Welcome Message

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"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 clinicians 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 clinical information in this training has been excerpted from a satellite broadcast on smallpox that first aired on December 13, 2001. The program that you are about to use has been developed as an additional medium for health care practitioners to learn about smallpox.

After completing this training, you should be able to:

- describe the clinical characteristics and pathogenesis of smallpox;
- differentiate between smallpox and other rash illnesses;
• describe the characteristics, administration, indications, contraindications, and adverse events for smallpox vaccine.

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.

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. Contact information for the National Immunization Program is included in the reference section of this training.

(Welcome video)

Practice Exercise

Page 1 (Practice Exercise Notebook Cover Options)

Begin the Training

Videos

Additional Info:

• Patient Education Materials
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• Self-Test
• About This Training

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.
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.

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
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 smallpox.

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.

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 decent 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.

(Gayle Mack)

Review her chart below.
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:
  - Acutely ill
  - Pale
- Fever 102°F
- Vesicular rash on face, arms, palms of the hands, and soles of the feet
- 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.

(Close up of Gayle's arm today, Day 5 of rash)

(Close up of Gayle's face today, Day 5)

What do you think is Gayle Mack's illness?

- You think this is a serious case of adult chickenpox.
- You think she is experiencing a drug reaction to the over-the-counter medication.
- You think she has disseminated herpes zoster.
- 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 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.

![Classic Chickenpox Lesions](image1.png) ![Classic Smallpox Lesions](image2.png)

Gayle has a classical smallpox presentation. If you suspected a rash illness other than smallpox, please review the [differential diagnosis 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 reached at home and is brought to the hospital and placed in a negative air pressure room.

CDC staff members are sent immediately to the hospital to collect clinical specimens. A CDC response team is also sent on-site with smallpox vaccine. The staff members take specimens from the patients' skin lesions as well as blood samples, and they return to the CDC laboratory in Atlanta to conduct specific tests.

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**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 close contacts of the patients, 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.

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 currently 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 events 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.

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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 is a contraindication for people who have ever had eczema 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 should not be vaccinated. His risk of an adverse event to the vaccine outweighs his risk of developing smallpox—he has not been exposed to the virus.

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Current smallpox vaccine is an investigational product, and vaccinees must be informed of this. 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 events of smallpox vaccine.

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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.

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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.

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 (on the .pdf format link to open the summary).

This concludes the scenario portion of this practice exercise.

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

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

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

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

Videos (transcripts)

- Clinical Features
- Differential Diagnosis
- Laboratory Diagnosis
- Vaccine
- Vaccine Administration
- Vaccine Adverse Events
Clinical Features (slides; video)

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

(Background)
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, and is accompanied by the first symptoms of illness - the prodrome, which is characterized by fever and other symptoms. In the skin, the virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. The result is the characteristic rash.

(Variola Major)
There are two major forms of smallpox. Variola major is a severe illness with a high fatality rate. Variola minor is much less frequently fatal. We will discuss only variola major during this program.

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 determines the clinical presentation.

The most frequent presentation is ordinary smallpox. Modified smallpox is milder and occurs in previously vaccinated people. Flat and hemorrhagic smallpox are very severe but uncommon variants of the disease.

The incubation period of smallpox averages 12 days, with a range of seven to 17 days. During this period the patient is well and not infectious. 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 illnesses.

More than 90% 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.

The first visible lesions appear in the mouth as minute red spots and on the tongue and oral 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 patient is most infectious.

(Skin rash)
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.

By the second day of the rash, the macules becomes raised papules. This child has only a few papules on the forehead and arm.

By the third or fourth day the lesions become vesicular, containing first an opalescent fluid, which then becomes opaque and turbid within 24 to 48 hours. The skin lesions of smallpox typically are surrounded by a faint erythematous halo. 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. 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, especially in varicella.

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 are often described as "shotty", similar to a small bead embedded in the skin.

Between seven 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 development. Although lesions are dense around the nose and mouth, the majority of lesions are discrete, separated by normal appearing skin.

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 toxic even after scabs had formed over all the lesions. In one case series, the case-fatality rate in confluent smallpox was 62%.

