Smallpox

Smallpox is an acute infectious disease caused by the variola virus. Smallpox is believed to have emerged in human populations about 10,000 BCE. A description of smallpox first appeared in a Chinese text in the 4th century. The name variola was first used during the 6th century and is a derivative of the Latin varius, meaning spotted, or varus, meaning pimple. The first efforts to prevent smallpox occurred in China and India sometime before the year 1000 and involved intentional inoculation of a susceptible person with pustular or scab material from a person with smallpox. The term smallpox was first used in Europe in the 15th century to distinguish variola from the great pox (syphilis). In 1796, Edward Jenner demonstrated that smallpox could be prevented by inoculating a person with material from a cowpox lesion; this led to the first smallpox vaccine. The last case of smallpox in the United States was reported in Texas in 1949. In 1966, the World Health Organization initiated an intensified global smallpox eradication program. The last indigenous case of smallpox on earth occurred in Somalia in October 1977. The World Health Assembly officially certified the global eradication of smallpox in May 1980.

Variola and Other Orthopoxviruses

Smallpox is caused by variola virus. Variola virus belongs to the genus Orthopoxvirus, family Poxviridae. Poxviruses are large brick-shaped viruses with a double stranded DNA genome. They are different from most other DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To do this, they produce a variety of proteins not produced by other DNA viruses (e.g., herpesvirus). Four orthopoxviruses are known to infect humans: variola, vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals have been infected in a laboratory. Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.

In laboratory experiments, 90% of aerosolized variola virus is inactivated within 24 hours. In the presence of ultraviolet light, this percentage would be even greater. In temperate climates, crusts from the skin lesions from smallpox patients, in which the virus is contained in a fibrin matrix, can retain viable virus for several years when held at room temperature. The virus survives longer at low temperature and humidity than at higher temperature or humidity. All poxviruses are rapidly inactivated by exposure to ultraviolet light, and chemical disinfectants such as bleach or Lysol®.

Some persons infected with variola major virus have particularly severe illnesses. This suggests that there could be differences
Smallpox

in the virulence of strains of the virus. However, no laboratory test has been devised that correlates virus strains with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

Smallpox vaccine contains vaccinia virus, not variola virus. Vaccinia is rarely isolated from animals outside the laboratory. There are multiple strains of vaccinia virus that have different levels of virulence for humans and animals. Vaccinia virus can also be genetically engineered to accept DNA and express other antigens, and has been used as a vector in laboratory experiments. Cowpox virus was probably the virus that Edward Jenner originally used as a vaccine for smallpox. The virus has many natural hosts, including cows, rodents, cats, elephants, and is found in nature primarily in Europe. Monkeypox was first found in monkeys and later in other animals such as rats, rabbits, and squirrels. It was reported in humans for the first time in 1970. It is found primarily in western and central Africa, although a cluster of monkeypox cases occurred in the United States in 2003 and was associated with pet prairie dogs from Africa.

Pathogenesis

Variola virus infection is initiated when the virus comes into contact with the oropharyngeal or respiratory mucosa of a susceptible person. The virus then multiplies in regional lymph nodes. An asymptomatic viremia develops 3 or 4 days after infection, which is followed by further virus replication, probably in the bone marrow, spleen, and lymphatics. A second viremia begins about 8–10 days after infection and is followed by the first symptoms of illness (prodromal stage), fever and toxemia. The virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. In the skin, this results in the characteristic maculopapular rash, which evolves into vesicles, then pustules.

Clinical Features

Two clinical forms of smallpox have been described. While both forms are caused by variola virus, they are caused by different strains of the virus distinguishable by specific biologic properties (such as growth characteristics in cell culture and DNA structure). Variola major is the severe form of smallpox, with a more extensive rash, higher fever, and a greater degree of prostration. Variola major has a case-fatality rate of 30% or more. The last case of variola major occurred in Bangladesh in 1975. Variola minor was first described in South Africa and the United States in the late 19th century. Variola minor is a much less severe disease, with a case-fatality rate of 1% or less. Variola minor was endemic in some countries of Europe and of North and
South America and in many parts of Africa. The last case of variola minor occurred in Somalia in October 1977, and was the last case of indigenous smallpox on earth.

There are four principal clinical presentations of variola major, based on the Rao classification (1972). The relative vigor of the immune response to the infection probably determined the clinical presentation of the infection. The classification is based on the nature and evolution of the lesions: ordinary (most frequent), modified (mild and occurring in previously vaccinated persons), flat, and hemorrhagic. Flat and hemorrhagic smallpox are severe, uncommon forms and are usually fatal. In addition, variola sine eruptione (smallpox without rash) is a febrile illness occurring after the usual incubation period. It is seen generally in vaccinated persons and can be confirmed only by antibody studies or, rarely, by virus isolation. Subclinical (asymptomatic) infections with variola virus also occurred, but are not believed to be common.

The incubation period of smallpox averages 12 days, with a range of 7 to 17 days. During this period the patient is well. The prodrome or preeruptive stage of the illness then starts abruptly, with fever (usually 101°–104°F [38.3°–40°C]), malaise, headache, muscle pain, prostration, and often nausea and vomiting and backache. The person usually appears quite ill. The prodrome usually lasts 2–4 days. The person is not infectious until the end of the prodrome, when lesions develop in the mouth.

Ordinary Smallpox

Ninety percent or more of smallpox cases among unvaccinated persons are of the ordinary type. The prodromal stage varies in severity. By the third or fourth day of illness, the temperature usually falls and the patient feels somewhat better. At this point the rash appears. The rash appears first as an enanthem—minute red spots on the tongue and oral and pharyngeal mucosa—about 24 hours before the appearance of rash on the skin. Lesions in the mouth and pharynx enlarge and ulcerate quickly, releasing large amounts of virus into the saliva about the time the cutaneous rash first becomes visible. Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious.

The exanthem (skin rash) usually appears 2–4 days after the onset of fever as a few macules (known as “herald spots”) on the face, particularly on the forehead. Lesions then appear on the proximal portions of the extremities, then spread to the distal extremities and the trunk. Usually the rash appears on all parts of the body within 24 hours.
Smallpox Rash

- Macules: 0-1 days after rash onset
- Papules: 2-3 days
- Vesicles: 3-5 days
- Pustules: 6-12 days
- Crusts: 13-20 days
- All crusts separated: 21-28 days

Smallpox Rash

- Vesicles often have a central depression ("umbilication")
- Pustules raised, round, firm to the touch, deeply embedded in the skin
- Lesions in any one part of the body are in same stage of development
- Most dense on face and distal extremities (centrifugal distribution)
- Lesions on palms and soles (50% of cases)

Modified Smallpox

- Occurs in previously vaccinated persons
- Prodrome may be less severe
- No fever during evolution of rash
- Skin lesions evolve more quickly
- Rarely fatal
- More easily confused with chickenpox

By the second or third day of the rash, the macules become raised papules. By the third or fourth day the lesions become vesicular, containing first an opalescent fluid, which then becomes opaque and turbid within 24–48 hours. The skin lesions of smallpox typically are surrounded by a faint erythematous halo. The distended vesicles often have a central depression or dimple of varying size, referred to as “umbilication.” Umbilication often persists into the pustular stage, but as the lesion progresses it usually becomes flattened because of adsorption of fluid. Umbilication is less common in other vesicular or pustular rash illnesses, particularly in varicella.

By the sixth or seventh day, all the skin lesions are pustules. Between 7 and 10 days the pustules mature and reach their maximum size. The pustules are sharply raised, typically round, tense, and firm to the touch. The pustules are deeply embedded in the dermis, giving them the feel of a small bead in the skin. Fluid is slowly absorbed from the pustules, and by the end of the second week the pustules begin to form a crust. During the third week the crusts separate, leaving depigmented skin and, frequently, pitted scars. Fever usually rises again by the seventh or eighth day of the illness and continues to remain high throughout the vesicular and pustular stages, until crusts have formed over all the lesions.

The rash usually develops as a single crop. Consequently, lesions in a particular part of the body are at about the same stage of development, although they may be different sizes. The distribution of the rash is centrifugal: most dense on the face; more dense on the extremities than on the trunk; and on the extremities, more dense on the distal parts than on the proximal. The palms of the hands and soles of the feet are involved in the majority of cases.

In general, the severity of the clinical picture parallels the extent of the rash. In some cases, the pustular skin lesions on the extensor surfaces of the extremities and face are so numerous they became confluent. Patients with confluent smallpox often remain febrile and toxic even after scabs have formed over all the lesions. In one case series, the case-fatality rate in confluent smallpox was 62%.

Modified Smallpox

Modified smallpox refers to the character of the eruption and the rapidity of its development. This form of smallpox occurs mostly in previously vaccinated patients. The prodromal illness occurs but may be less severe than in ordinary-type smallpox. Fever during evolution of the rash is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity
characteristic of more typical smallpox. The lesions are often few in number, but even when they are numerous, or even confluent, they usually evolve rapidly. Modified smallpox is rarely, if ever, fatal. This form of variola major is more easily confused with chickenpox.

**Flat (Malignant) Smallpox**

Flat-type smallpox is so called because the lesions remain almost flush with the skin at the time when raised vesicles form in ordinary-type smallpox. It is not known with certainty why some persons develop this type of disease. In a large series of persons hospitalized with smallpox in India, flat-type smallpox accounted for 5%–10% of cases, and the majority (72%) were in children. The prodrome is severe and lasts 3–4 days. Constitutional symptoms are severe and continue after the appearance of the rash. The fever remains elevated throughout and the patient has severe toxemic symptoms. The rash on the tongue and palate is usually extensive. The skin lesions mature very slowly. By the seventh or eighth day the lesions are flat and appear to be buried in the skin. Unlike ordinary-type smallpox, the vesicles contain very little fluid and do not appear umbilicated. The lesions are soft and velvety to the touch, and may contain hemorrhages. Respiratory complications are common. The prognosis for flat-type smallpox is grave and most cases are fatal.

**Hemorrhagic Smallpox**

Hemorrhagic smallpox is a severe and uncommon form of smallpox that is accompanied by extensive bleeding into the skin, mucous membranes, and gastrointestinal tract. In the large Indian series, hemorrhagic disease occurred in about 2% of hospitalized patients; the majority of cases were among adults, and pregnant women appear to be at increased risk. The prodromal stage, which can be prolonged, is characterized by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. There is little or no remission of fever throughout the illness. Hemorrhagic manifestations can occur early or late in the course of the illness. In the early, or fulminating, form, hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, bleeding from the mouth or gums and other mucous membranes, petechiae in the skin, epistaxis, and hematuria. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant maculopapular cutaneous lesions are present. In patients who survive for 8–10 days the hemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.
Variola Sine Eruptione and Subclinical Infection

Febrile illness sometimes occurs among vaccinated contacts of smallpox patients, with the sudden onset of temperature of about 102°F (39°C), headache and sometimes backache. The attack often subsides within 48 hours and the temperature returns to normal. Although these symptoms could be caused by other infections, laboratory investigation may show a significant increase in variola antibody following such an attack. There is evidence of true subclinical infection with variola major virus (i.e., serologic evidence of infection with no symptoms), typically in recently vaccinated household contacts of smallpox patients. Persons with subclinical infections have not been shown to transmit the infection to contacts.

Complications

Secondary bacterial infection of the skin is a relatively uncommon complication of smallpox. When this occurs, the fever usually remains elevated. Arthritis occurs in up to 2% of cases, most commonly in children. Respiratory complications (e.g., bronchitis, pneumonitis, or pneumonia) sometimes develop on about the eighth day of the illness and can be either viral or bacterial in origin. Encephalitis occasionally occurs and is indistinguishable from the acute perivascular demyelination observed as a complication of infection due to vaccinia, measles, or varicella.

In fatal cases, death usually occurs between the tenth and sixteenth days of the illness. The cause of death from smallpox is not clear, but the infection is now known to involve multiple organs. Circulating immune complexes, overwhelming viremia, or an uncontrolled immune response may be contributing factors. The overall case-fatality rate for ordinary-type smallpox is about 30%. However, the fatality rate for children younger than 1 year of age is 40%–50%. The fatality rate for flat-type and hemorrhagic smallpox is 90% or greater. The case-fatality rate for variola minor is 1% or less.

Sequelae of smallpox include scarring, which is most common on the face, blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis. There is no evidence of chronic or recurrent infection with variola virus.

Differential Diagnosis

The disease that most closely resembles smallpox is varicella (chickenpox). The most important differentiating feature between smallpox and varicella, as well as other rash illnesses, is the presence of a prodrome with fever and
other symptoms before rash onset. A person with smallpox will have a severe, febrile prodrome that begins 1–4 days before the onset of the rash. The fever is high, usually 102°–104°F (38.8°–40°C), but always at least 101°F (38.3°C). Most children with varicella have a short, mild prodrome or no prodrome at all before onset of the rash and have little or no fever before rash onset. Adults, who may develop more severe varicella, are more likely to have fever or other symptoms before rash onset. If there is no history of a febrile prodrome, smallpox is not likely. In addition to fever, the prodrome of smallpox is associated with one or more additional symptoms, such as prostration, headache, backache, chills, abdominal pain or vomiting. Patients are frequently too ill to engage in normal activities and typically confine themselves to bed.

Another important differentiating feature of smallpox and varicella is the appearance, evolution, and distribution of the rash. Although there may be some similarity in the appearance of the lesions, particularly early after rash onset, classic smallpox looks very different from varicella. Smallpox lesions are deep in the dermis and feel hard to the touch, described as feeling like a pea under the skin. They are round and well circumscribed. As they evolve, they may become confluent or umbilicated. The varicella rash is superficial, and the lesions appear to be delicate and not as well circumscribed. Confluence and umbilication are uncommon in varicella. Smallpox rash lesions appear in a single crop, and lesions on any part of the body are in the same stage of development. Lesions are more dense on the extremities than on the trunk and often involve the palms and soles (i.e., centrifugal distribution). In contrast, the rash of varicella appears in several crops, so papules, vesicles, and crusts are seen simultaneously on the same part of the body and new lesions continue to appear for several days. Lesions are typically more dense on the trunk than on the extremities. In severe cases of varicella, rash distribution may not be a useful differentiating feature and rash may occur everywhere on the body, including the palms and soles.

For the first 2–3 days, the smallpox rash is maculopapular. At this stage of the illness smallpox could be confused with other febrile illnesses with maculopapular rash, such as measles, rubella, and other evolving vesicular rashes including varicella.

Other common conditions that might be confused with smallpox are summarized in the table below. As the United States re-institutes smallpox vaccination, at least in limited groups, generalized vesicular rashes (generalized vaccinia and eczema vaccinatum) caused by vaccinia vaccine adverse reactions could be seen among persons with a history of recent smallpox vaccination or contact close with a vaccinee.
In addition there are exceedingly rare causes of smallpox-like rash, such as ricketsial pox and monkeypox. A small percentage of smallpox cases present as hemorrhagic smallpox or a flat-type rash. Both variants are highly lethal. Hemorrhagic smallpox can be mistaken for meningococcemia.

### Common Conditions that Might be Confused with Smallpox

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Clues</th>
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<tbody>
<tr>
<td>Varicella (primary infection with varicella-zoster virus)</td>
<td>Most common in children &lt;10 years; children usually do not have a viral prodrome</td>
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<tr>
<td>Disseminated herpes zoster</td>
<td>Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution</td>
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<tr>
<td>Impetigo (<em>Streptococcus pyogenes, Staphylococcus aureus</em>)</td>
<td>Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional but not disseminated rash; patients generally not ill</td>
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<tr>
<td>Drug eruptions</td>
<td>Exposure to medications; rash often generalized</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Itching; contact with possible allergens; rash often localized in pattern suggesting external contact</td>
</tr>
<tr>
<td>Erythema multiforme minor</td>
<td>Target, “bull’s eye”, or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands &amp; feet (including palms &amp; soles)</td>
</tr>
<tr>
<td>Erythema multiforme (incl. Stevens-Johnson Syndrome)</td>
<td>Major form involves mucous membranes &amp; conjunctivae; may be target lesions or vesicles</td>
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<tr>
<td>Enteroviral infection esp. Hand, Foot and Mouth disease</td>
<td>Summer &amp; fall; fever &amp; mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey tender, flat often oval vesicles; peripheral distribution (hands, feet, mouth, or disseminated)</td>
</tr>
<tr>
<td>Disseminated herpes simplex</td>
<td>Lesions indistinguishable from varicella; immunocompromised host</td>
</tr>
<tr>
<td>Scabies; insect bites (incl. fleas)</td>
<td>Itching is a major symptom; patient is not febrile &amp; is otherwise well</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>May disseminate in immunosuppressed persons</td>
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</table>

CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize patients into high, moderate or low risk for smallpox. There are three major and five minor smallpox criteria:

### Major Criteria

1. The patient has had a febrile prodrome (temperature 101°F [38.3°C] or higher) 1–4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain.
2. Rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent as they evolve.
3. On any one part of the body all the lesions are in the same stage of development (i.e., all are vesicles or all are pustules).
Minor criteria
1. The distribution of the rash is centrifugal (i.e., the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk).
2. The first lesions of the rash appear on the oral mucosa or palate, or on the face or forearms.
3. The patient appears toxic or moribund.
4. Lesions have progressed slowly (i.e., the individual lesions evolved from macules to papules to pustules, each stage lasting 1–2 days).
5. Lesions are present on the palms or soles.

A person is considered at high risk for smallpox if he or she meets all three major criteria. Immediate action should be taken to make sure that contact precautions and respiratory isolation are implemented. These patients should be reported to local and/or state health authorities immediately. Obtain digital photographs if possible, and consult with dermatology and/or infectious disease experts. Following such consultation, if the patient is still considered to be at high risk, the state health department will immediately report the case to CDC and arrangements will be made for laboratory testing for smallpox virus.

A person considered at moderate risk for smallpox must have a febrile prodrome and either one other major criterion or four or more minor criteria. These patients should be isolated and be evaluated urgently to determine the cause of the illness. Persons classified as high or moderate risk should be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible. Any person who did not have a febrile prodrome is considered at low risk, as are persons who had a febrile prodrome and fewer than four minor criteria. These patients should be managed as clinically indicated.

A case investigation worksheet and a poster that includes the rash illness algorithm, and information on differential diagnosis is available from the CDC smallpox website at http://www.bt.cdc.gov/agent/smallpox/

Laboratory and Pathology Diagnosis
If a case is classified as high risk after evaluation using the algorithm, it fits the clinical case definition for smallpox and therefore should be considered a probable smallpox case until smallpox virus laboratory results are completed. For such a case, do not perform other laboratory testing for other diagnoses.

Currently, laboratory procedures for isolation of variola virus in clinical specimens should be done only by CDC in

Laboratory Confirmation
- Rapid diagnostic testing for varicella zoster virus (DFA, IFA, PCR)
- Electron microscopy (may identify Orthopoxvirus but not specific for variola)
- Culture
- Nucleic acid-based testing
- Serologic testing
If the patient’s clinical characteristics indicate a high risk for smallpox, the state health department should be contacted immediately. The diagnosis of an Orthopoxvirus infection can be made rapidly by electron microscopic examination of pustular fluid or scabs. Orthopox generic polymerase chain reaction (PCR) tests are available but do not distinguish between vaccinia, variola and other poxvirus infections. Differentiation of orthopoxviruses is made by nucleic acid–based testing, such as PCR. Serologic tests have also been developed to assist in the diagnosis of acute Orthopoxvirus infection, and direct antigen detection tests for variola virus are under development.

For a patient who meets the criteria for moderate risk, the most important laboratory procedure is rapid diagnostic testing for varicella zoster virus (VZV). Laboratory testing should be done in consultation with an infectious disease or dermatology specialist. Smallpox virus testing is not indicated for cases that do not meet the clinical case definition. In the absence of smallpox (disease prevalence of zero), the predictive value of a positive laboratory test is extremely low (close to zero). Limiting requests for smallpox testing to cases that fit the clinical case definition will minimize the risks of a false-positive laboratory result, which would have extremely serious consequences.

Since varicella was the most common disease confused with smallpox in the past and the most common diagnosis in smallpox false alarms in the immediate posteraicidal era, rapid VZV diagnostic tests are important for evaluation of suspected smallpox cases. A variety of rapid methods are available for detecting VZV in clinical material. The most useful is direct fluorescent antibody (DFA). This method detects VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye. DFA is very sensitive and specific but is critically dependent on careful collection of material from a lesion. Detection of VZV DNA by PCR testing of vesicular fluid or scabs can also be used for rapid detection of VZV in clinical material. Real time PCR assays take 4–6 hours to perform. Virus particles consistent with VZV can be detected using electron microscopy. Rapid diagnostic testing for VZV is generally available in at least one facility (private laboratories, academic hospital centers) in all large cities and in some local and in all state health department facilities. Other testing should be done as clinically indicated and may include testing for herpes simplex viruses (HSV), enteroviruses and syphilis.

Tzanck smear, although not diagnostic of VZV infection, is a rapid and easily performed test in hospitals with a pathology laboratory and is frequently available at the local level. A positive Tzanck smear confirms an alphaherpesvirus infection (either VZV or HSV).
Skin biopsies, if clinically indicated, can assist with a diagnosis on the basis of histopathology or can be confirmatory if immunohistochemistry tests are available.

**Medical Management**

_A suspected case of smallpox is a public health and medical emergency._ Any person whose clinical characteristics meet the clinical case definition for smallpox must be isolated and reported immediately to the local and/or state health department.

Strict respiratory and contact isolation of confirmed or suspected smallpox patients is critical to limit the exposure to the virus. Smallpox patients are infectious until all crusts have separated. Although droplet spread is the major mode of person-to-person smallpox transmission, airborne transmission through fine particle aerosol can occur. Therefore, airborne precautions using a negative air pressure room with high-efficiency particulate air filtration should be initiated immediately for hospitalized high-risk or confirmed smallpox patients. This is the same isolation precaution that is taken for other infectious diseases with respiratory transmission, such as varicella.

All personnel who have contact with a patient with suspected or confirmed smallpox should use appropriate protective equipment. This includes properly fitted respirators (masks) of N95 quality or higher. In addition, personnel should use disposable gloves, gowns and shoe covers for all contact with patients. This precaution is to prevent inadvertent transmission of variola virus from clothing or other contaminated items to susceptible persons. Personnel should remove and correctly dispose of all protective clothing before contact with other people. Reusable bedding and clothing can be autoclaved or laundered in hot water with bleach to inactivate the virus. Persons such as laundry handlers, housekeepers, and laboratory personnel, who come into contact with materials potentially contaminated with smallpox virus, should use appropriate protective equipment. If a case of smallpox is confirmed, these personnel should be vaccinated before handling contaminated materials.

Medical management of a person with smallpox is primarily supportive. No antiviral drug is currently approved by the Food and Drug Administration for the treatment of smallpox. Recent studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. However, the drug must be administered intravenously and can cause serious renal toxicity. Cidofovir administered for the treatment of smallpox would be an off-label use. Antiviral therapy with cidofovir or other drugs subsequently found to have antivariola activity might be considered but should be used under an investigational new drug (IND) protocol and by an infectious diseases specialist.
Epidemiology

Reservoir
Although animals can be infected with variola in laboratory conditions, humans are the only natural host. There is no chronic carrier state and no known animal reservoir. Since the early 1980s (i.e., following global smallpox eradication), the only known locations of variola virus are at CDC in Atlanta and at the State Research Center of Virology and Biotechnology in Koltsvo, Russia.

Transmission
Transmission of smallpox occurs through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. Most transmission results from direct face-to-face contact with an infected person, usually within a distance of 6 feet, or from physical contact with a person with smallpox or with contaminated articles. Although variola virus could remain viable for years in dried crusts of skin lesions, transmission from crusts is uncommon, probably because virus is enmeshed in a fibrin matrix.

Communicability
A person infected with variola virus is not infectious during the incubation period or the first day or two of the prodromal stage of the illness. The patient becomes infectious with the first appearance of the rash, which is often accompanied by lesions in the mouth and pharynx. The virus can be transmitted throughout the course of the illness (i.e., until all crusts separate). Transmission is most frequent during the first week of the rash, while most skin lesions are intact (i.e., vesicular or pustular). Virus is present in material draining from ruptured pustules and in crusts for a longer period, but infection from this source appears to be less frequent. In general, persons with a severe rash and involvement of the mouth and pharynx, and those with a cough are more infectious than those with a slight rash. Secondary attack rates among household members are generally 50%–60%.

Natural transmission of smallpox in a population is relatively slow. There is an interval of 2 to 3 weeks between each generation of cases. Smallpox generally spreads less widely and less rapidly than does varicella or measles, probably because transmission of variola virus does not occur until the onset of rash and generally requires close face-to-face contact for spread. At the time of rash onset, most patients are already confined to bed because of the high fever and toxemia of the prodromal stage of the illness. However, persons with severe prodromal illness may seek medical
attention; therefore, hospitals are a frequent source of infection because of transmission from hospitalized persons with unrecognized cases.

Secondary cases of smallpox are usually limited to those who come in contact with the infected person in the household or hospital. During the global eradication program, the chain of transmission of smallpox was interrupted by isolating smallpox patients in a setting in which they had contact only with adequately vaccinated or previously infected persons. This limited the next potential generation of cases to the household and close contacts of the index patient or patients. Contacts were identified and immediately vaccinated. Contacts who became ill were also isolated to establish a barrier to further transmission. This strategy was found to be effective even if community vaccination levels were low.

**Temporal Pattern**

In temperate areas, the seasonality of smallpox was similar to that of measles and varicella, with incidence highest during the winter and spring. In tropical areas, seasonal variation was less evident and the disease was present throughout the year.

**Secular Trends**

The last case of smallpox in the United States was reported in 1949. In the early 1950s, an estimated 50 million cases of smallpox occurred worldwide each year. Ten to 15 million cases occurred in 1966, when the disease had already been eliminated in 80% of the world.

**Smallpox Eradication**

The intensified global smallpox eradication program began in 1966. The initial campaign was based on a twofold strategy: 1) mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population; and 2) development of surveillance systems to detect and contain cases and outbreaks. The program had to surmount numerous problems, including lack of organization in national health services, epidemic smallpox among refugees fleeing areas stricken by civil war and famine, shortages of funds and vaccine, and a host of other problems posed by difficult terrain, climate, and cultural beliefs. In addition, it was soon learned that even when 80% of the population was vaccinated, smallpox often persisted. Soon after the program began, it became apparent that by isolating persons with smallpox and vaccinating their contacts, outbreaks could be more rapidly contained, even in areas where vaccination coverage was low. This strategy was called **surveillance and containment**, and it became the key element in the global eradication program.
Although setbacks occurred, the surveillance and containment strategy was an enormous success. The last case of smallpox in Brazil was reported in 1971, and Indonesia's last case occurred in 1972. India, Pakistan and Bangladesh, with a population at that time of more than 700 million, were a particular challenge. But with intensive house-to-house searches and strict containment, the last case of variola major—the most deadly type of smallpox—occurred in Bangladesh in October 1975.

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. An intensive surveillance and containment and vaccination program was undertaken in the spring and summer of 1977. As a result, the world’s last person with indigenous smallpox was a hospital cook in Merka, Somalia, on October 26, 1977. Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox.

The last cases of smallpox on earth occurred in an outbreak of 2 cases (one of which was fatal) in Birmingham, England in 1978. This outbreak occurred because variola virus was carried by the ventilation system from a research laboratory to an office one floor above the laboratory. In 1980 the World Health Assembly certified the global eradication of smallpox and recommended that all countries cease vaccination. The World Health Organization also recommended that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories, the Institute of Viral Preparations in Moscow or CDC in Atlanta. All laboratories were believed to have complied with this request.

**Case Definition**
A clinical case of smallpox is defined as an illness with acute onset of fever (101°F [38.3°C] or higher) followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

This case definition will not detect an atypical presentation of smallpox such as hemorrhagic or flat-type disease. In addition, given the extremely low likelihood of smallpox occurring, the case definition provides a high level of specificity (i.e., vesicular rash illness) rather than a high level of sensitivity (i.e., maculopapular rash illness). In the event of a smallpox outbreak, the case definition would be modified to increase sensitivity.
**Smallpox [Vaccinia] Vaccine**

The first attempts to prevent smallpox were in China and India before the year 1000 century, and involved either nasal insufflation of powdered smallpox scabs, or scratching material from a smallpox lesion into the skin. This procedure was known as variolation and, if successful, produced lasting immunity to smallpox. However, because the person was infected with variola virus, a severe infection could result, and the person could transmit smallpox to others.

In 1796 Edward Jenner, a doctor in rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is a poxvirus in the same family as variola. Jenner called the material used for inoculation vaccine, from the root word *vacca*, which is Latin for cow. The procedure was much safer than variolation, and did not involve a risk of smallpox transmission. Vaccination to prevent smallpox was soon practiced all over the world.

At some time during the 19th century, the cowpox virus used for smallpox vaccination was replaced by vaccinia virus. Vaccinia is in the same family as cowpox and variola but is genetically distinct from both. The origin of vaccinia virus and how it came to be in the vaccine are not known.

**Characteristics**

The smallpox vaccine currently available in the United States (Dryvax, produced by Wyeth) is a live virus preparation of infectious vaccinia virus. Smallpox vaccine does not contain smallpox (variola) virus. The current vaccine was prepared in the early 1980s from calf lymph with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus. The vaccine is provided as a lyophilized (freeze-dried) powder in a 100-dose vial and contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin and contains a small amount of phenol as a preservative.

Approximately 15 million doses of vaccine are available now in the United States. Testing has shown that existing supplies of vaccine could be diluted by a 1:5 ratio and still remain as effective and safe as full-strength vaccine. An additional 85 million doses of vaccine based on the NYCBOH strain have been found to be immunogenic at 1:5 or 1:10 dilution. This could potentially provide an additional 850 million doses.

The vaccine is administered by using a multiple puncture technique with a special bifurcated needle. Detailed information concerning reconstitution and administration...
Immunogenicity and Vaccine Efficacy
Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other orthopoxviruses (e.g., monkeypox, cowpox, and variola viruses). Neutralizing antibodies are detectable 10 days after primary vaccination, and 7 days after revaccination. Although the level of antibody that protects against smallpox infection is unknown, after percutaneous administration of a standard dose of vaccinia vaccine, more than 95% of primary vaccinees (i.e., persons receiving their first dose of vaccine) will develop neutralizing or hemagglutination inhibition antibody at a titer of higher than 1:10. Neutralizing antibody titers of higher than 1:10 persist in 75% of persons for 10 years after receiving second doses and up to 30 years after receiving three doses of vaccine.

The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of persons exposed to a smallpox patient in their household. These studies indicated a 91%–97% reduction in smallpox among contacts with a vaccination scar compared with contacts without a scar. However, these studies did not always consider the time since vaccination or potency of vaccine, so they may underestimate protection.

Epidemiologic studies demonstrated that a high level of protection (nearly 100%) against smallpox persists for up to 5 years after primary vaccination, and substantial but waning immunity for 10 years or more. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Although smallpox vaccination received in the remote past may not completely protect against smallpox, vaccinated persons appear to have less severe disease. Studies of smallpox cases imported into Europe in the 1950s and 1960s demonstrated fewer fatalities among vaccinated persons compared with those who were unvaccinated. The fatality rate among persons vaccinated less than 10 years before exposure was 1.3%; it was 7% among those vaccinated 11 to 20 years prior, and 11% among those vaccinated 20 or more years prior to infection. In contrast, 52% of unvaccinated persons died.

Smallpox vaccination also provides protection if administered after an exposure to smallpox. Postexposure efficacy has been estimated in household contact studies in Pakistan and India. These studies indicate that rates of secondary cases in
households were up to 91% lower than rates among unvaccinated persons. The lowest secondary attack rates occurred in persons vaccinated less than 7 days after exposure. In these studies, smallpox was generally less severe (i.e., modified type) in persons who received postexposure vaccination.

Following vaccination, vaccinia virus replicates in the basal cells of the epidermis, resulting in the development of a lesion at the site of vaccination. A papule develops at the inoculation site 3–4 days after primary vaccination. Approximately 7 days following primary vaccination, a vesicle (a blister containing clear fluid) surrounded by erythema (a “Jennerian vesicle”) forms at the site. The vesicle becomes pustular by 7–11 days after vaccination. Maximum erythema occurs 8–12 days after vaccination. The erythema then subsides, the pustule dries, and a crust develops 2–3 weeks after vaccination. In the third week, the crust separates, leaving a permanent scar at the vaccination site. This response to vaccination is called a major reaction, and indicates that virus replication has taken place and vaccination was successful. A person is considered protected with the development of a major reaction at the vaccination site. A revaccinated person often develops a skin reaction similar to that after primary vaccination, but the lesion progresses faster than after primary vaccination.

Some persons do not develop a typical skin lesion after vaccination. All responses other than major reactions are referred to as equivocal. There are several possible causes of equivocal reactions. The person may be sufficiently immune to suppress viral replication or may be allergic to a component of the vaccine, leading to a hypersensitivity reaction at the site. An equivocal reaction could also be caused by insufficiently potent vaccine or incorrect administration technique. In general, a person who has an equivocal response to vaccination should be revaccinated using vaccine from another vial if possible. More information on interpretation of response to vaccination is available in the ACIP recommendations for smallpox vaccine, available at http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf.

Live vaccinia virus is present at the vaccination site beginning 3 to 4 days after vaccination and remains until the crust separates from the skin. Since the developing vaccinia lesion usually itches, care must be taken to avoid scratching, then touching other parts of the body, such as the eye, or other people. This could transfer the vaccine virus to these sites or individuals. Washing hands immediately after touching the vaccination site or dressing is very important in preventing this type of transmission.
Vaccination Schedule and Use

Routine childhood smallpox vaccination was discontinued in the United States in 1972. Routine vaccination of healthcare workers was discontinued in 1976, and among military recruits in 1990. In 1980, smallpox vaccine was recommended for laboratory workers who were at occupational risk for exposure to vaccinia or other orthopoxviruses. In 1991, the Advisory Committee on Immunization Practices recommended that other healthcare workers who could be exposed to vaccinia or recombinant vaccinia be considered for vaccination. Guidelines for use of smallpox vaccine in the event of an intentional release of smallpox virus were first published in 2001.

For routine nonemergency use (i.e., in the absence of smallpox disease) vaccination is recommended for laboratory workers who directly handle cultures or animals infected with non–highly attenuated vaccinia viruses (e.g., the NYCBOH, Temple of Heaven, Copenhagen, or Lister vaccinia strains), and recombinant vaccinia viruses derived from non–highly attenuated vaccinia strains. Vaccination is also recommended for laboratory workers exposed to other orthopoxviruses that infect humans (e.g., monkeypox or cowpox). Vaccination can be considered for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were administered vaccines containing recombinant vaccinia viruses. Vaccination is also recommended for public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak, and for persons who administer the vaccine to others.

In the event of an intentional release of variola virus, vaccination would be recommended for those exposed to the initial release, contacts of persons with smallpox, and others at risk of exposure. Persons at risk of exposure would include those involved in the direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients; laboratory personnel who collect or process clinical specimens from confirmed or suspected smallpox patients; persons who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present; and other groups (e.g., medical, law enforcement, emergency response, or military personnel) as recommended by public health authorities.

The schedule for smallpox vaccine is one successful dose (i.e., a dose that results in a major reaction at the vaccination site). In routine circumstances the vaccine should not be
administered to persons younger than 18 years of age. In an emergency (postrelease) situation, there would be no age limit for vaccination of persons exposed to a person with confirmed smallpox.

Persons with occupational exposure to non–highly attenuated vaccinia viruses, recombinant viruses derived from non–highly attenuated vaccinia viruses, or other nonvariola orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola orthopoxviruses (e.g., monkeypox), empiric revaccination every 3 years can be considered.

**Adverse Reactions Following Vaccination**

A vesicular or pustular skin lesion at the site of inoculation indicates a successful vaccination, or “take.” In a 2002 study of old and new vaccines given to unvaccinated adults, the average size of the pustule at 2 weeks after vaccination was 12 millimeters. The average size of erythema surrounding the pustule was 16–24 millimeters, and average induration was 11–15 millimeters.

Some vaccinees may have larger degrees of erythema and induration that can be mistaken for cellulitis. These reactions generally improve within 24 to 48 hours without specific therapy but may require clinical evaluation to rule out bacterial cellulitis.

Fever is common after administration of smallpox vaccine. In a recent study of Dryvax given to unvaccinated adults, 5%–9% reported a temperature of 100°F (37.7°C) or higher, and 3% reported temperature of 102°F (38.8°C) or higher. Fever is most common 7–12 days after vaccination. In addition to fever, adult vaccinees also report a variety of constitutional symptoms, including headache, myalgias, chills, nausea, and fatigue on or about the eighth or ninth day after vaccination. One or 2 percent of recipients reported these symptoms as severe.

Historically, fever was more common among children. In past studies, about 70% of children experienced 1 or more days of temperature 100°F (37.7°C) or higher after primary vaccination. Fifteen to 20 percent of children experienced temperatures 102°F (38.8°C) or higher.
Vaccinia virus is present at the site of vaccination beginning about 4 days after vaccination. Maximum viral shedding from the vaccination site occurs 4–14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin. Inadvertent inoculation (i.e., transfer of vaccinia from the vaccination site to another part of the body) is the most frequent complication of smallpox vaccination and accounts for approximately half of all complications of primary vaccination and revaccination. Studies in 1968 estimated the rate of inadvertent inoculation to be 529 cases per million primary vaccinations. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Most lesions heal without specific treatment. Involvement of the eye may result in scarring of the cornea and significant impairment of vision.

A variety of erythematous or urticarial rashes can occur approximately 10 days after primary vaccination. The vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within 2–4 days. In rare instances, bullous erythema multiforme (Stevens-Johnson syndrome) occurs.

Generalized vaccinia is another type of rash following smallpox vaccination. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without eczema or other preexisting skin disease. It consists of vesicles or pustules appearing on normal skin distant from the vaccination site. Most rashes labeled as generalized vaccinia produce only minor illness with little residual damage. The rash is generally self-limited and requires minor or no therapy except among patients whose conditions might be toxic or who have serious underlying immunosuppressive illnesses. In the 1968 studies, rashes diagnosed as generalized vaccinia occurred at a rate of 242 per million primary vaccinations.

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, progressive vaccinia, and post-vaccinal encephalitis. These complications are rare but occur at least 10 times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults. It is estimated that 14–52 persons per million primary vaccinations will experience potentially life-threatening adverse reactions.

Myopericarditis is the inflammation of heart muscle and/or the membrane that surrounds the heart. There were reports of this condition following smallpox vaccination in the 1950s and 1960s, but these cases were associated with vaccine strains not currently used. Myopericarditis was not an anticipated adverse reaction to the smallpox vaccine when the National Smallpox Vaccination Program began in
December 2002. During January–October 2003, 31 serious cardiac adverse events were reported among approximately 38,000 civilian recipients of smallpox vaccine (21 myopericarditis and 10 ischemic events).

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in persons who have eczema or atopic dermatitis or a history of either of these conditions, or among contacts of vaccinees with eczema or atopic dermatitis or a history of these skin conditions. Eczema vaccinatum can occur regardless of whether the skin disease is active or quiescent. Usually the illness is mild and self limited, but it can be severe or fatal. The most serious cases among vaccine recipients occur among primary vaccinees. Severe cases have been observed after recently vaccinated persons have been in contact with persons who have active eczema or atopic dermatitis or a history of these skin conditions. In the 1968 studies, eczema vaccinatum was estimated to occur in 10–39 persons per million primary vaccinations.

Progressive vaccinia, also known as vaccinia necrosum, is a severe illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among persons with cellular immunodeficiency, but it can occur in persons with humoral immunodeficiency. In the 1968 studies, it occurred in approximately 1–2 persons per million primary vaccinations. Progressive vaccinia was almost always fatal before the introduction of vaccinia immune globulin and antiviral agents. Progressive vaccinia may be more common now, with human immunodeficiency virus (HIV) and post-transplant immunosuppression widely prevalent. Therapy includes aggressive treatment with vaccinia immune globulin and possibly antiviral drugs.

Postvaccinal encephalitis has been reported in 3–12 persons per million primary vaccinations. In the majority of cases, postvaccinal encephalitis affects primary vaccinees younger than 12 months of age or adolescents and adults receiving a primary vaccination. It presents with any of a variety of central nervous system signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system. Approximately 15%–25% percent of affected vaccinees with this complication die, and 25% develop permanent neurologic sequelae. There is no specific therapy for postvaccinal encephalitis.

Fetal vaccinia is a rare complication of smallpox vaccination. Fewer than 50 cases of fetal vaccinia infection have been reported, usually after primary vaccination of the mother in early pregnancy. Fetal vaccinia usually results in stillbirth or death of the infant soon after delivery. Smallpox vaccine is not known to cause congenital malformations.
Death resulting from smallpox vaccination is rare, with approximately one death per million primary vaccinations and one death per 4 million revaccinations. Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

Guidelines for the evaluation and management of adverse reactions following smallpox vaccine were published in 2003 in the *Morbidity and Mortality Weekly Report* (MMWR). These guidelines are available on the CDC smallpox website at http://www.bt.cdc.gov/agent/smallpox/

### Contraindications and Precautions to Vaccination

As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a severe allergic reaction to a prior dose of vaccine or to a vaccine component. Calf lymph vaccine (Dryvax) contains trace amounts of polymyxin B, streptomycin, tetracycline, and neomycin. The diluent contains glycerin and phenol. The vaccine does not contain sulfa-type antibiotics or penicillin. The new cell-culture vaccines do not contain antibiotics.

Persons with significant immunosuppression or those who have an immunosuppressed household contact should not receive smallpox vaccine in a nonemergency situation. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression. Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, or generalized malignancy; solid organ or stem cell transplantation; and cellular or humoral immunity disorders, including HIV infection. Some autoimmune conditions and/or drugs used to treat autoimmune conditions may cause significant immunosuppression. Therapies that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high-dose corticosteroid therapy. Many experts suggest that prednisone doses of 2 milligrams per kilogram of body weight per day or higher, or 20 milligrams per day or higher for 14 days or more be considered immunosuppressive for the purpose of live virus vaccination. As with other live vaccines, those receiving high levels of these drugs should not be immunized for 3 months after their last dose.

Persons with physician-diagnosed heart disease should not receive the smallpox vaccine. This recommendation is based on findings of cardiac symptoms such as chest pain, palpitations and shortness of breath that were first detected in late March 2003, and is further supported by the recognition of myopericarditis as an adverse reaction. In addition to physician-diagnosed heart disease, persons with three of the
five heart disease risk factors (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of 50) are contraindicated from receiving the smallpox vaccine.

Live viral vaccines are contraindicated during pregnancy. For nonemergency indications, smallpox vaccine should not be administered to pregnant women or persons with a pregnant household contact. Pregnancy should also be avoided for at least 4 weeks after vaccination. Women who are breastfeeding should not be vaccinated because the close contact that occurs during this activity could increase the chance of transmission of the vaccine virus to the breastfeeding infant.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to persons with eczema or atopic dermatitis or a past history of these conditions. Persons who have a household contact with eczema or atopic dermatitis or a history of these conditions should also not be vaccinated.

Persons with other types of acute, chronic, or exfoliative skin conditions (e.g., burns, varicella, herpes zoster, impetigo, severe acne, or psoriasis) may be at increased risk of inadvertent inoculation. People with exfoliative skin conditions should not be vaccinated until the condition is controlled or resolves. In addition, persons with household contacts with acute, chronic, or exfoliative skin conditions should not be vaccinated until the skin condition in the household contact is controlled or resolves.

Children younger than 12 months of age should not be vaccinated. All vaccinated persons should take precautions to prevent virus transmission to young children and other household contacts. Since smallpox vaccine is currently recommended only for persons with occupational risk of exposure to vaccinia or recombinant vaccinia viruses, and for healthcare and public health response team members, vaccination is not indicated for infants or children younger than 18 years of age.

As with all vaccines, vaccination should be deferred for persons with moderate or severe acute illnesses.

In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine. In a postrelease situation, contraindications and precautions for use of smallpox vaccine in a person who has not been exposed to smallpox would be the same as those in a nonemergency situation.
Vaccinia Immune Globulin Intravenous

Vaccinia immune globulin intravenous (VIGIV) is the only product currently available for treatment of complications of vaccinia vaccination. VIGIV is a solvent/detergent-treated sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to vaccinia virus. It is manufactured from plasma collected from healthy, screened donors with high titers of anti-vaccinia antibody. Each plasma donation used for the manufacture of VIGIV is tested for the presence of hepatitis B virus and antibodies to human immunodeficiency viruses 1 and 2 and hepatitis C virus.

VIGIV is indicated for treatment or modification of eczema vaccinatum, progressive vaccinia, and severe generalized vaccinia. It should also be used for vaccinia infections in persons who have skin conditions such as burns, impetigo, varicella zoster, or poison ivy; or for persons who have eczematous skin lesions when it is warranted because of either the activity or extensiveness of such lesions. It is also indicated for aberrant infections induced by vaccinia virus, which include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard. Since postvaccinial encephalitis is not due to virus multiplication, VIGIV is not likely to be effective in treating this adverse reaction. Immune globulin products have no role in the treatment of smallpox.

Supplies of VIGIV are stored in the Strategic National Stockpile. All releases of VIGIV from the stockpile must be approved by CDC.

Antiviral Drugs

Cidofovir is an antiviral medication that is currently licensed for the treatment of retinitis. In vitro and animal studies with this drug have shown some activity against vaccinia virus, but it is unclear how well it would work in treating vaccinia infections in humans. Because it is not licensed for this indication, use of cidofovir for treating vaccinia infections should be done through an investigational new drug (IND) protocol with careful monitoring. Cidofovir is a second-line treatment for complications of smallpox vaccination. VIGIV is still considered the standard treatment. CDC is developing the investigational protocol for use of this drug.

Vaccine Storage and Handling

Lyophilized smallpox vaccine is stable indefinitely at temperatures of -4°F (-20°C) or less. Unreconstituted vaccine should be stored at refrigerator temperature 35°–40°F (2°–8°C). The vaccine should be used within 90 days of reconstitution. Because the vaccine vial must be opened in
order to prepare a dose for administration (i.e., the bifurcated needle is dipped into the vaccine), care must be taken to avoid contamination. A needle should never contact the vaccine in a vial more than once.

Smallpox Preparedness and Response Planning

A smallpox response plan has been in place in the United States since the early 1970s. In 1999, efforts were begun to update the response plan in the context of an intentional release of smallpox virus as an act of terrorism. Following the anthrax attacks in 2001, the plan was revised further to provide detailed information on surveillance and response to a smallpox virus release.

The interim plan is intended to assist with local and state response planning by identifying actions that must be taken in the event of a suspected smallpox case. The key elements of preparedness for smallpox response are surveillance and diagnosis to achieve early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case-patient or patients. Sections of the plan provide detailed information on these critical aspects of the plan, including surveillance and contact tracing, smallpox vaccine, isolation guidelines for both confirmed and suspected cases and febrile contacts of patients, specimen collection and transport, decontamination, and communication.

In December 2002, the President announced a plan to better protect the American people against the threat of smallpox attack. The Department of Health and Human Services will work with state and local governments to form volunteer Smallpox Response Teams, which can provide critical services in the event of a smallpox attack. To ensure that Smallpox Response Teams can mobilize immediately in an emergency, healthcare workers and other critical personnel may be asked to volunteer to receive the vaccine. The Department of Defense will also vaccinate certain military and civilian personnel who are or may be deployed in high-threat areas. Some U.S. personnel assigned to certain overseas embassies may also be offered vaccination. The plan does not include a recommendation for vaccination of the general public.

Selected References

Smallpox


CDC. Notice to Readers: Supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. MMWR 2003;52:282–84.


Welcome Message

William L. Atkinson, MD, MPH
Medical Epidemiologist
National Immunization Program, CDC

I’m Dr. William Atkinson, a medical epidemiologist in CDC’s National Immunization Program. I would like to welcome you to this interactive presentation of Smallpox: What Every Clinician Should Know.

The main purpose of this training is to educate physicians and other health professionals about the clinical features, diagnosis, management, and prevention of smallpox. While we are pleased to offer continuing education credit for physicians, nurses, and health educators who successfully complete this training, the primary emphasis of this program is on smallpox clinical information, and in particular, the recognition of a smallpox case. In the future, we intend to develop other versions tailored for professionals without an extensive medical background.

The information in this training was excerpted from a satellite broadcast on smallpox that first aired in December 2001, and was revised in April 2003. The program that you are about to use has been developed as an additional medium for clinicians to learn about smallpox.

After completing this training, you should be able to describe the clinical characteristics of smallpox. Differentiate between smallpox and other rash illnesses. Describe the indications for smallpox vaccine in both prerelease and postrelease situations. And describe the components of the smallpox response plan.

The training begins with an interactive practice exercise that will involve you in a hypothetical outbreak setting. The exercise is NOT intended to encompass all situations that could arise during an outbreak. The exercise focuses on the role of the clinician in the event of an outbreak. Detailed information on outbreak control strategies, and other issues surrounding the public health response to an intentional release of smallpox virus can be found in the CDC Smallpox Response Plan. The Plan is included in the reference section of this training.
The Smallpox Response Plan, and recommendations for the use of smallpox vaccine will evolve over time. The most current recommendations can always be found on the CDC Smallpox Website.

Clinicians will play a vital role in the event of an outbreak of smallpox. We appreciate the time you are taking to learn about the disease and how to recognize it. We also welcome your feedback. Your comments will help guide us in developing future versions of this program. Contact information for the CDC Smallpox Program is included in the reference section of this training.

The following have disclosed that their presentations will include discussion of investigational use of smallpox vaccines and vaccinia immune globulin (VIG) and unlabeled use of cidofovir: William Atkinson, MD; Joanne Cono, MD; Lisa Rotz, MD.

(Welcome video)

How To Use

The following section describes how to navigate through the interactive version of this training program.

Before beginning, take a moment to review the layout and features used in this training. The course's main content is presented in video format. As time permits, you can watch them all in one sitting or a few at a time.

From start to finish, it takes approximately 2.5 hours to complete this training. The actual time you spend may be shorter or longer depending on how much of the additional information you choose to review.

There are two primary ways to use this program. You can work through the exercise, viewing the videos as you go. Or, you can view the videos first, then work through the exercise.

All videos are available from this Video menu (ref graphic below). You can open and close this menu as needed.
The practice exercise is presented on the left side of your screen, in the pages of this notebook (ref. graphic below). As the practice exercise unfolds, you are placed in a potential real-life setting at the beginning of a modern day smallpox outbreak. Proceeding through the exercise, you will play the role of a clinician in various health care settings and will be asked to make important decisions.

You are not expected to know the correct answers. Rather, the questions are there to guide you in gleaning important information from the upcoming video segment. As you work through the exercise, you will be directed to specific video segments at the appropriate places.

You can move through the practice exercise by the "Continue" and "Back" buttons located at the bottom.
You can go directly to any previously viewed page by clicking on one of the tabs shown here.

Additional information is available here, under this retractable menu. From this menu you can access: patient education materials, links to related references, and a Self-Test for this course.
Patient Education Materials are information pieces you can print and reproduce for your patients, should the need arise. Under references you will find additional reading, links to related Websites, supplementary video segments, links to referenced articles and publications, and other materials relating to smallpox.

At the end of the practice exercise, you will be prompted to take the Self-Test. The Self-Test score is not recorded, it is for your information only. Use it as a learning tool to assess your knowledge of the material covered in the videos and practice exercise. Persons who want to receive continuing education credit for this program must complete the Self-Test prior to applying for CE credit. You can access the Self-Test at anytime through this menu.

Finally, for more information pertaining to this course please refer to the "About This Training" link. In addition to the course goal and objectives, you will find information about how to receive continuing education credit, how to print the contents, and how to send your feedback on the methods and contents of this course.

This concludes the overview of how to use this training.

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Practice Exercise

The information in this program is current as of April 16, 2003. However, specific recommendations, the status of smallpox vaccine, and information on the use of anti-viral drugs will change. We encourage you to periodically review CDC's National Immunization Program (www.cdc.gov/nip/) and Public Health Emergency Preparedness & Response (www.bt.cdc.gov) Websites for updated information.

Since this program was produced, an outbreak of monkeypox occurred in the United States. For information about monkeypox, go to the CDC monkeypox Website at http://www.cdc.gov/ncidod/monkeypox/index.htm.

Page 2 (Instructions)

You are about to embark on a practice exercise that will take you through a fictitious scenario involving the beginning of a smallpox outbreak. In this practice exercise, people will be presented to you in different settings and you will be asked questions relevant to identifying smallpox. Do not worry about getting the answers correct during the practice exercise -- they are simply questions of intuition. Your answers are not scored.

As you begin, assume there have been no other reports of smallpox since 1980 when smallpox was officially declared eradicated from the world.

If you would like to review how to navigate and use this training before you see your first patient, see "Instructions."

Page 3 (David's first visit, 1st question)

You are a clinician seeing patients in your office.

Review David's symptoms from his chart below. Based on this limited information provided in his chart, what do you think is David's illness?

You suspect streptococcal pharyngitis and prescribe a course of antibiotics while awaiting laboratory confirmation.
You suspect smallpox and call the health department immediately.
You think he has a viral infection common in late winter. You send him home with instructions to drink fluids and take aspirin or ibuprofen for the muscle aches.

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**Patent Chart: David Johnson**

**When**: Today, Wednesday, February 18  
**Where**: Solo practice, City of "Americaville," population 1 million  
**Who**: David Johnson, male college student, age 22  
**What**:

- Has been sick for 1½ days  
- Severe muscle aches  
- Abdominal pain, several episodes of vomiting  
- Oral temperature 103°F  
- Pale  
- Slightly leukopenic WBC=4,500 (normal level=5,000-10,000)  
- Normal physical exam except for diffusely erythematous pharynx; no exudate

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**Page 4 (Clinical features)**

You selected that he may have a viral infection and that you would send him home with instructions to drink fluids and take aspirin or ibuprofen for the muscle aches.

That is a fair assumption and reasonable course of action.

David Johnson has symptoms of a viral infection-it is not possible to make a smallpox diagnosis because 1) his symptoms are non-specific, and 2) smallpox has not been seen in the world since the 1970s.

Streptococcal pharyngitis is unlikely because David has no exudate. Standard practice would be to send the patient home with aspirin or ibuprofen and instructions to drink fluids.

The next step is to learn about clinical features.

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**Page 5 (David's second visit, condition worsened, 2nd question)**

David's condition has not improved, and now he has a rash.

Review the update in his chart below.

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**Patent Chart**

**When:** Today, Saturday, February 21 (click here to see chart from 3 days ago, February 18)  
**Where:** local emergency room  
**What:**

- David Johnson has had fever and muscle aches for the past 5 days.  
- He has a negative or uncertain history of chickenpox.  
- The only medicine he is taking is ibuprofen to relieve fever and muscle aches.  
- He has never had any drug allergy and has taken ibuprofen many times in the past.  
- David has developed a rash on his face and arms.  
- Some raised spots (papules) appeared yesterday on his face.

(Close up of David's face)

- More papules are appearing today on his arms

(Close up of David's arm)

- Papules differ somewhat in size, but they all appear to be at the same stage of development in any given area of his body.  
- He appears acutely ill.  
- Oral temperature 100°F  
- Normal blood pressure
You're now a clinician in this emergency room. What do you think is David's illness?

- You think he has adult chickenpox (varicella), though he has not had contact with anyone else known to have chickenpox.
- You think he has impetigo.
- You think he is experiencing a drug reaction.
- You think he has smallpox.

Page 6 (decision answer)

Except for suspecting smallpox, all the other choices are reasonable assumptions, given that smallpox was officially declared eradicated in 1980.

Usually during the first two days of rash, it is difficult (just from looking at the rash) to differentiate smallpox from chickenpox or other causes of rash illness. David's illness is none of the choices listed in the previous question.

Key factors that distinguish smallpox from chickenpox, impetigo, or a drug allergy are:

1. febrile prodrome--severe illness 1 to 4 days before rash onset, and
2. classic smallpox lesions in the same stage of development on different parts of the body.

With impetigo, honey-colored crusted plaques with bullae are classic but may begin as regional vesicles.

Other than his elevated temperature, David's vital signs are normal, and he is not sick enough to be admitted into the hospital. Because he may represent an infectious disease risk to other patients-especially immunocompromised patients—you send him home as rapidly as possible.

Page 7 (video-differential diagnosis)

The next step is to learn more about differential diagnosis of smallpox and other rash illnesses.

Page 8 (Gayle's first visit, 3rd question)

You are the same emergency room clinician who saw David Johnson earlier today.

You are now seeing another patient, Gayle Mack.
Review her chart below.

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Patient Chart: Gayle Mack

**When:** Today, Saturday, February 21 (same day as David's visit to the emergency room)

**Where:** same emergency room

**Who:** Gayle Mack, age 45, mother of 2 children, ages 12 and 15

**What:** She gives the following history:

- 4 weeks ago (January 26): one of her children had a viral/flu-like illness
- 2 weeks ago (February 7): Gayle developed upper respiratory symptoms including rhinorrhea (runny nose), cough, and malaise. She took over-the-counter cold medications and she began to improve after four days.
- 8 days ago (February 14): Gayle went to the emergency room with a one-day history of high fever, chills, headache, and vomiting. She still has a bit of a residual cough. Chest X-ray and urinalysis were normal. She was diagnosed with a viral syndrome, possibly influenza, and was sent home to take fluids, ibuprofen, and rest.
- 5 days ago: rash onset (splotches of non-raised skin lesions, called macules)
- 4 days ago: macules became raised skin lesions, called papules

(What Gayle's arm looked like 4 days ago, the 2nd day of the rash)

(What Gayle's face looked like 4 days ago, the 2nd day of the rash)
• 3 days ago: more papules appeared, some became vesicular
• Yesterday: lesions appeared on her palms and hands
• Gayle has no idea how she got sick. She does not know of anyone with a similar illness to hers.
• She is sure she had chickenpox when she was 8 years old.
• Current physical findings:
  o Acutely ill
  o Pale
  o Fever 102°F
  o Vesicular rash on face, arms, palms of the hands, and soles of the feet
  o Vesicles are round and deep within the dermis and are between 5 and 10 mm in size. Rash appears to be in same stage of development on each area of her body.

What do you think is Gayle Mack's illness?
  o You think this is a serious case of adult chickenpox.
  o You think she is experiencing a drug reaction to the over-the-counter medication.
  o You think she has disseminated herpes zoster.
  o You move her into an isolation area immediately. Because she is the second adult patient with similar rash and febrile illness, you want an infectious disease consultant to see her.

Moving her into an isolation area immediately is the correct choice. On Day 5 of smallpox rash, the lesions are hard, ruling out most other types of rash illness.

Early in the course of her illness, a drug reaction would be strongly considered, but at Day 5 of her rash, Gayle has classic smallpox lesions. Disseminated herpes zoster starts with a localized rash, a band-like distribution of painful lesions that do not look like smallpox. Herpes zoster only disseminates in immunocompromised individuals.

Arguments against chickenpox:

1. her rash is at the same stage of development on any specific part of her body,
2. she had a severe febrile prodrome 1 to 4 days before rash onset,
3. her rash is on the palms of her hands and soles of her feet, and
4. if this were chickenpox, within 24 hours some lesions would have crusted, and by Day 5 many would have crusted.

Gayle has a classical smallpox presentation. If you suspected a rash illness other than smallpox, please review the Rash Illness Evaluation video.

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Both patients have developed skin lesions that are evolving in similar stages of development. Gayle Mack knows she had chickenpox as a child, but David Johnson is uncertain of his history.

The infection control practitioner examines Gayle and reviews the history and findings of David. Because chickenpox is infectious as well as unusual in adults, the infection control practitioner comes to see you, and she raises the possibility of smallpox. The two of you use the CDC Smallpox Protocol "Evaluating Patients for Smallpox" to determine Gayle Mack's risk of smallpox. Using the protocol, you realize that Gayle meets all three of the major criteria for smallpox risk:

1. severe, febrile prodrome
2. classic smallpox lesions
3. lesions in the same stage of development

Because the patient meets all three major criteria, there is a high risk of smallpox.

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The following happens within the next 45 minutes:

- You call the local health department.
- You use a digital camera to take high quality, close-up photos of Gayle's rash.
- The hospital infection control practitioner places Gayle in a negative pressure room to protect against airborne transmission.
- The local health department consults with bioterrorism experts at the state health department.
- The state health department immediately alerts the CDC.
- The CDC and state and local health departments communicate directly with you and the hospital infection control practitioner.
- David Johnson is contacted, and isolated at home if his condition allows.

Health department personnel are sent immediately to the hospital to collect clinical specimens and administer smallpox vaccine. A CDC response team is deployed to collect specimens to return to CDC laboratories in Atlanta.
Page 12 (test results reveal smallpox virus)

The next step is to learn about laboratory methods for diagnosis.

Test results at CDC reveal an orthopoxvirus consistent with the smallpox virus, variola.

The public health department closes the hospital, and smallpox vaccine is administered to family members and other close contacts of the patients, close contacts of the family members, certain hospital employees, and other individuals who were exposed to David and Gayle when they were sick.

Note:
If an outbreak were to actually occur, the specific exposure situation would determine who exactly would be vaccinated. As a clinician, you may be involved in assisting with vaccination administration.

To learn about the public health response to a smallpox outbreak, including security, quarantine, vaccination strategy, and other issues, please see the "CDC Smallpox Response Plan and Guidelines."

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The next step is to learn about smallpox vaccine and its administration:

- smallpox vaccine background
- smallpox vaccine indications
- smallpox vaccine precautions and contraindications

Then, review this short video that shows a smallpox vaccine being administered.

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In the city of "Americaville," two additional smallpox patients have been confirmed in other hospitals in the last two days. A CDC team has been asked to assist the local and state health departments with establishing multiple vaccination clinics.

You are now the medical director of one of the vaccination clinics. A nurse asks you if she should vaccinate two people: one person is David Johnson's mother, who lives with him and has been taking care of him at home ever since he got sick. David's mother has eczema. The other person is a man with eczema who did some electrical work at Gayle Mack's house one month before her illness began.

What do you tell the nurse to do?

- As long as both people are made aware of the risk of adverse reactions to the vaccine, it is their choice whether or not to get vaccinated.
- Do not vaccinate either person because eczema is a contraindication to smallpox vaccine.
- Vaccinate David's mother, but do not vaccinate the man.
- Vaccinate the man, but do not vaccinate David's mother.
You selected to vaccinate David's mother but not the man is the correct choice.

There is no contraindication to vaccinating anyone who has been exposed to smallpox. However, eczema and atopic dermatitis are contraindications for people who have ever had eczema or atopic dermatitis and who have not had direct exposure to variola virus.

David's mother should be vaccinated because she has had prolonged, direct exposure to a smallpox patient.

The man who did electrical work at Gayle's house should not be vaccinated. His risk of an adverse reaction to the vaccine outweighs his risk of developing smallpox—he has not been exposed to the virus.

If a person with known exposure to variola (smallpox) virus chooses not to be vaccinated, then that individual would need to be quarantined. For information on quarantine, please see Guide C of the CDC Smallpox Response Plan and Guidelines.

The next step is to learn about adverse reactions of smallpox vaccine.

Gayle Mack has become severely ill and her vesicles are close together. Some vesicles have merged. She looks extremely sick.

What can you do for treatment?

- Treat her with IV Acyclovir.
- Provide supportive therapy such as oxygen and IV fluids.
- Work with the infectious disease consultant to treat her with cidofovir.

You selected to provide supportive therapy such as oxygen and IV fluids. That is correct.

Acyclovir has not been shown to be effective in treating poxvirus infections. The effectiveness of cidofovir for treatment of smallpox is unclear because it has never been used on a smallpox patient. Cidofovir has not been approved by the FDA for
treating smallpox. Therefore, use of cidofovir for this cause would be an off-label use. Cidofovir has significant side effects and has only been approved for treatment of CMV retinitis in AIDS patients.

There is no proven antiviral treatment for smallpox, but research to evaluate new antiviral agents is ongoing. Patients with smallpox can benefit from supportive therapy such as intravenous fluids, medicine to control fever or pain, and antibiotics for any secondary bacterial infections that may occur. However, the case fatality rate in the past averaged 30%. That rate could be higher or lower now, due to:

- advances in medical supportive care
- higher numbers of immunosuppressed individuals
- lack of immunity in the general population

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The next step is to learn more about isolation and medical management for smallpox patients.


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It is now apparent that there has been an intentional release of smallpox virus in "Americaville," and a massive control program will commence immediately to contain the outbreak.

To learn how the response might unfold, review the Executive Summary of the Smallpox Response Plan and Guidelines.

This concludes the scenario portion of this practice exercise.

The next step is to learn about the epidemiology of smallpox.

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The next step is to learn about the global smallpox eradication program.

The next step is to learn about CDC's Smallpox Response Plan.

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Finally, assess your knowledge of smallpox by taking the Self-Test.

Videos (transcripts)

History of Smallpox—the Disease

Smallpox as a Biological Weapon

Virus

Clinical Features

Rash Illness Evaluation

Laboratory Diagnosis

Vaccine Background

Vaccine Indications

Vaccine Precautions and Contraindications

Vaccine Administration

Vaccine Adverse Reactions

Isolation and Management

Epidemiology

Global Smallpox Eradication

Surveillance and Containment Strategy

Smallpox Response Plan

History of Smallpox—the Disease (slides; video)

Lisa D. Rotz, MD
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

Smallpox is an acute infectious disease caused by the variola virus. It’s thought to have emerged in human populations about 10 thousand years BC.

(Graphic: image of Ramses V mummy)
The earliest evidence of smallpox is believed to be the vesicular skin lesions of the mummy of Ramses V, who died in Egypt in 1157 BC. The first clear description of smallpox appeared in a Chinese medical text in the fourth century AD. The term smallpox was first used in Europe in the fifteenth century to distinguish variola from the great pox - syphilis.

(Graphic: Variola major)
Variola major is the severe form of smallpox, with an extensive rash, higher fever, and a greater degree of prostration. Variola major has an overall case fatality rate of about 30 percent. During the first half of the twentieth century, all outbreaks of smallpox in Asia and most in Africa were due to variola major. The last case of naturally acquired variola major occurred in Bangladesh in 1975. The last case of indigenous smallpox on earth occurred in Somalia in 1977.
**Smallpox as a Biological Weapon** *(slides; video)*

*Lisa D. Rotz, MD*
*Medical Epidemiologist*
*Bioterrorism Preparedness and Response Program, CDC*

Smallpox is believed to have been used as a biological weapon during the French and Indian Wars in the mid-eighteenth century. British soldiers are thought to have intentionally distributed blankets to the Indians that had been used by smallpox patients. Smallpox outbreaks resulted, killing more than 50 percent of some north eastern tribes. With the declaration of global smallpox eradication in 1980, and subsequent suspension of vaccination, much of the population of the world is now susceptible to smallpox. In the United States alone, more than 100 million people have never been vaccinated. In addition, most people vaccinated decades ago may no longer have protective immunity from smallpox.

(Graphic: high priority bioterrorism agents)

Variola virus has been classified as a high priority bioterrorism agent. Other high priority agents include Bacillus anthracis, the cause of anthrax, Yersinia pestis, the agent of plague, Francisella tularensis, which causes tuleremia, botulinum toxin, and the Filo and Arenaviruses, which cause hemorrhagic fevers such as Ebola.

(Graphic: high priority bioterrorism agents - aerosol transmission)

Most high priority agents can cause infection by aerosol transmission, affect highly susceptible civilian populations, have a high morbidity and mortality, and are difficult to diagnosis and/or treat. Some are transmitted from person to person. Smallpox has all of these characteristics.

Although we have no direct evidence of anyone’s intent to use smallpox as a weapon, we must still be prepared. Few clinicians today have ever seen a case of smallpox. This is the reason for this program- to familiarize providers with the disease and it’s epidemiology, the vaccine to prevent it, and the action to take should a case be suspected.

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**Virus** *(slides; video)*

*William L. Atkinson, MD, MPH*
*Medical Epidemiologist*
*National Immunization Program, CDC*

Smallpox is caused by variola virus. Variola virus belongs to the family Poxviridae, and genus Orthopoxvirus.

(Graphic: virus photomicrograph)

Poxviruses are large brick-shaped viruses with a double stranded DNA genome. They are different from most other DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To do this, they produce a variety of proteins not produced by other DNA viruses, like herpes virus.

(Graphic: poxviruses that infect humans)

Four orthopoxviruses are known to infect humans- variola, vaccinia, cowpox, and monkeypox. Variola virus is strictly a human virus, although primates and other animals can be infected under laboratory conditions. The other 3 viruses can infect both humans and other animals in nature.

Smallpox vaccine contains vaccinia virus, not variola virus. Vaccinia is rarely isolated from animals outside the laboratory. Vaccinia virus can also be genetically engineered to accept DNA and express other antigens, and has been used as a vector in laboratory experiments for vaccine development. Cowpox was probably the virus that Edward Jenner originally used as a vaccine for smallpox. The virus has many natural hosts, including cows, rodents, cats, and elephants. It’s found in nature primarily in Europe. Monkeypox infects primates, anteaters and squirrels, and is found in western and central Africa.

Cell culture is used to rapidly indicate the presence of virus in a specimen, but cannot identify which poxvirus is present. DNA based tests, such as polymerase chain reaction, or PCR, are used for differentiation of orthopoxvirus species.

(Graphic: survival of poxviruses - Variola virus)
Variola virus can remain viable for several days in a controlled environment. Vaccinia virus can also remain viable at room temperature for up to a week. In temperate climates, scabs from smallpox patients, in which smallpox virus is contained in a fibrin matrix, can retain viable virus for several years when held at room temperature.

(Graphic: survival of poxviruses - survives longer)
The virus survives longer at low temperature and humidity than at higher temperature or humidity. This helps explain the seasonality of smallpox, in which transmission was greatest during the cooler months of the year. All poxviruses are rapidly inactivated by exposure to ultraviolet light, and chemical disinfectants such as bleach or Lysol.

Some people infected with variola virus have particularly severe illnesses. This suggests that there could be differences in the virulence of strains of the virus. But no laboratory test has been devised that correlates with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

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**Clinical Features** ([slides](http://www.cdc.gov/nip/ed/smallpox-trg/clinician-should-know/contents/printable_version.htm); [video](http://www.cdc.gov/nip/ed/smallpox-trg/clinician-should-know/contents/printable_version.htm))

Lisa D. Rotz, MD
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

Variola virus infection begins when the virus comes into contact with the oropharyngeal or respiratory mucosa. Virus multiplication then occurs in regional lymph nodes. A viremia begins about the eighth day of infection. The virus localizes and replicates in small blood vessels of the dermis and in the oral and pharyngeal mucosa. This leads to the characteristic rash.

Variola major is a severe illness with a high fatality rate. There are four clinical presentations of variola major, based on the nature and evolution of the lesions. The relative vigor of the immune response probably determined the clinical presentation.

(Graphic: types of Variola major)
The most frequent presentation is ordinary smallpox. Modified smallpox is milder and may occur in previously vaccinated people. Flat and hemorrhagic smallpox are very severe but uncommon variants.

(Graphic: clinical features)
The incubation period of smallpox averages 12 to 14 days, with a range of 7 to 17 days. During this period the patient is well. The prodrome or pre-eruptive stage of the illness begins abruptly, with fever, malaise, headache, muscle pain, prostration, and often nausea and vomiting and backache. The temperature usually rises to at least 101 F, and is often higher. The person usually appears quite ill. A severe febrile prodrome prior to rash onset is characteristic of smallpox, and helps differentiate it from many other causes of rash illness.

More than 90 percent of cases in both vaccinated and unvaccinated persons are of the ordinary type, which corresponds to the classical description of smallpox. By the third or fourth day of illness the temperature usually falls and the patient feels somewhat better. At this point, the first visible lesions appear and the person becomes infectious.

(Graphic: rash)
The first lesions appear in the mouth as minute red spots on the tongue and oral and pharyngeal mucosa, about 24 hours before the appearance of rash on the skin. Lesions in the mouth and pharynx enlarge and ulcerate quickly, releasing large amounts of virus into the saliva. Virus titers in saliva are highest during the first week of the skin rash, corresponding with the period during which patients are most infectious.

The skin rash usually appears first as a few macules, known as herald spots on the face, particularly on the forehead. Lesions then appear on the proximal portions of the extremities, then spread to the trunk and the distal portions of the limbs. Usually, the rash appears on all parts of the body within 24 hours.

(Graphic: skin rash, day 2)
By the second day of the rash, the macules become raised papules. This child has only a few papules on the forehead and arm.

(Graphic: skin rash, day 4)
By the third or fourth day the lesions become vesicular, containing first a clear fluid, which then becomes opaque and turbid within 24 to 48 hours. Fever usually rises again at about this time, and remains high throughout the vesicular and pustular stages until scabs have formed over all the lesions.

(Graphic: umbilication)
The distended vesicles often have a central depression of varying size, making them dimpled, or umbilicated. An umbilicated appearance often persists into the pustular stage, but as the lesion progresses they usually become flattened because of reabsorption of fluid. An umbilicated appearance is unusual in other rash illnesses, particularly in varicella.

(Graphic: skin rash, day 6)
By the sixth or seventh day, all the skin lesions have become pustules. The pustules are sharply raised, typically round, tense, and firm to the touch. The pustules are deeply imbedded in the dermis, and were often described as having a shotty feel, similar to a small bead embedded in the skin.

(Graphic: skin rash, day 8)
Between 7 and 10 days the pustules mature and reach their maximum size. Notice that many of the lesions remain umbilicated and that all the lesions are in about the same stage of evolution. Although lesions are dense around the nose and mouth, the majority of lesions are discrete, separated by normal appearing skin.

(Graphic: confluence)
In some cases, the lesions are so dense they become confluent. Confluence is most common on the face, but can involve the extremities, as in this image. Patients with confluent smallpox often remained febrile and more ill appearing even after scabs began to form over the lesions. In one case series the case-fatality rate in confluent smallpox reached 62 percent.

(Graphic: skin rash, day 13)
The pustules began to form a crust at about day 10 of the rash. By about 14 days, most of the lesions have scabbed, and some have begun to separate.

(Graphic: skin rash, day 20)
About three weeks after rash onset scabs have separated, except on the palms and soles. Skin at the site of each lesion is depigmented and would eventually become pitted scars because of deeper skin layer involvement.

(Graphic: rash – slow progression)
Here are a few more important points about the smallpox rash. The progression of the rash between stages is relatively slow compared to other rash illnesses. Each stage- papules, vesicles, and pustules- usually takes one or two days to develop. The rash usually appears as a single crop. Consequently, lesions in a particular part of the body are at the same stage of development, although they may be different sizes.

(Graphic: rash – centrifugal distribution)
The rash of smallpox has a centrifugal distribution, meaning it’s most dense on the face, and more dense on the extremities than on the trunk. On the extremities, it was more dense on the distal parts than on the proximal, and on the extensor than on the flexor surfaces. The palms of the hands and soles of the feet were involved in the majority of cases.

These clinical characteristics are important in differentiating smallpox from other causes of rash illness. We will discuss this in more detail later in the program. Bill?
Thank you Lisa. A second clinical type of smallpox is called modified smallpox. “Modified” refers to the character of the eruption and the rapidity of its development. Modified smallpox can occur in previously vaccinated people who are no longer fully protected. However, unvaccinated people may also present with this form of smallpox.

Two types of variola major were particularly severe, with a high fatality rate. These were flat, or malignant, smallpox, and hemorrhagic smallpox. Flat-type smallpox is so called because the lesions remain more or less flush with the skin at the time when raised vesicles form in ordinary type smallpox. In a large series of smallpox cases from India, flat type smallpox accounted for 5 to 10 percent of cases. It’s not known with certainty why some people developed this type of disease, but many cases occurred in children.

Hemorrhagic smallpox is a severe and uncommon form of smallpox that is almost always fatal. It involves extensive bleeding into the skin, mucous membranes and gastrointestinal tract. In the large Indian series, hemorrhagic disease occurred in about 2 percent of cases, and occurred mostly in adults.
easily misdiagnosed as meningococcal bacteremia because of the hemorrhages and lack of typical smallpox vesicles and pustules.

For all types of smallpox, the outcome of the infection is either recovery - with or without sequelae - or death. Those who survive usually have scars. If there is eye involvement, blindness could also occur. Recovery results in long lasting immunity to reinfection with variola virus. Second cases of smallpox are rare, if they occur at all. There is no evidence of chronic or recurrent infection with variola virus. In fatal cases, death usually occurs between the tenth and sixteenth days of the illness. The overall case fatality rate for variola major was about 30%. But the fatality rate for children less than 1 year of age was 40% to 50%. The cause of death from smallpox is not clear since the infection is now known to involve multiple organs. Circulating immune complexes or an uncontrolled immune response may have been contributing factors, as well as overwhelming viremia and soluble variola antigens.

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Rash Illness Evaluation (slides; video)

Joe Washington
Moderator

Clinicians who evaluate patients with rash illnesses need to be able to determine quickly if their patient may have smallpox. Because there are millions of cases of rash illness in the United States each year and no evidence that smallpox is being transmitted, the risk of smallpox is currently extremely low. For this reason we focus on identifying classic cases of smallpox. This means that the first case of smallpox might not be recognized in the first few days of rash, when the presentation is nonspecific. With appropriate infection control procedures the risk to others would be small. However, if a case of smallpox is ever confirmed in the U.S., our strategy for finding other cases would be altered to capture early and atypical cases. So keep in mind that the current strategy is intended to screen a large number of people with rash illnesses at a time when the risk of smallpox is extremely low. Here is Dr. Jane Seward, Chief of the Viral Vaccine Preventable Diseases Branch of the National Immunization Program, to discuss the differential diagnosis of rash illness.

Jane Seward, MBBS, MPH
Chief, Viral Vaccine-Preventable Diseases Branch, National Immunization Program, CDC

In this presentation I will discuss the evaluation of persons with febrile vesicular or pustular rash illness. This is important, because if a case of smallpox were ever to occur again in the United States, on the one hand, we would want to diagnose it as soon as possible so that appropriate public health actions could be implemented. On the other hand, we want to minimize laboratory testing for smallpox virus for suspected smallpox cases unless they meet the clinical case definition because of the very real danger of obtaining a false positive test.

There have been no naturally acquired cases of smallpox in the world since 1977. However, there are serious concerns about the use of smallpox virus as a bioterrorist agent. Recommencing smallpox vaccination in the United States has heightened concerns about febrile vesicular and pustular rash illnesses.

(Graphic: need for a diagnostic algorithm)
In the event of a bioterrorist release of smallpox virus, effective public health control strategy requires early recognition of a smallpox case. Most clinicians have never seen a case of smallpox and therefore lack experience with making a smallpox diagnosis. Because other rash illnesses may be confused with smallpox, a diagnostic algorithm or a standard approach to evaluating rash illness cases is useful.

Though varicella, or chickenpox, has declined significantly due to the use of varicella vaccine, there may be still about half a million to 1 million cases in the U.S. every year and many more millions of cases of other rash illnesses. If for example, 1 out of every thousand varicella cases were suspected to be smallpox, there would be 500 to 1000 false alarms per year. The health system cannot handle hundreds of false alarms.
We need a strategy with high specificity to accurately detect the first case of smallpox. This strategy will serve to minimize laboratory testing for smallpox, which will reduce the risk of producing a false positive lab test, and guide laboratory testing needed to rule in, or confirm, other conditions.

Let’s now review the clinical features of smallpox. The illness begins with a prodrome or pre-eruptive stage— with a fever and systemic complaints that occur 1 to 4 days before the rash. Although the rash starts as an eruption on the mucous membranes inside the mouth, frequently the first rash is noticed on the skin. The lesions start as macules and then progress to papules, vesicles, and finally pustules. The pustules crust and form scabs which separate and may leave deep scars.

These photographs show classic smallpox vesicles which are present four to five days after rash onset and pustules which reach their maximum size by day 11. Note that in smallpox, the lesions are all in the same stage of development on that part of the body.

The typical pattern of smallpox rash distribution is demonstrated in this drawing. The lesions are concentrated distally on the head and the extremities in contrast with the central distribution— meaning more lesions on the trunk— that is typically seen in varicella.

Varicella is the disease most likely to be confused with smallpox. It is important then for health care providers to recognize the differentiating features of varicella.

With varicella, there is generally no, or a mild, prodrome. There is likely to be no history of varicella or varicella vaccination. The skin lesions of varicella are superficial, that is they are located on the skin surface. They are classically described as a dew drop on a rose petal. They typically appear in multiple crops meaning that new lesions appear over several days. This leads to the next important differentiating feature.

Lesions are typically in different stages of development. Thus, on any one part of the body, there may be macules, papules, vesicles and crusted lesions. The varicella lesions evolve more rapidly than smallpox lesions; typically they progress from macule to vesicle and even crust within 24 hours. Unlike smallpox, there is a centripetal, or central, distribution of the rash. Lesions appear rarely on the palms or soles and the patient is rarely toxic or critically ill. However, a word of caution. Severe cases of varicella which occur more commonly among adults may present with a significant prodrome. They may also have so many lesions that distribution that may not be a useful differentiating feature and there may lesions on the palms and soles.

Varicella infected lesions may confuse the diagnosis. During the smallpox eradication era, varicella cases among adults, especially those with infected lesions, were the most difficult to differentiate from smallpox cases.

Apart from varicella, other conditions to consider in the differential diagnosis in a patient with fever and a vesicular or pustular rash are: disseminated herpes zoster; impetigo; drug eruptions; contact dermatitis; and erythema multiforme.

Apart from varicella, other conditions to consider in the differential diagnosis include: enteroviral infections - especially, hand, foot and mouth disease; disseminated herpes simplex virus infections; scabies and insect bites; and molluscum contagiosum...
in immunocompromised patients.

(Graphic: differential diagnosis – rare dermatological)
The differential diagnosis may also include other rare dermatological conditions, such as Bechet’s disease, acne, secondary syphilis, rickettsial diseases, such as Rocky Mountain Spotted Fever, typhus and diseases like monkeypox that are unlikely to be seen in the United States may also be rare causes of confusion. Now that we are again administering smallpox vaccine in the United States, generalized rashes due to smallpox vaccine may raise suspicions of smallpox.

CDC has developed a rash algorithm poster to assist clinicians in the diagnosis of vesicular and pustular rash illnesses. The poster lists these diagnoses as well as clinical clues for every condition, and images of smallpox and varicella.

(Graphic: rash illness poster)
The poster looks like this. It is available in 2 sizes, a wall size of 2 feet by 3 feet, and a smaller size 11 by 17 inches. In addition to images, it also lists features that differentiate varicella from smallpox and common conditions that might be confused with smallpox. Finally, it presents a method for classifying cases according to their risk of smallpox using major and minor criteria for smallpox.

(Graphic: smallpox major criteria)
We created 3 major criteria for the clinical diagnosis of smallpox that correspond to the 3 essential components of the clinical case definition. First, a prodrome that begins 1 to 4 days before rash onset and includes fever 101 degrees fahrenheit or higher, and at least one of the following symptoms: prostration, headache, backache, chills, vomiting, abdominal pain. Second, the presence of classic smallpox lesions: firm, round, deep-seated vesicles or pustules. And third, that the lesions are all in same stage of development on one part of the body.

(Graphic: smallpox minor criteria)
We created five minor criteria that are characteristic of smallpox cases. The lesions have a centrifugal, or distal distribution; the first lesions appear on the oral mucosa, face, or forearms; the patient appears toxic or moribund. Typically a patient is so sick that they are bed ridden. The rash has a slow evolution, in which each stage lasts for 1 or 2 days, so it takes more than a week to reach the height of the pustular stage. And finally, there are lesions on the palms of the hands and/or the soles of the feet.

(Graphic: evaluating patients for smallpox)
The major and minor criteria are combined to classify cases of rash illness as seen in this graphic, which is also on the rash algorithm poster. Depending on the major and minor criteria present, the case is classified as high risk for smallpox - the red boxes, moderate risk- the yellow boxes, or low risk, in the green boxes. The poster suggests evaluation steps and public health action based on level of assessed risk.

(Graphic: immediate action)
First, if a patient presents at an emergency room or a hospital with a fever and an acute, generalized vesicular or pustular rash illness, institute airborne and contact precautions immediately, and alert the infection control team if the patient is admitted. If there is concern that the patient may have smallpox, the patient should be assessed for smallpox risk using the major and minor criteria.

(Graphic: high risk)
Any patient presenting with all 3 major criteria is classified as high risk for smallpox - febrile prodrome, and classic smallpox lesion which are all in the same stage of development on one part of the body.

(Graphic: response to high risk)
The response to a high risk case should be to request an Infectious Diseases and/or dermatology consultation. If the high risk status is confirmed, then alert the local or state health department and obtain digital photos if possible. After concurrence, the state health department will alert the CDC rash illness response team to arrange for specimen collection and testing at CDC.

If a case is high risk, it fits the clinical case definition and therefore should be considered a probable case of smallpox until...
smallpox virus laboratory results are completed. For such a case, do not perform other lab testing to rule out other diagnoses, because exposure to potentially infectious material should be minimized until smallpox is ruled out.

(Graphic: moderate risk)
Moderate risk for smallpox is a patient presenting with a vesicular or pustular rash and reporting a prodrome and one other major criteria, or prodrome and at least 4 minor smallpox criteria.

(Graphic: response to moderate risk)
The response for a moderate risk case is to request an infectious diseases or dermatology consultation to confirm the risk status. Laboratory or pathology testing for varicella and other rash diseases should be conducted as appropriate at the hospital, local or state health lab or through a private lab. Obtain digital photos if possible. Re-evaluate at least daily to determine if risk level has changed.

(Graphic: low risk)
Low risk for smallpox is a patient presenting with a vesicular or pustular rash and reporting no febrile prodrome prior to rash eruption or reports a prodrome, and less than four minor smallpox criteria.

(Graphic: response to low risk)
The response for a low-risk patient is management and laboratory testing as clinically indicated.

In an era of no smallpox cases in the world, the goal of smallpox surveillance is to recognize the first case of smallpox early in the course of illness without generating a high number of false alarms. With no cases of smallpox disease, or zero prevalence, the predictive value of a positive lab test is essentially zero. If we test cases of rash illness that do not fit the case definition for smallpox, we will sooner or later get a false positive lab result. We need to minimize that risk given the extremely serious consequences of such a result.

Now I would like to share with you CDC’s experience using the algorithm since January 2002. Rash illness calls we receive are evaluated using this diagnostic algorithm. On average we receive about 2 calls a month.

(Graphic: CDC rash illness response team experience)
About two thirds of the cases have been among adults and one third have been in children. There have been no cases classified as high risk for smallpox. More than 80 percent of case were classified as low risk.

(Graphic: CDC rash illness response team experience 2)
More than half of the reported cases were varicella infections including some cases that resulted in death. Other diagnoses included drug reactions, erythema multiforme and Stevens Johnson syndrome, disseminated herpes zoster, disseminated herpes simplex and other dermatological conditions.

The CDC experience with implementation of the rash algorithm is that the evaluating team should test for varicella zoster virus. Varicella is the most common infection that has raised suspicions for smallpox. Very importantly, this algorithm has limited testing for smallpox virus. There have been no cases classified as high risk.

(Graphic: differential diagnosis: lessons from the past)
Our experience is similar to experience from earlier this century from the United Kingdom and Somalia. The majority of smallpox suspected cases in these series were varicella; other diagnoses included those described on the poster and those that have been reported to CDC.

(Graphic: differential diagnosis: lessons from the past 2)
Note that vaccinia is included in these series. Now that we have commenced smallpox vaccination in the United States, we will need to consider vaccine complications in the diagnosis of generalized febrile vesicular pustular rashes. Persons performing the evaluation will need to inquire about recent smallpox vaccination or contact with a vaccinee.

(Graphic: laboratory and pathology support)
Laboratory capacity is needed to diagnose conditions that may be confused with smallpox, especially moderate risk cases
which cause more concern. Lab and pathology capacities at the local level may include Tzanck smear, skin biopsy and less commonly, DFA for varicella which is a commercially available test. Capacity to perform rapid varicella zoster virus diagnostics using DFA or PCR is now available in every state health lab.

Electron microscopy can be useful looking for a pox virus, a herpes virus or other viruses. EM may be available in academic medical centers. Rapid tests for Herpes simplex virus infections may also assist in making a diagnosis. Testing for vaccinia may be considered in some clinical situations. Other tests should be performed as clinically indicated.

Support for local health departments and private physicians who are evaluating a case of rash illness suspected to be smallpox is provided by state health departments via their 24 hour emergency phone numbers. State health departments can also provide rapid laboratory testing for varicella and other rash illnesses, and may also be able to provide infectious disease and dermatology expertise.

The Centers for Disease Control and Prevention has on-call-staff available 24 hour a day, 7 days a week, every day of the year to assist state health departments. The on call staff have smallpox disease experts available for consultation. CDC can also provide laboratory and pathology support as requested. The smallpox algorithm poster is available through state health departments. It can be viewed and printed from the CDC Smallpox Website and can be ordered through the National Immunization Program on line ordering system.

In summary, the diagnostic algorithm is an important tool for evaluating cases of febrile vesicular or pustular rash illness suspected to be smallpox. Understanding the clinical features of smallpox disease and smallpox look alike illnesses, especially varicella, is important for evaluating these cases so that their risk of being smallpox can be assessed in a systematic way and an appropriate clinical and public health response can occur. Laboratory and pathology capacity are needed to support these evaluations.

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**Laboratory Diagnosis** *(slides; video)*

*Lisa D. Rotz, MD*

*Medical Epidemiologist*

*Bioterrorism Preparedness and Response Program, CDC*

The laboratory diagnosis of smallpox, and some other illnesses characterized by a vesicular or pustular rash is made by examination of material from a skin lesion. Recent advances in serologic testing and culture also will be useful for confirmation of an acute case.

For a patient who meets the criteria for moderate risk, the most important laboratory procedure is rapid diagnostic testing for varicella zoster virus, or VZV. Laboratory testing should be done in consultation with an infectious disease or dermatology specialist.

(Graphic: rapid diagnostic tests for varicella zoster virus)

There are a variety of rapid methods for detecting VZV in clinical material. The most common is direct fluorescent antibody, or DFA. This method detects VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye. This technique is very sensitive and specific but is critically dependent on careful collection of material from a lesion. Other methods for rapid detection of VZV in clinical material include electron microscopy and detection of VZV DNA by polymerase chain reaction testing of vesicular fluid or scabs.

Rapid diagnostic testing for VZV is generally available in at least one facility in all large cities, and is now available in all state health department laboratories.

Currently, laboratory procedures for variola virus in clinical specimens should be done only by the Centers for Disease Control and Prevention in Atlanta. If the patient’s clinical characteristics indicate a high risk for smallpox, state public health and CDC should be contacted immediately. Appropriate personnel can be quickly deployed to assist in confirming
the diagnosis, and to assist in implementation of control measures. Specimens for smallpox testing should only be collected by a recently vaccinated person, if possible.

(Graphic: electron photomicrograph of poxvirus)
The preliminary diagnosis of orthopoxvirus infection can be made by electron microscopic examination of vesicular or pustular fluid or scabs. Orthopoxviruses appear as large brick-shaped particles like this.

But confirmation of the specific orthopoxvirus involved in the infection must be made by nucleic acid based testing, such as polymerase chain reaction testing, and by culture.

It’s critical that clinical specimens for the laboratory diagnosis of smallpox and other rash illnesses be collected, preserved, and transported properly. Detailed instructions for the collection and transport of specimens are available on the Bioterrorism Preparedness Website. We recommend you obtain these instructions, and familiarize yourself with the types of specimens and methods of collection. In addition, we recommend you contact your state laboratory to determine what tests may be available from them, and specific instructions and the storage and handling of specimens.

**Vaccine Background** ([slides](#); [video](#))

*William L. Atkinson, MD, MPH*
*Medical Epidemiologist*
*National Immunization Program, CDC*

Smallpox has been a vaccine preventable disease for more than 200 years. In 1796, Edward Jenner demonstrated that immunity to smallpox could be produced by inoculating a human with material from a lesion on the udder of a cow. Jenner called this infectious material vaccine, and the procedure came to be called vaccination. The root of both these words is vacca, which is Latin for cow. The material Jenner used for his vaccine probably contained cowpox virus, a virus related to variola virus but not as virulent. At some time during the nineteenth century, the virus used for smallpox vaccination ceased to be cowpox and changed to vaccinia. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia, and how it came to replace cowpox virus in the vaccine is not known.

As many as three different smallpox vaccines are available, or will soon be available, in the United States. All three vaccines contain the New York City Board of Health strain of live vaccinia virus. Smallpox vaccine does NOT contain smallpox, or variola virus. So when we refer to smallpox vaccine in this program, we are actually talking about vaccinia vaccine.

(Graphic: Dryvax smallpox vaccine-prepared from calf lymph)
The currently licensed vaccine is Dryvax. It was produced by Wyeth Lederle in the early 1980s from calf lymph containing live vaccinia virus. This vaccine is provided as a freeze dried powder in a multi-dose vial.

(Graphic: Dryvax smallpox vaccine-contains polymyxin B)
Dryvax contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50 percent glycerin with a small amount of phenol as a preservative.

(Graphic: new smallpox vaccines)
The new smallpox vaccines also contain live New York City Board of Health vaccinia virus, but are produced using cell culture technology rather than live animals. These vaccines may also be distributed as a freeze dried powder but do not contain antibiotics. The diluent contains glycerin and phenol, like the Dryvax diluent.

Proper reconstitution of smallpox vaccine is critical to successful vaccination. Instructions for reconstitution are vaccine specific, and will be provided with your vaccine shipment. It’s important that you follow these instructions carefully.

(Graphic: bifurcated needle)
Smallpox vaccine is unique in that it is not administered by injection. It’s administered into the superficial layer of the skin with a two pronged, or bifurcated, needle like you see here. Bifurcated needles will be supplied in individual sterile packages.

Neutralizing antibodies induced by vaccinia vaccine are cross protective for other Orthopoxviruses, such as monkepox, cowpox, and variola viruses. That’s why immunity produced by vaccinia virus protects against smallpox. The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of people exposed to a smallpox patient in their household.

(Graphic: smallpox vaccine efficacy)
There was a 90 percent reduction in smallpox among contacts with a vaccination scar compared to contacts without a scar. Epidemiologic studies demonstrated that this high level of protection against smallpox persists for up to 5 years after primary vaccination and substantial but waning immunity can persist for ten years or more.

Although vaccination 30 or more years ago may not protect against smallpox, vaccinated people appear to have less severe disease. Studies of smallpox cases imported into Europe in the 1950s and 1960s showed fewer fatalities among vaccinated people compared to those who were unvaccinated.

(Graphic: case fatality rate among vaccinated bar graph)
This graph shows the smallpox fatality rate among people vaccinated at various intervals before exposure to smallpox. The data are from a series of 680 smallpox cases resulting from importation into Europe between 1950 and 1971. The fatality rate among people vaccinated less than 10 years before exposure was 1.3%. It was 7% among those vaccinated 11 to 20 years prior, and 11% among those vaccinated 20 or more years prior to infection. In contrast, 52% of unvaccinated people died.

Smallpox vaccination also provides post-exposure protection. Administration of vaccine within the first days after initial exposure to smallpox virus can reduce symptoms or even prevent disease. Studies in Pakistan and India showed that secondary cases in households were reduced up to 90% compared to unvaccinated people, if the vaccine was administered less than 7 days after exposure.

Vaccinia virus replicates in the basal cells of the epidermis, producing a papule surrounded by erythema 3 to 5 days after primary vaccination.

(Graphic: image of vaccination site, day 8)
A vesicle then forms, which becomes pustular by 7 to 11 days after vaccination. A person is considered protected with the development of a pustule like this at the vaccination site.

Vaccinia virus is present at the vaccination site beginning 3 to 4 days after vaccination until the scab separates. Care must be taken to avoid transferring virus to other parts of the body, such as the eye, or to other people.

**Vaccine Indications** ([slides](#); [video](#))

*Lisa D. Rotz, MD*
*Medical Epidemiologist*
*Bioterrorism Preparedness and Response Program, CDC*

Smallpox vaccine is currently recommended for use among two groups of people: certain laboratory workers who may be exposed to Orthopoxviruses, and public health and medical personnel who may be required to administer smallpox vaccine, investigate suspected cases, or provide care to persons hospitalized with smallpox.

(Graphic: smallpox vaccine indications- laboratory workers)
In the first group, vaccination is recommended for laboratory workers who directly handle cultures or animals contaminated...
or infected with some strains of vaccinia and recombinant vaccinia viruses. Vaccination is also recommended for laboratory workers exposed to other Orthopoxviruses that infect humans such as monkeypox or cowpox.

Vaccination can be considered for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were given vaccines containing recombinant vaccinia viruses.

In December 2002, the President announced a plan to develop smallpox response teams to provide critical services to other Americans in the event of a smallpox attack.

Smallpox vaccination is recommended for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were given vaccines containing recombinant vaccinia viruses.

In the event of an intentional release of variola virus, vaccination would be recommended for contacts of smallpox patients, and others at risk of exposure.

Persons at risk of exposure following a confirmed outbreak would include those involved in the direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients;

...laboratory personnel who collect or process the now higher volume of clinical specimens from confirmed or suspected smallpox patients; and people who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present.

Vaccination will be a key component of our response to an intentional release of variola virus. We will discuss vaccination...
All vaccines have precautions and contraindications to their use. Contraindications for smallpox vaccine are influenced by the live virus present, and by known risk factors for adverse reactions.

The vaccine is contraindicated for persons who have experienced a serious allergic reaction to a prior dose of vaccine, or to a vaccine component. Because all currently available smallpox vaccines in the U.S. contain live vaccinia virus, they are contraindicated for people with significant immunosuppression from any cause, or persons who have an immunosuppressed household contact. Pregnant women and persons with a pregnant household contact should not be vaccinated because of the risk of fetal vaccinia. Women who are breastfeeding should not be vaccinated because of the risk of contact transmission to the breastfeeding infant.

Atopic dermatitis, irrespective of disease severity or activity, is a risk factor for developing eczema vaccinatum among ether vaccinees or their close contacts. So smallpox vaccine should not be administered to people with eczema or atopic dermatitis, irrespective of disease severity or activity, or people whose household contacts have active eczema or atopic dermatitis, or a history of these conditions. People with other types of acute, chronic, or exfoliative skin conditions, such as psoriasis, contact dermatitis, or varicella zoster might be at higher risk for disseminated skin rashes from the vaccine, although these rashes are generally not as severe as eczema vaccinatum. People with exfoliative skin conditions should not be vaccinated until the condition resolves.

The vaccine is contraindicated for infants less than 12 months of age. However, ACIP also does not recommend smallpox vaccination of people less than 18 years of age in the current pre-event vaccination program. People with known underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors should not be vaccinated in the current pre-event vaccination program. These risk factors include hypertension, diabetes, hypercholesterolemia, a first degree relative diagnosed with heart disease before age 50 years, and smoking.

Vaccination should be deferred for people with inflammatory eye diseases requiring steroid therapy until the condition resolves and the course of therapy is complete. Finally, vaccination should be deferred for persons with moderate or severe acute illness until the acute illness resolves.

In the event of an exposure to smallpox, there would be no absolute contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine.

Details of contraindications and precautions to smallpox vaccine were published in two supplemental ACIP statements in April 2003. These reports also include strategies for screening potential vaccinees for atopic dermatitis, pregnancy, HIV infection, and cardiac risk factors. In addition, in February 2003, CDC published detailed recommendations on the diagnosis and management of smallpox vaccine adverse reactions. These documents are available on the CDC smallpox Website.
In this segment of the program we will discuss the administration of smallpox vaccine, and demonstrate the recommended method of administration.

We recommend that you wear gloves when administering smallpox vaccine. Because of the risk of inadvertent exposure to vaccine virus, persons administering the vaccine should be vaccinated. Healthcare providers or vaccinators who themselves have a contraindication to vaccination should not handle or administer the vaccine.

You should consult the package insert or protocol that comes with the vaccine for instructions on vaccine reconstitution. Once you have prepared the vaccine, you are ready to administer it.

To administer the smallpox vaccine, a special bifurcated needle is used. No other vaccine uses this type of needle, and smallpox vaccine must never be administered with by any other method. You should review the package insert or protocol that is provided with the vaccine for any additional instructions regarding vaccine administration.

When the bifurcated needle is dipped into the vaccine vial and withdrawn, the tiny amount of vaccine required for a single dose is captured between the two prongs of the needle. [SC]

A stopper for the vial and sterilized, individually packaged needles will be provided within the vaccine packaging.

In general, alcohol, soap and water, or other chemical agents are not needed for preparation of the skin for vaccination unless the area is grossly contaminated. If needed, soap and water are the preferred cleaning agents. If any cleaning agent is used, the skin must be thoroughly dry in order to prevent inactivation of the vaccine.

Remove the bifurcated needle from its packaging. The needle is sterile, so be careful not to touch the bifurcated, pointed end.

Dip the bifurcated point of needle into the vaccine solution - so that the needle is perpendicular to the floor. The needle will pick up a drop of the vaccine in the space between the two prongs.

Remember- do not re-dip the needle into the vaccine solution once it has touched the patient’s skin. This will prevent contamination of the vaccine vial.

Prior to the administration of smallpox vaccine, please refer to the package insert for the appropriate number of needle punctures to administer. The following is a demonstration of 15 punctures, which would be used for revaccination.

Pull the skin on the arm taut, rest your wrist on the arm, and prick the skin 15 times as shown here. This should be done rapidly, perpendicular to the skin, within an area 5 millimeters in diameter. The intention is to break the skin and introduce the vaccine into the skin.

The wrist of the vaccinator should be resting on the arm while pricking the skin. Enough pressure should be used to visibly push down the skin and produce a trace of blood at the vaccination site that appears 10 to 20 seconds after vaccination.
Administering the strokes rapidly, within about 3 seconds, also helps induce enough pressure by the needle to produce this small amount of bleeding and assure that the vaccine was administered appropriately. This method allows the live vaccinia virus to penetrate the superficial layers of the skin so that viral multiplication can occur and produce immunity.

Once the vaccine is administered, you should dispose of the needle into an appropriate sharps disposal container.

Cover the vaccination site with a piece of gauze or other appropriate dressing.

Here is the vaccination procedure again.

Instructions are included with each vaccine shipment that outline the vaccination procedure you’ve just seen. The instructions also contain other important information about smallpox vaccine.

Vaccine Adverse Reactions (slides; video)

The following have disclosed that their presentations will include discussion of investigational use of smallpox vaccines and vaccinia immune globulin (VIG) and unlabeled use of cidofovir: William Atkinson, MD; Joanne Cono, MD; Lisa Rotz, MD.

Lisa D. Rotz, MD
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

Smallpox vaccine contains live vaccinia virus, and is administered differently than any other vaccine. Adverse events following smallpox vaccine are also unique. We asked Dr. Joanne Cono, a medical epidemiologist CDC’s Bioterrorism Preparedness and Response Program, to talk about smallpox vaccine adverse events, and factors that increased the risk for these reactions.

Joanne Cono, MD, ScM
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

Smallpox vaccine has been used for more than 200 years, first to prevent smallpox, and most recently to prevent infection with vaccinia and recombinant vaccinia viruses. Complications of vaccination have been recognized for many years. Smallpox vaccine complications, or adverse reactions, range from frequent and innocuous to rare and fatal. More severe complications are rare but occur more than 10 times more often among those being vaccinated for the first time than among people being revaccinated.

To produce immunity, live vaccinia virus is introduced into the superficial layer of the skin. In a successful vaccination, a skin lesion develops at the vaccination site.

This graphic shows the normal progression of the vaccination site for a first-time vaccinee. By day 4, vesicles have appeared. The lesion evolves into a pustule by day 7. The presence of a pustule between days 6 and 8 verifies that the vaccinee has responded to the vaccine. This response is called a major reaction or a positive take. By day 14, the pustule has dried and a scab has formed. By day 21, the scab has thickened and will soon separate, usually by 28 days post-vaccination.
Most first-time vaccinees or distant re-vaccinees can expect some amount of pain, swelling, and erythema at the vaccination site. They can also expect to develop axillary lymphadenopathy in the vaccinated arm. Lymphadenopathy usually develops 3 to 5 days after vaccination, and can persist for up to 4 weeks. These are normal reactions to vaccination.

Some vaccinees can have a large amount of erythema, swelling, pain, and warmth at the vaccine site. This is called a robust primary take and is a normal variant, occurring in up to 16% of vaccinees. The redness and swelling can sometimes be greater than 3 inches or even involve the entire upper arm. There may also be lymphangitis present. This reaction is usually seen around days 8 through 10 and can be confused with bacterial cellulitis. However, unlike bacterial cellulitis, the clinical course isn’t progressive, and the symptoms improve over a few days without antibacterial therapy. More information about vaccination site reactions, including normal variants, is available on the CDC Smallpox Website.

Fever most often occurs in people being vaccinated for the first time. In a recent study, 17% of first time adult vaccinees experienced a fever of 100 degrees Fahrenheit or higher within two weeks of vaccination. 1.4% experienced fever of 102 Fahrenheit or higher. Peak temperature elevation generally occurs about the time the vaccine site inflammatory reaction is at its greatest, on about days 8 through 10. Systemic symptoms, such as malaise and muscle aches may also occur. About a third of first time recipients may be sufficiently ill to miss work or otherwise alter their normal activities for a day or two.

A variety of rashes may occur after smallpox vaccination. They are erythematous, macular, or urticarial lesions, and appear about 10 days after vaccination. These rashes are probably due to a non-specific immune reaction to the vaccine. They usually don’t become vesicular, and don’t appear to involve viral multiplication or systemic dissemination. The rashes resolve spontaneously within 2 to 4 days. No treatment is needed, although symptomatic therapy such as antihistamines may be used to make the person more comfortable.

Occasionally, more severe immune reactions such as erythema multiforme or Stevens-Johnson syndrome can be seen. Erythema multiforme can present as macules, papules, urticarial lesions or the typical bulls eye lesions. The lesions do not progress to vesicles and don’t contain live vaccinia virus. Vaccinia Immune Globulin, or VIG, is not effective or indicated for the treatment of this complication.

Two studies were done in the US during the late 1960’s that quantified the rates of adverse reactions associated with smallpox vaccination. One was a national surveillance study, while the other was a survey of physicians in 10 states.

This table shows the range of adverse event rates reported from both of these studies, in cases per million primary vaccinations. The ranges shown for some reactions reflect the different data collection methods for the two studies. The 10 state survey probably more accurately reflects the rates for the less serious complications that were frequently unreported. The national study captured the rates of the more serious adverse events through national reporting and VIG distribution mechanisms. The most common adverse events associated with vaccination in these studies included inadvertent inoculation, generalized vaccinia, and eczema vaccinatum. Progressive vaccinia, also called vaccinia necrosum and post-vaccinal encephalitis were much less common.

The rate of adverse reactions may be higher today than during the smallpox vaccination program of the 1960s. This would be due mostly to the increased numbers of persons living with immunocompromising conditions and with a history of eczema and atopic dermatitis. Adverse events are expected to occur more frequently among first-time vaccinees; currently there are a higher percentage of individuals who will receive their first vaccine because routine childhood smallpox vaccination was stopped in 1972.

Inadvertent inoculation is the transfer of vaccinia virus from the vaccine site to another area of the body or to another person. This is the most common adverse event seen following vaccination, with a rate of up to 500 cases per million primary vaccinations in the 1960s studies. Inadvertent inoculation results in a second skin lesion that contains vaccinia
virus, and progresses through the same stages of resolution as the vaccination site. The most common body areas affected are the face, eyelid, nose, mouth, and other mucosal surfaces. Transfer of vaccinia virus to another person can result in a lesion similar to a typical vaccine site lesion, or can lead to other more severe adverse reactions, especially in people with certain underlying medical conditions like eczema, atopic dermatitis, or immune suppression.

(Graphic: image of eye with lesion)
Inadvertent inoculation of the eyelid can lead to significant swelling and redness of the eyelid and periorbital area, as you see here. In the past, ocular vaccinial disease accounted for the majority of inadvertent inoculations and often occurred within 7 to 10 days of vaccination in first time vaccinees. An ophthalmologist should be consulted to assist in evaluating patients with ocular vaccinia. Sometimes ophthalmologists may consider the use of topical antiviral medications and possibly topical steroids. VIG may also be considered for severe ocular disease, except for isolated keratitis.

Another type of rash following smallpox vaccination is called as generalized vaccinia. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without underlying illnesses. In the 1960s studies, rashes diagnosed as generalized vaccinia occurred at a rate of up to 240 per million primary vaccinations.

(Graphic: generalized vaccinia)
Generalized vaccinia usually presents as a rash that develops into vesicular or pustular lesions on normal skin away from the vaccination site. This rash may involve only a few, scattered lesions or can be more extensive and generalized. Fever and other systemic symptoms, such as headache and myalgias, may be present but are usually not severe. Generalized vaccinia usually occurs 6 to 9 days after vaccination. In a person with a normal immune system, generalized vaccinia is usually self-limited, and doesn’t require specific therapy.

(Graphic: image of legs with lesions)
Here is an example of generalized vaccinia. This image shows typical vaccinial lesions on the legs of a 14-year-old primary vaccinee approximately 8 days after vaccination. The lesions are similar to small vaccinations, but the child had few systemic symptoms.

Three complications of smallpox vaccination are rare, but can be very severe or fatal. These are eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis, or central nervous system disease.

(Graphic: eczema vaccinatum)
Eczema vaccinatum is a localized or generalized papular, vesicular, or pustular rash which can occur anywhere on the body, with a predilection for areas of previous atopic dermatitis lesions. This complication can occur in individuals with active eczema or atopic dermatitis, and in those with a history of these conditions even when the condition is not active. Some of the most severe cases of eczema vaccinatum have occurred in people with eczema or atopic dermatitis who were not vaccinated but were contacts to recently vaccinated individuals. Onset of the skin lesions can occur either concurrent with or shortly after the development of the lesion at the vaccination site. In the 1960s studies, eczema vaccinatum occurred at a rate of up to about 40 cases per million primary vaccinations. Good medical history screening of potential vaccine recipients and their close contacts for the presence or a history of atopic dermatitis or eczema is the most important way to reduce the occurrence of this adverse event.

(Graphic: image of woman with rash on face)
This image demonstrates the extensive skin involvement of eczema vaccinatum in a close contact to a recently vaccinated person. Eczema vaccinatum can be quite severe and even result in death, although this particular patient survived. She required multiple doses of VIG and was left with extensive scarring.

(Graphic: progressive vaccinia)
Progressive vaccinia or vaccinia necrosum is a rare but serious adverse event that can occur in people with cellular immunodeficiencies or in individuals with humoral or immune globulin deficiencies. People with progressive vaccinia usually present with a non-healing, expanding vaccination site. The site often ulcerates and necrosis of the surrounding skin can occur. There is generally little or no inflammation at the site initially, because of poor local immune response. This absence of adequate immune response presumably allows the virus to spread locally and systemically.

The woman in this photo had chronic lymphocytic leukemia. Notice how the infection from the vaccine site has spread to involve the surrounding skin, causing necrosis. She also has metastatic lesions on her neck and other areas of her body from hematogenous spread of the virus.

Postvaccinal central nervous system disease is a rare but serious vaccine complication. It was most frequently seen in infants younger than 12 months of age or in adolescents and adults receiving their first vaccination. It can present with a variety of central nervous system manifestations, ranging from ataxia or confusion to seizures or coma. Symptoms of postvaccinal CNS disease usually begin around 9 to 14 days following vaccination and its diagnosis involves exclusion of other potential causes of brain dysfunction. Death results in about 15 to 25 percent of cases, while another 25 percent are left with neurologic sequellae. The pathophysiology of postvaccinal central nervous system disease is not well understood but thought to be a result of a post vaccination immune response. Postvaccinal CNS disease has NOT been causally linked to the presence of vaccinia virus in the CNS and use of VIG is not indicated.

Fetal vaccinia is a very rare complication that can occur following vaccination of a pregnant woman. It is manifested by skin lesions and organ involvement and often results in fetal or neonatal death. Only about 50 cases of this complication have been reported in the literature. It is not clear how the virus infects the fetus and there is no known reliable intrauterine diagnostic test for this condition. This image shows fetal vaccinia in a 28 week premature infant. The infant’s mother was vaccinated at 23 weeks gestation. The infant died at 8 days of age and vaccinia was isolated from the placenta.

Since the pre-event smallpox vaccination program began in January 2003, a small number of people with cardiac symptoms following smallpox vaccination have been reported. Most of these cases are among members of the military being vaccinated for the first time. Most symptoms have resembled those for myocarditis - inflammation of the heart muscle, or pericarditis, inflammation of the pericardial sac surrounding the heart. We have grouped these conditions using the term myopericarditis. The incidence of this occurrence is higher than that expected among non-vaccinated military personnel. The Department of Defense and CDC have not yet established that the vaccine is causing myopericarditis. However, CDC has recommended new screening criteria to defer potential vaccinees with a history of or risk factors for cardiac conditions. These screening parameters will be described later in this program, and can be reviewed on the CDC Smallpox Website.

Vaccinia Immune Globulin, or VIG, is a first-line therapy to treat certain adverse reactions following smallpox vaccination.

VIG is a sterile solution of the immunoglobulin fraction of plasma from persons who were vaccinated with smallpox vaccine. VIG has demonstrated efficacy in the treatment of smallpox vaccine adverse reactions caused by continued replication of vaccinia virus, such as eczema vaccinatum, progressive vaccinia, and severe cases of generalized vaccinia. VIG has no proven effectiveness for postvaccinal central nervous system disease. VIG is currently available from CDC under an investigational new drug protocol.

Cidofovir is an antiviral medication not previously used in humans to treat vaccinia infection. It is considered a second line therapy for smallpox vaccine adverse reactions, and is also available through CDC under an Investigational New Drug protocol. In addition, for certain cases of ocular vaccinia, ophthalmologists may consider the use of topical antiviral medications.

Clinicians seeking assistance in the diagnosis of vaccine related adverse events should contact their State Health Department before calling CDC. Prior to requesting consultation, healthcare providers should complete a thorough history and physical examination of the person with a suspected adverse event. If possible, high resolution digital photographs of skin rashes should be obtained to help in the diagnosis of specific dermatological manifestations of adverse events.

CDC has established a Clinician Information Line [877-554-4625] to provide 24-hours a day, 7-days a week consultation for evaluation and care of patients who are suspected of experiencing smallpox vaccine-related adverse events. Requests for
the 2 Investigational New Drug treatments, VIG and cidofovir, also can be made at this telephone number. In addition, CDC will provide consultation for evaluation and care of persons with contraindications to smallpox vaccination that have an inadvertent exposure to vaccinia virus. These persons also may be enrolled in vaccination registries so that they can receive careful, prospective follow-up. More information about smallpox vaccine, and the diagnosis and treatment of smallpox vaccine related adverse reactions can be found on the CDC Smallpox Websites.

Isolation and Management (slides; video)

William L. Atkinson, MD, MPH
Medical Epidemiologist
National Immunization Program, CDC

A suspected case of smallpox is a public health and medical emergency. Any person whose clinical characteristics meet the clinical case definition for smallpox must be isolated, then reported IMMEDIATELY to the local and/or state health department.

(Graphic: smallpox clinical case definition)
Here is the clinical case definition of smallpox. It’s an illness with an acute onset of fever of 101 Farenheit or higher, followed by a rash. The rash is characterized by firm, deep seated vesicles or pustules in the same state of development without other apparent cause.

Isolation of confirmed or suspected smallpox patients is critical to limit exposure to the virus. Although droplet spread is the major mode of person to person smallpox transmission, airborne transmission through fine particle aerosol can rarely occur. So airborne precautions using a negative air pressure room with high efficiency particulate air filtration should be initiated immediately for hospitalized high risk or confirmed smallpox patients. This is the same isolation precaution you would take for other infectious diseases with respiratory transmission, such as varicella. Standard Precautions should be used for all patient care.

(Graphic: protective equipment)
In addition, all personnel who have contact with a suspected or confirmed case of smallpox should utilize appropriate airborne and contact precautions. This includes using fit-tested N95 masks, and use of disposable gloves and gowns for all contact with patients. Contact precautions are implemented to prevent inadvertent transmission of variola virus from clothing or other contaminated items to susceptible persons. Personnel should remove and correctly dispose of all protective clothing before contact with other people.

Reuseable bedding and clothing can be autoclaved or laundered in hot water with bleach and hot air drying to inactivate the virus. People who come into contact with materials potentially contaminated with smallpox virus, such as laundry handlers, housekeeping, and laboratory personnel should utilize appropriate protective equipment. If a case of smallpox is confirmed, these personnel should be vaccinated before handling contaminated materials.

There is no proven treatment for smallpox. Medical management of a person with suspected smallpox is supportive. It is unknown how effective antiviral medications may be against variola virus, and these medications can cause serious side effects. Antiviral therapy with cidofovir or other drugs found to have anti-variola activity might be considered but would be used under an investigational new drug protocol and by an infectious diseases specialist.

Epidemiology (slides; video)

Lisa D. Rotz, MD
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

Knowledge of the epidemiology of smallpox is critical to understanding how smallpox was eradicated and how it would be contained and controlled in the event of an introduction. Humans are the only natural host for variola virus, and there is no chronic carrier state.

Transmission of smallpox is respiratory, through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. Most transmission results from direct face to face contact with an infected person, usually within a distance of 6 feet, or from physical contact with a person with smallpox or contaminated articles. Rarely, transmission has occurred over greater distances, such as when the person has a prominent cough, when certain building airflow patterns are present, or under favorable environmental conditions. Secondary cases generally occur in people who live in the same household as the patient. People in nearby houses are rarely infected unless they enter a patient’s dwelling or otherwise has close contact.

A person infected with variola virus is not infectious during the incubation period, or during the first day or two of the prodromal stage of the illness. The patient becomes infectious with the first appearance of the lesions in the mouth, which occurs at about the time the skin rash appears. The infected person can transmit the virus throughout the course of the rash illness - that is until all scabs have separated.

Many epidemiologic observations during the global eradication program indicated that transmission to contacts is most frequent during the first week of the rash, and while most skin lesions are in the vesicular or pustular stage while the oral lesions are still healing. Virus is present in material draining from ruptured pustules and in scabs for a longer period, but infection from this source appears to be less frequent.

In general persons with a severe rash and involvement of the mouth and pharynx are more infectious than those with a slight rash.

Natural transmission of smallpox in a population is relatively slow. There is an interval of two to three weeks between each generation of cases. Smallpox generally spreads less widely and less rapidly than varicella or measles. This is probably because transmission of variola virus doesn’t occur until about the time of rash onset, and generally requires closer contact for spread. At the time of rash onset, most patients are already confined to bed because of the high fever and toxemia of the prodromal stage of the illness. But people with severe prodromal illness may seek medical attention. Consequently, hospitals were a frequent source of infection because of transmission from unrecognized hospitalized cases.

The majority of secondary cases of smallpox usually consist of those who come in contact with the infected person in the household or hospital. During the global eradication program, it was possible to interrupt the chain of transmission of smallpox by isolating smallpox patients in a setting in which they had contact only with adequately protected or vaccinated people. This limited the next potential generation of cases to those already exposed, such as the household and close contacts of the case. Contacts were identified, and they and their family members were immediately vaccinated. Contacts who became ill were also isolated to establish a barrier to further transmission. This strategy was found to be effective even if community vaccination levels were low.

Global Smallpox Eradication (slides; video)

Lisa D. Rotz, MD
Medical Epidemiologist
Bioterrorism Preparedness and Response Program, CDC

It’s estimated that in the early 1950s, there were about 50 million cases of smallpox occurring worldwide each year. Ten to

15 million cases occurred in 1967, when the disease had already been eliminated in 80% of the world. The last naturally occurring case of smallpox occurred in Somalia in October 1977. The eradication of smallpox from the earth was one of the greatest accomplishments in human history. The methods that were used, and the lessons learned from the eradication program are relevant in planning a response to an intentional release of the virus.

We asked Dr. D. A. Henderson, former director of the Global Eradication Program for the World Health Organization, to review the program and his experiences with smallpox eradication.

D.A. Henderson, MD, MPH
Former Director of the Global Smallpox Eradication Program for the World Health Organization

For centuries, smallpox stalked the world with impunity, causing unmeasured suffering, death and blindness. It existed as an endemic infection wherever concentrations of population were sufficient to sustain transmission. The impact of smallpox on history and human affairs was profound. At the end of the 18th century in Europe, an estimated 400 thousand people were dying annually from smallpox, and survivors accounted for one third of all cases of blindness.

During the 18th century alone, five reigning European monarchs died of smallpox, and the Austrian Hapsburg line of succession shifted four times in four generations. With Jenner’s discovery of vaccination in 1796, and subsequent improvements in production and distribution of vaccine in the 19th century, the incidence of smallpox in industrialized countries diminished rapidly.

Most of Europe became smallpox free in the early 20th century...

...and transmission was stopped throughout Europe and North America soon after World War 2.

In 1950, the Pan American Sanitary Organization, the predecessor to the Pan American Health Organization, undertook a hemisphere-wide eradication program, and by 1967 had eliminated smallpox from all countries of the Americas except Brazil.

The first proposal for global eradication was made to the World Health Assembly by the USSR in 1958. They proposed a world wide vaccination program to be completed in a 3 to 5 year period. Some progress was made during the next 7 years, but the results overall were disappointing. Finally, in 1966, the World Health Assembly decided to intensify the eradication program by providing a special budget of $2.4 million per year specifically for this effort.

During 1967, the year the Intensified Global Eradication program began, an estimated 10 to 15 million smallpox cases occurred in 31 countries in which the disease was endemic. More than 1 billion people lived in these endemic areas.

A major reservoir was Africa, where most countries south of the Sahara were infected.

A second major reservoir was in Asia, extending from Bangladesh through India, Nepal, Pakistan, and Afghanistan.

The third was the Indonesian archipelago...

and the fourth was Brazil, which comprised half of South America.
The initial campaign was based on a two fold strategy. First, mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population.

Second, the development of surveillance systems to detect and contain cases and outbreaks. Of the two strategies, the second - case detection and containment- proved to be the more crucial.

The program had to surmount numerous problems, including lack of organization and discipline in national health services epidemic smallpox among refugees fleeing areas stricken by civil war and famine, shortages of funds and vaccine, and a host of other problems posed by difficult terrain, climate, and cultural beliefs. In addition, it was soon learned that even when 80% of the population was vaccinated, smallpox often persisted.

Soon after the program began it became apparent that by isolating people with smallpox and vaccinating their contacts, outbreaks could be more rapidly contained. Even in areas where vaccination coverage was low. This strategy was called surveillance and containment, and it became the key element in the global eradication program.

Special surveillance teams were recruited and trained. They visited each health unit in an area to ensure that each week it submitted a report indicating the number of cases seen. When cases were reported the teams worked with local health staff to discover additional cases and to contain the outbreaks. They visited schools and public places to inquire about rumors of smallpox.

A special WHO smallpox recognition card was printed and distributed to help in the search.

Although setbacks occurred, the surveillance and containment strategy was an enormous success. Using it, the last case of smallpox in Brazil was reported in 1971, and Indonesia’s last case occurred in 1972. India, Pakistan and Bangladesh, with a population at that time of more than 700 million, was a particular challenge. But with intensive house to house searches and strict containment, the last case of variola major- the most deadly type of smallpox- occurred in Bangladesh in October 1975.

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. With the interruption of smallpox transmission in Asia, more resources were made available in Africa, including more staff and transport.

Just as it seemed that the last outbreaks had been controlled, nomads in Somalia disseminated the disease throughout the southern part of that country. An intensive surveillance and containment and vaccination program was undertaken in the spring and summer of 1977. As a result, the world’s last indigenous patient with smallpox on earth was a hospital cook in Merka, Somalia, on October 26, 1977.

Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox. Although 2 cases of smallpox occurred in England in 1978 as a result of a laboratory accident, smallpox was gone.

The World Health Organization officially certified that smallpox had been eradicated on December 9, 1979, 2 years after the last case in Somalia. In 1980 the World Health Assembly recommended that all countries cease vaccination. The World Health Organization also recommended that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories- the Institute of Viral Preparations in Moscow, or the Centers for Disease Control and Prevention in Atlanta. All laboratories were believed to have complied with this request.

However, in 1993, the former deputy director of the Soviet Union’s civilian bioweapons program reported that his government had produced large quantities of variola virus for use as a biologic weapon. With the break up of the USSR, and unemployment of many scientists, there is concern that both the virus, and expertise to produce it, may have become available to other governments or terrorist groups.

The deliberate reintroduction of smallpox as an epidemic disease would be an international crime of unprecedented...
proportions. Although this has not occurred, it is now considered to be a possibility.

It is critical that physicians and other front line health care providers be familiar with the disease, and maintain vigilance for suspected cases. It is also critical that a plan be in place for the public health response should a case occur. Such plans are now under development.

The global eradication of smallpox ranks as one of the greatest triumphs in medicine. The strategies successfully used in that program would be used again should the need arise. We hope this will never be necessary.

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**Surveillance and Containment Strategy** (video)

_Cynthia Good_

_Moderator_

As you have heard, the surveillance and containment strategy of finding people with smallpox, then locating and vaccinating their contacts, was central to the global smallpox eradication program. This strategy will also be central to our response to an intentional release of smallpox virus. We wanted to get perspective on this strategy from someone who had really used it.

We had the opportunity to talk to Dr. Steve Jones, a CDC medical epidemiologist who served in the smallpox eradication program in Bangladesh, about this approach to smallpox outbreak control.

**Q (on screen): What was the strategy of global smallpox eradication program?**

_T. Stephen Jones, MD, MPH_

_Medical Epidemiologist, CDC_

The strategy was based on an understanding of the biology of the smallpox virus. We know there's no animal reservoir. We know that people are infectious for a short period of time, for a couple of weeks, so that the transmission occurs from that infected person to a person that is susceptible usually through real close contact. So the strategy then is to find the people who are currently infected with smallpox, actively sick, and concentrate your activities in the general area of those people, do the vaccination, do the isolation and containment in that area. The strategy was called surveillance and containment, and it was the basis for the successful eradication of smallpox in the world.

**Q (on screen): What are the components of the surveillance and containment strategy?**

_T. Stephen Jones, MD, MPH_

_Medical Epidemiologist, CDC_

The components of the surveillance and containment strategy for smallpox are based on what we know about the biology of smallpox. And we know that the first and most important step is to find each and every case, each and every person who is actively infected with smallpox because they are the potential source of the next generation of cases. When you find that person who has got active smallpox, you want to make sure that they are in an isolation set up so that their chances that they would come in contact with any new people are reduced to zero if possible. You also want to talk to those people and their family members. You want to find out the people at risk of being the next cases of smallpox. At risk because they're contacts. And contacts doesn't mean that they live in the same city. It means that they had some close contact, that they were within, say, six or seven feet of the person, that they had some time exposure, 30 minutes, an hour, a couple of hours, live in the same household, work in the same office, some real identifiable contact.

And once you've got the names of those people who are at risk, you need to go out, you need to find every one of them, you need to make sure that they're vaccinated as early as possible because that vaccination can prevent them potentially from becoming a case of smallpox, and you also want to make sure you keep track of them because the last component is a...
systematic follow up of all of these people who are at risk that you've vaccinated for two purposes. One, you want to make sure that they get a very successful take on their vaccination so that they are personally protected. And two, you want to make sure you find any one of them who develops a fever, or a fever and a rash because that could be an early sign or warning that they are developing smallpox. And if they develop smallpox and you get at it early, you can prevent the transmission by putting them in an isolation so they don't have contact with people who might be susceptible. And those are the steps that put together the successful surveillance and containment strategy.

Q: (on screen): What are the options for vaccination against smallpox in the case of an outbreak?

T. Stephen Jones, MD, MPH
Medical Epidemiologist, CDC

There are lots of options and approaches to how to do vaccination to control a smallpox outbreak. One of them would be to vaccinate everybody. Let's say there was a case of smallpox in Atlanta. You would vaccinate all the population, all the people living in Atlanta. And there are some downsides to that. You would need a lot of vaccine, lots of vaccinators, you would also be exposing a large number of people to the known complications of smallpox vaccination, some of which are serious. And those, the vast majority of the people you vaccinated would have little or no risk of developing smallpox because they hadn't been exposed. The alternative to that is the surveillance and containment approach in which you focus your vaccination activities, you focus your public health activities among people who are known to be exposed. People who are contacts of cases of smallpox. So you're using your vaccine and your public health resources in the most efficient possible way. Some of those resources are always limited. We, at the moment, have a limited amount of vaccine. And in the situation of limited resources, the surveillance and containment approach or strategy seems to be the best use of those limited resources.

Q (on screen): Would surveillance and containment strategy work in the United States?

T. Stephen Jones, MD, MPH
Medical Epidemiologist, CDC

Well, if there were a smallpox outbreak in the United States, that would be because someone had introduced smallpox in the United States, a willful attempt to hurt us. We don't know exactly how that would be done. We're not sure of the methods that would be used. But even with that uncertainty of how it would be introduced, we do know that we have a proven effective approach. We have the strategy of surveillance and containment. That's the way that we were able to eradicate smallpox from the world. And in the case of an introduction of smallpox into the United States, this strategy would be a key part, and a central part of the response to smallpox in the United States or anywhere in the world.

Smallpox Response Plan (slides; video)

Julie Louise Gerberding, MD, MPH
Director
Centers for Disease Control and Prevention

The global eradication of smallpox in 1977 was a landmark event in the world public health community. Today, we find ourselves preparing for an almost unimaginable event- an intentional release of smallpox. Although such a release is not imminent, we must prepare so that should it happen, we can protect people in all communities across America.

In 2001, the CDC released Interim Smallpox Response Plans and Guidelines, which outline strategies for responding to a smallpox emergency. The plan provides state and local public health officials with a framework to guide their smallpox planning and readiness efforts. Guidelines for general public health activities that would be undertaken during a smallpox emergency are also included.

Many of the strategies and concepts included in the plan were used successfully in the global eradication of smallpox. The http://www.cdc.gov/nip/ed/smallpox-trg/clinician-should-know/contents/printable_version.htm

Smallpox Plan is a working document that is updated as needed to reflect changes in overall public health strategies for responding to a smallpox emergency. The most current version is available on the CDC Website. State, local, and private health officials should continue to evaluate and update their own response plans to address gaps and maintain flexibility. We hope it will never be necessary to put the smallpox response plans into effect. However, we must be sure that we are ready should the need arise.

Lisa D. Rotz, MD  
Medical Epidemiologist  
Bioterrorism Preparedness and Response Program, CDC

A smallpox response plan has been in place in the United States since the early 1970s. Until recently, the plan only considered an importation of smallpox, and provided guidance for actions to be taken by a State Health Officer in the event of a suspected case. In 1999, efforts began to update the response plan in the context of an intentional release of smallpox virus as an act of terrorism. Following the anthrax attacks in 2001 the plan was revised further to provide detailed information on surveillance and response to a smallpox virus release. The smallpox response plan will change as resources and capabilities change, and additional needs are identified. Like the original plan, the current plan is intended to assist with local and state response planning by identifying actions that must be taken in the event of a suspected smallpox case.

The key elements of preparedness for smallpox response are surveillance and diagnosis to achieve the early detection of an introduced case; isolation of the case or cases; and priority identification, vaccination, and monitoring of the contacts of the case or cases, as these people are at the greatest risk for developing the disease and spreading it to others.

A series of chapters, or guides, give detailed information on critical aspects of the plan. Guide A contains surveillance, contact tracing, and epidemiologic investigations guidelines. This includes pre-event rash surveillance, information on differential diagnosis, case definitions, contact identification, tracing and surveillance, as well as data collection forms to support these activities. This guide describes the basic smallpox control strategy - isolation of patients with smallpox, identification and vaccination of contacts, and monitoring contacts for development of disease. This strategy is called surveillance and containment, or ring vaccination, and was the fundamental approach to smallpox outbreaks during the global eradication program.

Guide B contains details on smallpox vaccination guidelines for state and local health agencies, including strategies, indications, contraindications, reconstitution, administration, and storage. It also describes recognition and surveillance of vaccine adverse events, and guidelines for the use of vaccinia immune globulin.

Guide C contains isolation and infection control guidelines and strategies for both confirmed and suspected cases and febrile contacts of cases. The issue of quarantine - that is, isolation of people before they become ill - is also discussed.

Guide D details specimen collection and transport, including specimen collection supply kits, collection procedures, and instructions on packing and labeling specimens. State health departments should be contacted for directions on where to ship specimens.

Guide E includes the communication plan and activities. In the event of a smallpox outbreak, communications will be critical. This guide details strategies for communicating with the media, the public, and with providers.

Finally, Guide F describes general strategies on environmental infection control and decontamination in settings where care is given to smallpox patients.

Several annexes to the plan contain details of other issues likely to be encountered, including the general care of smallpox patients, vaccination clinic procedures, and vaccine adverse event reporting. The information on vaccination clinic procedures includes guidance for vaccination clinics that can support large scale vaccination if this is implemented to support focused outbreak control vaccination.

The Response Plan was released in November 2001 and has been continuously updated. The plan will continue to be updated as needed to address changes in resources or response planning strategies. The CDC response plan should used as a resource for local and state planning efforts. Obviously, we can’t plan for everything. But we believe the underlying concepts included in the plan will remain even if the strategies for implementing the concepts require adaptation in the ever-changing environment of an outbreak response. The current version of the Smallpox Response Plan and Guidelines is available on the CDC Smallpox Website. We encourage you to get a copy, and familiarize yourself with it.

Self-Test

You are about to take a Self-Test on the clinical characteristics, diagnosis, treatment, vaccine, and other medical management issues of smallpox. This Self-Test is for practice only and is not related to the post-test for continuing education credit.

NOTE: A self-test summary page, containing the questions and answers is provided at the end of this page.

1. Of the four types of variola major, the most FREQUENT presentation is
   a) ordinary  
   b) modified  
   c) flat  
   d) hemorrhagic

2. The incubation period of smallpox averages
   a) 6 - 7 days  
   b) 9 - 10 days  
   c) 12 - 14 days  
   d) 17 - 19 days

3. Which of the following symptoms is NOT part of the prodrome?
   a) temperature 101°F or higher  
   b) cough  
   c) malaise  
   d) headache

4. A person with smallpox becomes infectious when
   a) temperature rises  
   b) scabs develop  
   c) scabs fall off  
   d) first lesions appear

5. With ordinary type smallpox, confluent (overlapping) lesions are most common on the

6. Compared with other rash illnesses, the progression of the smallpox rash is

a) relatively slow  
b) relatively fast  
c) about the same speed  
d) faster for adults and slower for children

7. The type of smallpox that occurs mostly in PREVIOUSLY VACCINATED people is

a) ordinary  
b) modified  
c) flat  
d) hemorrhagic

8. Refer to this photo showing ordinary-type smallpox rash development through consecutive stages. The numbers indicate the days after rash onset. The lesion shown on day 7 is best described as

(Source: WHO slide set, October 24, 2001)

a) vesicle  
b) macule  
c) pustule  
d) papule  
e) scab

9. Refer to the photo. At this stage of rash, and from looking at the rash only, the patient MOST LIKELY has
a) chickenpox
b) smallpox
c) cannot differentiate at this stage

10. Referring to rash in this photo, which, if any, of the following can you determine solely by looking?

(Source: WHO slide set, October 24, 2001)

a) the patient has chickenpox
b) the patient has smallpox
c) cannot differentiate at this stage

11. Which of the following figures represents the rash distribution of smallpox?

(a) Figure A
(b) Figure B
b) Figure B
c) Figure A and Figure B are both smallpox rash distributions
d) none of the above

12. The patient in this photo has

![Image of smallpox rash]

a) hemorrhagic-type smallpox
b) ordinary-type smallpox with confluent lesions
c) flat-type smallpox
d) modified-type smallpox

13. The patient in this photo has

![Image of smallpox rash]

a) hemorrhagic-type smallpox
b) ordinary smallpox with confluent lesions
c) flat-type smallpox
d) modified-type smallpox

14. The most important laboratory procedure for a patient who meets the criteria for "moderate risk for smallpox" is

a) gram stain of a lesion
b) serologic test for syphilis
c) culture of orthopoxvirus
d) rapid diagnostic testing for varicella zoster virus (VZV)

15. Laboratory procedures for detection of variola virus in clinical specimens should be done by the

a) local health department or local hospital lab
b) state health department
16. What is the reporting procedure for a person whose clinical characteristics meet the clinical case definition of smallpox?

a) Report immediately to the local and/or state health department  
b) Report immediately to CDC in Atlanta  
c) Report to the local and/or state health department by the end of the month  
d) Report only after laboratory confirmation is done

17. Which of the following is NOT part of the clinical case definition?

a) acute onset of fever, 101°F or higher  
b) rash has firm, deep-seated vesicles or pustules  
c) nonproductive cough for 7 or more days  
d) vesicles or pustules are in the same stage of development without other apparent cause

18. Which of the following should be used as protective equipment for personnel in contact with a suspected or confirmed case of smallpox?

a) disposable gloves  
b) properly fitted masks of N95 quality or higher  
c) disposable gowns  
d) all of the above

19. Which of the following is NOT common following first-time smallpox vaccination?

a) pain at vaccination site  
b) fever  
c) lymphadenopathy  
d) paresthesia in the vaccinated arm

20. Most transmission results from direct face-to-face contact with an infected person, USUALLY within a distance of

a) 6 feet  
b) 8 feet  
c) 10 feet  
d) 12 feet

21. A smallpox patient can transmit the virus UNTIL

a) rash onset  
b) vesicles appear  
c) pustules appear  
d) all scabs have separated

22. Currently, all available smallpox vaccines are

a) inactivated variola (smallpox) virus  
b) inactivated vaccinia virus  
c) live virus preparations of infectious variola (smallpox) virus  
d) live virus preparations of infectious vaccinia virus

23. Upon vaccination, a person is considered to be protected when a _______ develops at the vaccination site.

a) macule  
b) papule  
c) pustule  
d) scab

24. Which of the following is NOT a key element for the response to a case of smallpox?

a) smallpox vaccination of the general public  
b) surveillance for rash illnesses  
c) isolation of persons with smallpox  
d) vaccination of contacts of smallpox cases  
e) monitoring contacts for development of smallpox

25. In a post-release situation, vaccination would be recommended for

a) contacts of cases  
b) laboratory personnel who collect or process clinical specimens and other persons who may have contact with infectious materials  
c) persons providing direct medical or public health evaluation, care, and transportation services to suspected smallpox cases  
d) all of the above

26. The most FREQUENT complication of smallpox vaccination is

a) eczema vaccinatum  
b) generalized vaccinia  
c) inadvertent inoculation  
d) progressive vaccinia

27. What is the most important risk factor for developing progressive vaccinia?

a) age less than 1 year  
b) eczema  
c) pregnancy  
d) immunodeficiency  
e) first exposure to smallpox vaccine

28. In the event of an exposure to smallpox, the vaccine is contraindicated for

a) no one  
b) pregnant women  
c) immunocompromised persons or persons who have an immunocompromised household contact  
d) persons who have had a serious allergic reaction to a prior dose of vaccine or to a vaccine component  
e) persons with eczema or history of eczema, household contacts with active eczema, or household contacts with history of eczema

NOTE: The verification code for this self-study is NT013F.
To receive Continuing Education (CE) credit, you will be required to provide this verification code. Be sure to write down this code for later reference. For more information about receiving CE credit for this training, see "Continuing Education Credit Information."

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**Patient Education Materials**

- Patient Education Materials on the CDC Smallpox Website ([http://www.bt.cdc.gov/agent/smallpox/vaccination/clinicians.asp#patient](http://www.bt.cdc.gov/agent/smallpox/vaccination/clinicians.asp#patient))

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**References**

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**Contact Information**

- To ask smallpox-related questions via telephone, call:
  
  **CDC Public Response Hotline:**
  
  (888) 246-2675 (English)  
  (888) 246-2857 (Spanish)  
  (866) 874-2646 (TTY)

  Monday-Friday 8 a.m. to 11 p.m. EST  
  Saturday-Sunday 10 a.m. to 8 p.m. EST

  **CDC Clinician Information Line for Smallpox and Smallpox Vaccination:**

  (877) 554-4625 (English)

  To ask smallpox-related questions via e-mail, send to SMALLPOX@CDC.GOV

  To send questions and comments about this training program to the National Immunization Program, Centers for Disease Control and Prevention:

  e-mail: NIPINFO@CDC.GOV

**Differential Diagnosis**

- Illustration of Clinical Course of Ordinary-type Smallpox ([clinicalchart.htm](http://www.cdc.gov/nip/ed/smallpox-trg/clinician-should-know/contents/printable_version.htm))
- Smallpox Protocol Poster:

**Preview Version**

Print Version

The print version has been split into two 8½" x 11" (22 cm x 28 cm) pieces for easy printing:

1st Half of Poster PDF (spox-poster-1st-half.pdf, 2.09 MB/1 page)
2nd Half of Poster PDF (spox-poster-2nd-half.pdf, 2.18 MB/1 page)

(Copy on Web: http://www.bt.cdc.gov/agent/smallpox/diagnosis/evalposter.asp)


Photos and Videos

- Smallpox Reference Photos
- Videos Segments Used In Activity
  - Clinical Features
  - Rash Illness Evaluation
  - Laboratory Diagnosis
  - Vaccine Background
  - Vaccine Indications
  - Vaccine Precautions and Contraindications
  - Vaccine Administration
  - Vaccine Adverse Reactions
  - Isolation and Management
  - Epidemiology
  - Global Smallpox Eradication
  - Smallpox Response Plan
- Supplemental Video Segments
  - History of Smallpox-the Disease
  - Smallpox as a Biological Weapon
  - Surveillance and Containment Strategy
  - Virus

Smallpox Response Plan and Guidelines


Websites

- CDC Public Health Emergency Preparedness and Response
  Topic areas include fact sheets/overviews, preparation and planning, vaccination, exposure management/prophylaxis, infection control, evaluation and diagnosis, laboratory testing, surveillance and investigation, and training materials. http://www.bt.cdc.gov/Agent/Smallpox/Smallpox.asp
- Current References on CDC Smallpox Website http://www.bt.cdc.gov/agent/smallpox/reference/index.asp#other
- WHO Website on smallpox. http://www.who.int/EMC/diseases/smallpox/

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About This Training

**Purpose**

The purpose of *Smallpox: What Every Clinician Should Know 2003* is to provide clinicians with information on the virology, epidemiology, clinical features, and diagnosis of smallpox; the characteristics and use of smallpox vaccine; and proper management of smallpox vaccine recipients.

The activity is based on a satellite broadcast that was produced by the National Immunization Program (NIP) and the Public Health Training Network (PHTN) of the Centers for Disease Control and Prevention (CDC). The broadcast first aired on December 13, 2001. It was updated April 16, 2003 to reflect changes in recommendations. This activity has been developed to provide clinicians with access to training materials in a variety of media.

**Goal**

To improve the clinicians' ability to recognize, diagnose, treat, and prevent smallpox.

**Objectives**

After completing this activity you will be able to:

- Describe the clinical characteristics of smallpox.
- Differentiate between smallpox and other rash illnesses.
- Describe the indications for smallpox vaccine.
- Describe the components of the smallpox response plan.

**Time**

You should allow approximately 2.5 hours to complete this activity. The actual time you spend will depend on how much of the supplementary material you review.
Audience

The intended audience for this activity is: physicians, nurses, health educators, immunization program managers, pharmacists, and other healthcare providers working in private offices, hospitals, and public health settings.

Instructions

For information on how to navigate and use the interactive format of this training, see "How To Use." To setup your computer with the necessary plug-ins, see "Computer Settings Guide." To view a video welcome message, see "Welcome."

As you participate in this practice exercise you will progress through a fictitious scenario involving the beginning of a smallpox outbreak. People will be presented to you in different venues and you will be asked thought-provoking questions along the way.

As you move through the practice exercise, you will be directed to stop and learn specific information about the disease. After learning the information, you will return to the next step in the exercise.

You may also access any of these important segments at any time by using the retractable "Videos" menu on the top right or the "Additional Info" on the bottom right.

Disclaimer

The following have disclosed that their presentations will include discussion of investigational use of smallpox vaccines and vaccinia immune globulin (VIG) and unlabeled use of cidofovir: William Atkinson, MD; Joanne Cono, MD; Lisa Rotz, MD.

Continuing Education Credit Information

How to Register

In order to register for this course you must complete the Self-Test.

To register for the course and receive continuing education credit:

- Go to www.phppo.cdc.gov/phtnonline
- Login as a participant (note: the first time you use the online system you will need to login as a new participant and create a participant profile).
- Find the course by searching the catalog using the following course numbers
  - If you completed this course on a CD-ROM the course number is: CB3074.
  - If you completed this course using the Internet the course number is: WB3084.
- Select the type of credit you wish to receive and register for the course.
- Take the exam and complete the course evaluation.
- Print your continuing education certificate.

To receive continuing education credit, you must complete the entire course and take the post-test and evaluation online.

At the time you complete the online evaluation you will be required to provide a verification code. Watch for this verification code as you complete the activity.

For assistance with the online system, call (800) 41-TRAIN or (404) 639-1262 Monday through Friday, 8:00 AM to 4:30 PM Eastern Standard Time or send an e-mail to CE@cdc.gov.
General Information

The content for this activity was finalized in April 2003 and is valid for continuing education credit until September 30, 2004. However, smallpox-related recommendations are likely to change. We encourage you to periodically review the CDC Smallpox Website (http://www.bt.cdc.gov/agent/smallpox/) for updated information.

Credit

CME: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this educational activity for a maximum of 2.5 hours in category 1 credits towards the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

CNE: This activity for 3.1 contact hours is provided by the Centers for Disease Control and Prevention, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center’s Commission on Accreditation.

CECH: The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialists (CHES) to receive 2 1/2 category 1 contact hours in health education, CDC provider number GA0082.

CEU: The Centers for Disease Control and Prevention has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.25 Continuing Education Units (CEUs).

Printing

Many articles are available online. Scripts of the video-based presentations as well as patient educational materials may be printed directly from the browser. Reference articles and documents that are available in PDF format can be printed through Adobe Acrobat Reader®. If you do not have Acrobat Reader® already installed on your computer, you may install it by using the Computer Settings Guide, step 4.

In addition, you can access a printable version of this program. This version contains text and graphics only.

Contact Us

Send questions and comments about this training program to the National Immunization Program, Centers for Disease Control and Prevention:

e-mail: NIPINFO@CDC.GOV

Acknowledgments

Co-developed and produced by:

Centers for Disease Control and Prevention (CDC)
National Immunization Program (NIP)
http://www.cdc.gov/nip
Self-Test Summary

The questions, correct answers, and explanations for all questions are displayed below.

1. Of the four types of variola major, the most FREQUENT presentation is

   a) ordinary  
   b) modified  
   c) flat  
   d) hemorrhagic

Correct Answer: a) ordinary

Explanation: More than 90% of cases in both vaccinated and unvaccinated persons are of the ordinary type.

2. The incubation period of smallpox averages

   a) 6 - 7 days  
   b) 9 - 10 days  
   c) 12 - 14 days  
   d) 17 - 19 days

Correct Answer: c) 12 - 14 days

Explanation: The average incubation period is 12 - 14 days, with a range of 7 to 18 days.

3. Which of the following symptoms is NOT part of the prodrome?

   a) temperature 101°F or higher  
   b) cough  
   c) malaise  
   d) headache

Correct Answer: b) sinus pain
Explanation: The prodrome begins abruptly, with fever, malaise, headache, muscle pain, prostration (being bed-ridden), and often nausea and vomiting and backache.

4. A person with smallpox becomes infectious when

a) temperature rises
b) scabs develop
c) scabs fall off
d) first lesions appear

Correct Answer: d) first lesions appear

Explanation: The person with smallpox becomes infectious with rash onset and is most infectious during the first week of the rash.

5. With ordinary type smallpox, confluent (overlapping) lesions are most common on the

a) palms of the hands
b) soles of the feet
c) face
d) trunk

Correct Answer: c) face

Explanation: Confluence is most common on the face, but can involve the extremities.

6. Compared with other rash illnesses, the progression of the smallpox rash is

a) relatively slow
b) relatively fast
c) about the same speed
d) faster for adults and slower for children

Correct Answer: a) relatively slow

Explanation: In ordinary-type smallpox, each stage - papules, vesicles, and pustules - usually takes one or two days to develop.

7. The type of smallpox that occurs mostly in PREVIOUSLY VACCINATED people is

a) ordinary
b) modified
c) flat
d) hemorrhagic

Correct Answer: b) modified

Explanation: The prodromal illness still occurs but may be less severe than in ordinary type. Modified smallpox is rarely, if ever, fatal.

8. Refer to this photo showing ordinary-type smallpox rash development through consecutive stages. The numbers indicate the days after rash onset. The lesion shown on day 7 is best described as
9. Refer to the photo. At this stage of rash, and from looking at the rash only, the patient MOST LIKELY has

a) chickenpox
b) smallpox
c) cannot differentiate at this stage

Correct Answer: a) chickenpox

Explanation: Notice the rash is at different stages of development on his face. Some lesions are papules, some are vesicles, and some have crusted.

10. Referring to rash in this photo, which, if any, of the following can you determine solely by looking?
(Source: WHO slide set, October 24, 2001)

a) the patient has chickenpox
b) the patient has smallpox
c) cannot differentiate at this stage

Correct Answer: c) can't differentiate at this stage

Explanation: Just from looking at the rash without knowing the patient's clinical history, it is impossible to distinguish smallpox from chickenpox at this early stage of development. It turns out, though, that a few days later the rash developed into a classic smallpox presentation. Here you see smallpox and chickenpox side-by-side during the very early stage of rash onset, which is why the rashes are still indistinguishable.

(Source: WHO slide set, October 24, 2001)

11. Which of the following figures represents the rash distribution of smallpox?

a) Figure A  
b) Figure B

c) Figure A and Figure B are both smallpox rash distributions
d) none of the above

Correct Answer: a) Figure A

Explanation: The rash of smallpox has a centrifugal distribution, meaning that it is most dense on the face. It is also more dense on the distal extremities than on the trunk.

12. The patient in this photo has


a) hemorrhagic-type smallpox
b) ordinary-type smallpox with confluent lesions
c) flat-type smallpox
d) modified-type smallpox

Correct Answer: b) ordinary-type smallpox with confluent lesions

Explanation: This photo was taken on the 9th day of illness.

13. The patient in this photo has


a) hemorrhagic-type smallpox
b) ordinary smallpox with confluent lesions
c) flat-type smallpox
d) modified-type smallpox

Correct Answer: c) flat-type smallpox

Explanation: Notice extensive flat pustules.
14. The most important laboratory procedure for a patient who meets the criteria for "moderate risk for smallpox" is

a) gram stain of a lesion
b) serologic test for syphilis
c) culture of orthopoxvirus
d) rapid diagnostic testing for varicella zoster virus (VZV)

Correct Answer: d) rapid diagnostic testing for varicella zoster virus (VZV)

Explanation: The most common rapid method for detecting VZV in clinical material is direct fluorescent antibody (DFA). Chickenpox (varicella) is the most likely illness to be confused with smallpox, but in a given clinical situation, other diagnoses may be considered more highly.

15. Laboratory procedures for detection of variola virus in clinical specimens should be done by the

a) local health department or local hospital lab
b) state health department
c) CDC in Atlanta
d) private reference laboratory

Correct Answer: c) CDC in Atlanta

Explanation: Currently, lab procedures for detection of smallpox virus in clinical specimens should be done ONLY by the CDC.

16. What is the reporting procedure for a person whose clinical characteristics meet the clinical case definition of smallpox?

a) Report immediately to the local and/or state health department
b) Report immediately to CDC in Atlanta
c) Report to the local and/or state health department by the end of the month
d) Report only after laboratory confirmation is done

Correct Answer: a) Report immediately to the local and/or state health department

Explanation: A suspected case of smallpox is a public health and medical emergency.

17. Which of the following is NOT part of the clinical case definition?

a) acute onset of fever, 101°F or higher
b) rash has firm, deep-seated vesicles or pustules
c) nonproductive cough for 7 or more days
d) vesicles or pustules are in the same stage of development without other apparent cause

Correct Answer: c) nonproductive cough for 7 or more days

Explanation: The clinical case definition is an illness with an acute onset of fever of 101°F or higher, followed by a rash. The rash is characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

18. Which of the following should be used as protective equipment for personnel in contact with a suspected or confirmed case of smallpox?
a) disposable gloves
b) properly fitted masks of N95 quality or higher
c) disposable gowns
d) all of the above

Correct Answer: d) all of the above

Explanation: The CDC Smallpox Response Plan provides more information on protective equipment.

19. Which of the following is NOT common following first-time smallpox vaccination?

a) pain at vaccination site
b) fever
c) lymphadenopathy
d) paresthesia in the vaccinated arm

Correct Answer: d) paresthesia in the vaccinated arm

Explanation: Local reactions, fever, and lymphadenopathy are common following first-time smallpox vaccination. Smallpox vaccine is not known to cause peripheral nerve damage or paresthesias.

20. Most transmission results from direct face-to-face contact with an infected person, USUALLY within a distance of

a) 6 feet
b) 8 feet
c) 10 feet
d) 12 feet

Correct Answer: a) 6 feet

Explanation: Physical contact with a smallpox patient or contaminated articles is another common mode of transmission.

21. A smallpox patient can transmit the virus UNTIL

a) rash onset
b) vesicles appear
c) pustules appear
d) all scabs have separated

Correct Answer: d) all scabs have separated

Explanation: The patient can transmit the virus throughout the course of the rash illness.

22. Currently, all available smallpox vaccines are

a) inactivated variola (smallpox) virus
b) inactivated vaccinia virus
c) live virus preparations of infectious variola (smallpox) virus
d) live virus preparations of infectious vaccinia virus

Correct Answer: d) live virus preparations of infectious vaccinia virus

Explanation: Smallpox vaccine does NOT contain variola (smallpox) virus.
23. Upon vaccination, a person is considered to be protected when a _______ develops at the vaccination site.

a) macule  
b) papule  
c) pustule  
d) scab  

Correct Answer: c) pustule  
Explanation: The pustule appears by 7 to 11 days after vaccination.

24. Which of the following is NOT a key element for the response to a case of smallpox?

a) smallpox vaccination of the general public  
b) surveillance for rash illnesses  
c) isolation of persons with smallpox  
d) vaccination of contacts of smallpox cases  
e) monitoring contacts for development of smallpox  

Correct Answer: a) smallpox vaccination of the general public  
Explanation: At the present time, the risk of an attack using smallpox virus is considered to be low. Vaccination of the general public is not currently part of the response preparedness plan. Smallpox vaccine may be made available to the general public in the future.

25. In a post-release situation, vaccination would be recommended for

a) contacts of cases  
b) laboratory personnel who collect or process clinical specimens and other persons who may have contact with infectious materials  
c) persons providing direct medical or public health evaluation, care, and transportation services to suspected smallpox cases  
d) all of the above  

Correct Answer: d) all of the above  
Explanation: Vaccination will be a key component of our response to an intentional release of variola virus.

26. The most FREQUENT complication of smallpox vaccination is

a) eczema vaccinatum  
b) generalized vaccinia  
c) inadvertent inoculation  
d) progressive vaccinia  

Correct Answer: c) inadvertent inoculation  
Explanation: Inadvertent inoculation accounts for approximately one half of all complications of primary vaccination and revaccination.

27. What is the most important risk factor for developing progressive vaccinia?

a) age less than 1 year  
b) eczema
c) pregnancy

d) immunodeficiency

e) first exposure to smallpox vaccine

Correct Answer: d) immunodeficiency

Explanation: Almost all known cases of progressive vaccinia (vaccinia necrosum) have occurred in persons with cellular immunodeficiency. Humoral immunodeficiency also increases the risk of this adverse reaction.

28. In the event of an exposure to smallpox, the vaccine is contraindicated for

a) no one
b) pregnant women
c) immunocompromised persons or persons who have an immunocompromised household contact
d) persons who have had a serious allergic reaction to a prior dose of vaccine or to a vaccine component
e) persons with eczema or history of eczema, household contacts with active eczema, or household contacts with history of eczema

Correct Answer: a) no one

Explanation: In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine.