed 2003 Oct 4).
34. Grabenstein JD, Winkenweerder W. U.S. military smallpox vaccination program experience. JAMA 2003;289:3278-82.
35. Finlay-Jones LR. Fatal myocarditis after vaccination against small pox: report of a case. N Engl J Med 1964;270:41-3.
36. Lane JM, Ruben FL, Abrutyn E, Millar JD. Deaths attributable to smallpox vaccination, 1959 to 1966, and 1968. JAMA 1970;212:441-4.
37. Ferry BJ. Adverse reactions after smallpox vaccination. Med J Aust 1997;2:180-3.
38. Karjalainen J, Heikkila J, Nieminen MS. Etiology of acute infectious myocarditis. Acta Medica Scand 1983;213:65-73.
39. Helle EJ, Koskenvuo K, Heikkila J, Pikkaranien J, Weckstrom P. Myocardial complications of immunizations. Ann Clin Res 1978;10:280-7.
40. Supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. JAMA 2003;289: 2064-5.
41. Cardiac deaths after a mass smallpox vaccination campaign—New York City, 1947. MMWR Weekly October 3, 2003;52:933-6. www.cdc.gov/mmwr/preview/mmwrhtml/mm5239a1.htm (accessed 2003 Oct 6).
42. Grady D. Exclude more from smallpox vaccinations. New York Times, March 29, 2003. www.nytimes.com/2003/03/29international/worldspecial/29SAL.html?ex=1050117048&ei=1&en+cdec90c387ad0cb0 (accessed 2003 Mar 31).
43. Heart patients not to receive smallpox vaccine for now. ASHP News, March 29, 2003. www.ashp.org/news/showarticle.cfm?id=3357 (accessed 2003 Apr 1).
44. Stillsmoking K. Bioterrorism—are you ready for the silent killer? AORN J 2002;76(3):433-4,437-40,442,444-50.
45. Beeching NJ, Dance DA, Miller AR, Spencer RC. Biological warfare and bioterrorism. BMJ 2002;324:336-9.
46. Henderson DA. The looming threat of bioterrorism. Science 1999;283: 1279-82.
47. Nierengarten MD. Positive response to US smallpox vaccine policy. Lancet Infect Dis 2003;3:60.
48. Franz DR, Jahrling PB, Friedlander AM, McClain DJ, Hoover DL, Bryne WR, et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278:399-411.
49. Steinhauer R. Bioterrorism. RN 2002;65(3):48-55.
50. Veenema TG. The smallpox vaccine debate. Am J Nursing 2002;102(9): 33-9.
51. Atlas RM. Bioterrorism. From threat to reality. Ann Rev Microbiol 2002;56:167-85.
52. Lane MJ, Goldstein J. Evaluation of 21st-century risks of smallpox vaccination and policy options. Ann Intern Med 2003;138:488-93.
53. Frey SE, Couch RB, Tacket CO, Treanor JJ, Wolff M, Newman FD, et al. Clinical responses to undiluted and diluted smallpox vaccine. N Engl J Med 2002;346:1265-80.

EXTRACTO

OBJETIVO: Proveer un repaso sobre la viruela, incluyendo su presentación clínica, diagnosis, eventos adversos, y manejo de la vacunación antes y después de la exposición al virus.

FUENTES DE INFORMACIÓN: Se identificó literatura por medio de una búsqueda en los bancos de datos MEDLINE (1966–junio del 2003) y *International Pharmaceutical Abstracts* (1966–mayo del 2003) usando los términos tales como la viruela, arma bacteriológica, terrorismo biológico, y vacuna contra la viruela.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluó los artículos identificados y se incluyó toda la información relevante en este repaso.

SÍNTESIS DE DATOS: La viruela se despliega por medio de un contagio interhumano con un paciente infectado y por lo tanto puede ser contagiosa. La tasa de mortalidad para la viruela es aproximadamente 30%. Mientras que la enfermedad fue totalmente erradicada en el año 1980 con el uso exitoso de la vacuna contra la viruela, se ha surgido la preocupación que la viruela puede emerger como herramienta del bioterrorismo. Esta preocupación combinada con la realidad del programa actual de la vacunación contra la viruela en los militares y en una población civil seleccionada demanda una comprensión clara de los efectos adversos y contraindicaciones relacionados a la vacunación de

todos los profesionales del cuidado médico. La vacuna puede causar eventos adversos moderados o severos tales como el eczema vaccinatum, vaccinia progresiva, y vaccinia generalizada. Recientemente, la viruela ha emergido como agente potencial para el bioterrorismo.

CONCLUSIONES: El equilibrio entre los riesgos y las ventajas de la vacunación total en la prevención de una epidemia no está claro, y el Centro para el Control y Prevención de Enfermedades ha establecido una guía para el uso apropiado de la vacuna de la viruela en la población civil.

Carlos C da Camara

RÉSUMÉ

OBJECTIF: Faire une revue de la variole, plus particulièrement décrire la présentation clinique, le diagnostic, ainsi que les effets indésirables et les indications de la vaccination pré-exposition et post-exposition.

REVUE DE LITTÉRATURE: La documentation scientifique a été identifiée par une recherche sur les banques de données MEDLINE et *International Pharmaceutical Abstracts* (de 1966 à mai-juin 2003) avec les mots-clé suivants: variole, bioterrorisme, guerre biologique, et vaccin antivariolique.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les articles identifiés ont été évalués et les informations pertinentes ont été inclues dans le présent article.

RÉSUMÉ: La variole est une maladie contagieuse qui se propage par contact direct avec un hôte infecté. Le taux de mortalité de la variole peut atteindre 30%. Alors que la maladie était complètement éradiquée en 1980 grâce à la vaccination, une hypothèse a été émise à propos de l'utilisation de la variole comme une arme de bioterrorisme. Cette hypothèse, ainsi que les programmes actuels de vaccination chez les militaires et chez une population civile sélectionnée font qu'il est essentiel que les professionnels de la santé soient au courant des effets indésirables de la vaccination et ses contre-indications. Le vaccin antivariolique peut entraîner des effets indésirables modérés à sévères, tels l'eczéma vaccinatum, la vaccine progressive, et la vaccine généralisée.

CONCLUSIONS: Le ratio entre les risques et les bénéfices d'une vaccination de masse pour la prévention d'un épidémie n'est pas clair, et le Centre pour Contrôler et Prévention de Maladie a établi des lignes directrices pour l'utilisation appropriée du vaccin antivariolique dans la population civile.

Esthel Rochefort