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. The scabs contain variola virus and are infectious. 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 eventually become pitted scars.

There are a few more important points about the smallpox rash. The progression of the rash 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 about the same stage of development, although they may be different sizes.
The rash of smallpox has a centrifugal distribution, meaning it's most dense on the face, and more dense on the extremities than is on the trunk. On the extremities, it is 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 are often 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?

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

(Modified Smallpox)  
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 occurs mostly in previously vaccinated people. The prodromal illness still occurs but may be less severe than in the ordinary type. There's usually no fever during evolution of the rash. The skin lesions tend to evolve more quickly, and are more superficial, and may not show the uniform characteristic of more typical smallpox. The lesions are often few in number, but could be numerous, or even confluent. Regardless of the number of lesions, they usually evolve rapidly. Modified smallpox is rarely, if ever, fatal.

(Flat and Hemorrhagic)  
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 was so called because the lesions remained more or less flush with the skin at the time when raised vesicles formed in ordinary smallpox. In a large series of smallpox cases from India, flat type smallpox accounted for 5%-10% of cases. It's not known with certainty why some people develop this type of disease, but many cases occurred in children. The prodrome and constitutional symptoms are severe, and last three or four days. The fever remains elevated throughout the course of the illness and the patient has severe toxic symptoms. The rash on the tongue and palate is usually extensive, and the skin lesions develop very slowly.

This man has flat type smallpox. 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. Lesions may contain hemorrhages.

This woman also has flat type smallpox. She looks very toxic, and she has crusting around her mouth from the oral lesions. The prognosis for this form smallpox is grave and most cases are fatal. Flat type smallpox can be difficult to diagnose, mainly because the typical skin lesions do not develop.

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% of cases, and occurred mostly in adults. The prodrome, which can be prolonged, is characterized by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the skin, 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 disease.
This woman has the early, or fulminating form of the disease. Hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, as you see here, and bleeding from the mouth and gums, or other mucous membranes, petechia 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. This woman has late hemorrhagic manifestations. In patients who survive for eight to 10 days the hemorrhages appear in the early eruptive period. The rash is flat and does not progress beyond the vesicular stage. Hemorrhagic smallpox could be easily misdiagnosed as meningococcal bacteremia because of the hemorrhages and lack of typical smallpox vesicles and pustules.

(Disease Outcome)
For all types of smallpox, the outcome of the infection is either recovery- with or without sequelae- or death. Those who survive are permanently scarred. Blindness from eye involvement is also common. Recovery results in long lasting immunity to reinfection with variola virus, and 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 10th and 16th days of the illness. The overall case fatality rate for variola major was about 30%. But the fatality rate for children less than one year of age was 40%-50%.

The cause of death from smallpox is not clear, but the infection is now known to involve multiple organs. Circulating immune complexes or an uncontrolled immune response may be contributing factors, as well as overwhelming viremia and soluble variola antigens.

Differential Diagnosis (slides; video)
(See also: http://www.cdc.gov/nip/smallpox/poster-protocol.pdf and illustration of clinical course of ordinary-type smallpox (clinicalchart.htm)

Cynthia Good, Moderator

(Background and Introduction)
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. But if a case of smallpox is ever confirmed here in the United States, 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. Karin Galil, a medical epidemiologist in the National Immunization Program, to discuss the differential diagnosis of rash illness.

Karin Galil, MD, MPH
Medical Epidemiologist
National Immunization Program, CDC
Within a few days of rash onset, patients with smallpox develop a distinctive generalized vesicular or pustular rash. Although there are many other rash illnesses that can present with vesicles or with pustules, by paying careful attention to the patient's history, the evolution, distribution and appearance of the rash, and associated symptoms, you can differentiate smallpox from other conditions.

By far, the most common rash illness that's likely to be confused with smallpox is varicella, or chickenpox. Since a varicella vaccine was licensed in 1995 there has been a dramatic decrease in the number of cases of varicella in the United States. But even with this decrease, we expect there to be about a million and a half cases of varicella in the United States this year. I will discuss some of the important features that will help you tell these two diseases apart.

The most important differentiating feature between smallpox and any other rash illnesses is the presence of a prodrome: fever and other symptoms before rash onset. A febrile prodrome is absolutely characteristic of smallpox. Patients with smallpox have a severe, febrile prodrome that starts one to four days before the onset of the rash. The fever is usually high, in the range of 102 to 104 degrees, but it's always at least 101°F. People with varicella will have a short, mild prodrome, and some of them will have no prodrome at all before the onset of their rash. The prodrome is associated with little or no fever. If there is no history of a febrile prodrome, smallpox is not the likely diagnosis.

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 sick to engage in their normal activities. During its prodromal phase, some persons with varicella may also feel tired or have a low—grade fever, but most don't feel very sick.

The second important differentiating feature of smallpox and varicella is the appearance, evolution, and the distribution of the rash. Although there may be some overlap in the appearance of the lesions, particularly soon after rash onset, classic smallpox looks very different than varicella. Smallpox lesions are deep in the dermis, and they feel hard to the touch. They are round and they're well circumscribed. As they evolve they might become confluent or umbilicated. By contrast, the varicella rash is superficial and the lesions appear to be delicate. They are not as well circumscribed.

Here is a typical lesion of smallpox. It is circumscribed with definite edges. These lesions are firm to the touch lesions have been described as feeling shotty. The classic varicella or chickenpox lesion is a delicate appearing fluid—filled vesicle surrounded by an erythematous base. It is said to look like a dewdrop on a rose petal.

The rash of smallpox evolves much more slowly than the rash of chickenpox. In a typical case of smallpox, lesions evolve from macules to papules to vesicles and then to crusts, with each stage taking one or two days. By contrast with varicella, some lesions will have evolved from macules to crusts within 24 hours. Because of the slow rate of evolution of smallpox lesions, all the lesions on any one part of the body will be in the same stage of development, such as all vesicles or all pustules. Varicella lesions typically appear in crops and they evolve quickly, so in any one area of the body you
will find lesions in all stages of evolution: papules, vesicles, and crusting lesions.

(Rash distribution)
The third important clinical feature that differentiates smallpox and varicella is the distribution of the rash. With smallpox, the rash has what is known as a centrifugal distribution. By that I mean that it's most dense on the face and distal extremities. The lesions are less dense on the abdomen and on the back. By contrast, the rash of varicella is generally most dense on the abdomen and back, and less dense on the extremities.

Here is an infant with varicella. Notice the concentration of lesions is highest on the back, and becomes less dense on the arms and the legs.

This child has smallpox. Here you can see that the lesions are most concentrated on the arms and the legs, and there are fewer lesions on the back. It's important to examine the palms and the soles. Lesions on the palms or soles are seen in the majority of cases of smallpox, but are very rare in varicella.

(Toxemia)
Finally, smallpox patients are usually extremely ill, and may be toxic in appearance or even moribund, whereas most persons with varicella can feel unwell but are usually not extremely ill unless they develop a severe complication.

Here is an adult with varicella. Notice that he doesn't look particularly ill. There are lesions on the face, but they look superficial, they are of different sizes, and they are all in different stages of evolution.

(Lesion size)
Here is a person with smallpox. These lesions are very well circumscribed, and they're similar in size. You can tell that the lesions are larger than varicella lesions as we saw before. Also, all the lesions visible in this picture are in the same stage of evolution.

(Other issues to consider)
There are other issues to consider when you're evaluating a person with a vesicular rash illness. First, in the U.S., varicella is primarily a disease of children. Ninety-five percent of US adults who are 20 years of age and older and 99% of those 30 years and older have had varicella. Since second cases of varicella are really rare, asking whether a person has had chickenpox in the past helps in determining the likelihood that the rash you are evaluating is varicella. When varicella does occur in an adult it tends to be more severe than a typical childhood case.

Second, a history of varicella vaccination. Generalized varicella is unlikely in a person who has received the varicella vaccine. Although some vaccinees may still get varicella, it's usually a very mild illness with few lesions and is not likely to be confused with smallpox.

Third, a history of exposure to a person with varicella or herpes zoster 10 to 21 days before rash onset. About 80% of children and half of adults with varicella will recall an exposure to a case of chickenpox or shingles. A strong exposure history can increase the probability of varicella but it doesn't help in making the diagnosis if it is lacking.
Varicella is the most common rash illness that's likely to be confused with smallpox. Since varicella is now a vaccine-preventable disease, we encourage health care providers to vaccinate susceptible children, adolescents, and adults. There are other illnesses and conditions to consider in the differential diagnosis of a person with a generalized rash illness. These include a variety of infections and noninfectious causes.

Drug eruptions can present with a variety of generalized rashes, and they may have concurrent symptoms, such as fever. For this reason it is important to take a detailed history of all medications including prescription and over-the-counter medications.

Herpes zoster, or shingles, usually presents as a localized and painful rash in one or two dermatomes on one side of the body. In immunocompromised persons it can disseminated and can present with a generalized vesicular rash. People with this condition have a history of varicella.

Hand, Foot, and Mouth Disease is an enteroviral disease that most commonly occurs in the summer or the autumn. Ulcerative lesions can be seen in the mouth, and tender vesicular or pustular lesions on the hands and feet including the palms and soles. This distribution sometimes raises concern about smallpox. However the individual lesions are really easy to distinguish from the hard pustules of smallpox and the lesions clear up in about a week.

Molluscum contagiosum is a common viral infection of the skin and mucous membranes and is caused by poxvirus. When the lesions disseminate, the rash can be confused with smallpox, particularly in an HIV-infected person with concurrent illnesses. Molluscum contagiosum also occurs in healthy children, who are perfectly well and afebrile.

Secondary syphilis can produce almost any type of generalized rash, including pustular rash. The rash may appear anywhere on the body, and they may involve the palms and soles. Fortunately syphilis is becoming a rare illness in the United States, but it should be ruled out in someone who is sexually active and has a generalized rash.

There are many other causes of generalized rash illnesses, from common etiologies like insect bites, scabies, and contact dermatitis to less common conditions such as disseminated herpes simplex, or erythema multiforme. In addition there are some exceedingly rare causes, such as rickettsial pox and monkeypox.

Although we have focused on differentiating smallpox from conditions that can present with generalized vesicular or pustular rashes, a small percentage of smallpox cases will present with either a hemorrhagic rash or flat type rash. Both variants are highly lethal. Hemorrhagic smallpox can be mistaken for meningococcemia.

(Precautions)
Whether or not you think the person you are evaluating has smallpox, it is important to institute appropriate precautions to prevent the spread of an infectious agent. Always wear gloves when touching a patient with a rash illness, and institute respiratory precautions if there is any chance of airborne spread, as occurs with both varicella and smallpox. The next actions you take will depend on the likelihood that the person you are evaluating has smallpox.
(Risk criteria)
We have developed a set of criteria that can be used to categorize patients into high, moderate, or low risk for smallpox, using major and minor diagnostic criteria.

There are three major smallpox criteria. And if a person meets all three criteria he or she is considered a high-risk case. The first criterion is that the person had a significant febrile prodrome one to four days before rash onset. The person must have had a fever greater than or equal to 101°F, and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting, or abdominal pain. Second, the rash lesions are deep in the skin, firm or hard to the touch and well circumscribed. Third, on any one part of the body, all of the lesions are in the same stage of development.

There are five minor smallpox criteria. The distribution of the rash is centrifugal, meaning that the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk. The first lesions of the rash appeared on the oral mucosa or palate, or else on the face or forearms. The patient appears toxic or moribund. Lesions progressed slowly, by which I mean that the individual lesions evolved from macules to papules to pustules over several days. Finally, there are lesions on the palms or the 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 in place. These patients should be reported to local health authorities immediately. A person is considered at moderate risk of smallpox if he or she had a febrile either a prodrome and either one other major criterion or at least four minor. These patients should be isolated and be evaluated urgently to determine the cause of the illness. We recommend that persons who are classified at high or moderate risk be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible. All other conditions are considered low risk. Any person who did not have a febrile prodrome is considered low risk, as are persons who had a febrile prodrome, but less than four minor criteria. These patients should be managed as clinically indicated.

(Protocol)
We have produced a protocol that will be useful to primary care providers who encounter patients with acute, generalized rash illnesses. The protocol includes a diagnostic algorithm, a chart with the major and minor criteria I just discussed, and a chart of common rash illnesses along with clinical and diagnostic clues. In addition there are photographs of the classic lesions of smallpox and varicella. The protocol is available free from the National Immunization Program Web site.

Laboratory Diagnosis (slides; video)

Lisa D. Rotz, MD
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 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.

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 in some local and 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, or if VZV testing of a vesicular or pox-like rash is negative, the local or state health department and CDC should be contacted immediately. Personnel can be quickly deployed to assist in confirming the diagnosis by collecting clinical material for laboratory testing, and to assist in implementation of control measures if necessary.

The diagnosis of orthopoxvirus infection in general can be made rapidly by electron microscopic examination of vesicular or pustular fluid or scabs. Orthopoxviruses appear as large brick shaped particles. Differentiation of orthopoxviruses is made by nucleic acid based testing, such as polymerase chain reaction, and by culture. The CDC laboratory has also developed serologic tests to assist in diagnosis of acute orthopox virus infection. So blood samples will be an important part of the laboratory evaluation of a suspected case.

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 is available on the Bioterrorism Preparedness and National Immunization Program Web sites. We recommend you obtain these instructions, and familiarize yourself with the types of specimens and methods of collection.

Vaccine (slides; video)

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

(History)
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 material Jenner used for his vaccine probably contained cowpox virus, a virus related to variola
but not as virulent. At some time during the 19th 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 of them. The origin of vaccinia, and how it came to replace cowpox virus in the vaccine, is not known.

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

Approximately 15 million doses of smallpox vaccine are available now in the United States. More than 200 million additional doses of vaccine are being produced to be available in case of an introduction of smallpox. The new vaccine is being produced by cell culture methods similar to those used to produce other human vaccines.

Smallpox vaccine is unique in that it is not administered by injection. It's administered with a two—pronged, or bifurcated, needle like this one into the superficial layer of the skin.

(Efficacy)
Neutralizing antibodies induced by vaccinia vaccine are cross protective for other orthopox viruses, such as monkeypox, cowpox, and variola. That's why immunity produced by vaccinia virus protects against smallpox. The efficacy of smallpox vaccine has never been measured precisely in controlled trials. But, protection has been determined in studies of people exposed to a smallpox patient in their households. There was a 90% 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 five years after primary vaccination and substantial but waning immunity can persist for 10 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. 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 the vaccine within the first few days after initial exposure to smallpox virus can reduce symptoms or prevent disease. Studies in Pakistan and India showed that secondary cases in households were reduced up to 91% compared to unvaccinated people, if the vaccine was administered less than seven days after exposure.
Vaccinia virus replicates in the basal cells of the epidermis, producing a papule surrounded by erythema three to five days after primary vaccination. A vesicle then forms, which becomes pustular by seven 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 three to four 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.

In the absence of an intentional release of variola virus, there are very few indications for smallpox vaccination. Vaccination is routinely 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 health care 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 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; and people who may have contact with infectious materials. This includes 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 strategies again later in the program in the context of the smallpox response plan.

Vaccine Administration (video)

Dip the bifurcated point of the 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 vile.

Hold the skin on the arm taught and begin to prick the skin 15 times as shown here. This should be done rapidly in a perpendicular fashion within a 5 millimeter diameter area.

The intention is to break the skin and introduce the vaccine into the skin. Enough pressure should be used to produce a trace of blood at the vaccination site that appears 10 to 20 seconds after vaccination. This method allows the live vaccinia virus to penetrate the superficial layers of the skin so that viral multiplication can take place and immunity to smallpox will develop.
Once the vaccine is administered you should dispose of the needle and cover the site with a piece of gauze.

**Vaccine Adverse Events** (slides; video)

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

(Introduction, Introduce Mike Lane)
Smallpox vaccine contains live vaccinia virus, and is administered differently than any other vaccine. Adverse events following smallpox vaccine are also unique. The risk of adverse events after smallpox vaccination were enumerated in a series of studies conducted by CDC in the late 1960s.

We asked Dr. Mike Lane, the principle investigator for these landmark CDC studies, to talk to us about smallpox vaccine adverse events, and factors that increased the risk for these reactions.

*Mike Lane, MD, MPH*
*Former Director, Smallpox Eradication Program, CDC*

(Background)
Smallpox vaccine has been used for over 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. The risk of these complications was clarified in a series of studies CDC performed in 1968.

Smallpox vaccine complications, or adverse events, range from frequent and innocuous to rare and fatal. More severe complications are rare but occur more than 10 times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults.

(Fever)
Fever is common after administration of smallpox vaccine. Approximately 70% of children experience one or more days of temperature 100°F or higher for 4-14 days after primary vaccination. 15%-20% of children experience temperatures higher than 102°F. After revaccination, 35% of children experience temperature of 100°F or higher, and 5% experience temperatures of 102°F or higher. Fever is less common among adults after vaccination or revaccination.

(Inadvertent inoculation)
Successful vaccination produces a lesion like this at the vaccination site. The lesion contains vaccinia virus beginning about four days after vaccination. If the lesion is touched, virus can be transferred to another part of the body. Transfer, or autoinoculation, of vaccinia from the vaccination site is called inadvertent inoculation. This is the most frequent complication of smallpox vaccination. When this occurs at the time of vaccination, it may produce coprimary lesions. When it occurs at the time when the primary lesion is well developed, small or attenuated lesions may be produced. Inadvertent
inoculation accounts for approximately half of all complications of primary vaccination and revaccination. In our 1968 studies, inadvertent inoculation occurred once per 1,800 primary vaccinations.

Lesions of inadvertent inoculation could occur anywhere on the body, but the most common sites involved were the face, eyelid, nose, mouth, genitalia, and rectum. This is an example of inadvertent inoculation of vaccinia virus. This girl had severe periorbital swelling from vaccinial lesions on her right lower and upper eyelids. These lesions, as well as those on most other locations, heal without specific therapy. Vaccinia immune globulin, or VIG, was frequently used for ocular implantation. However, if vaccinial keratitis was present, VIG was contraindicated because it might increase corneal scarring.

(Rashes)
A variety of erythematous or urticarial rashes occurs approximately 10 days after primary vaccination. These rashes are referred to as erythema multiforme, roseola vaccinia, toxic erythema, and postvaccinial urticaria. They are flat, erythematous, macular, or urticarial lesions, usually with microscopic vasculitis. The pathophysiology of these rashes is not well understood. They don't become vesicular, and don't appear to involve viral multiplication. The rash resolves spontaneously within two to four days. Patients with erythematous urticarial rashes associated with vaccinia are generally not severely ill and are usually afebrile despite extensive skin involvement, except upon the rare occasions when Stevens-Johnson syndrome, or bullous erythema multiforme develops.

This 14-month-old infant had a primary vaccination on the small of his back. He had extensive erythematous patches over his entire body except for relative sparing of the soles of the feet.

Another type of rash following smallpox vaccination is labeled as generalized vaccinia. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without underlying illnesses. Rashes diagnosed as generalized vaccinia occurs at a rate of about once per 4,000 primary vaccinations. It consists of vesicles or pustules appearing on normal skin at a distance from the vaccination site. Most rashes labeled as generalized vaccinia produces only minor illness with little residual damage. The rash is generally self—limited and requires no specific therapy. VIG may be considered among patients whose conditions suggest viremia, true generalization of the virus, or who have serious underlying immunosuppressive illnesses, such as acquired immunodeficiency syndrome.

This photograph shows typical vaccinial lesions on the legs of a 14-year-old primary vaccinee approximately eight days after vaccination. The lesions are similar to small vaccinations, but the child did not have considerable systemic symptoms. This is typical generalized vaccinia in a 10-month old infant, with a scattering of vaccinia lesions predominantly around the vaccination site. The child recovered without specific therapy.

(Severe complications)
Three complications of smallpox vaccination are rare, but can be very severe or fatal. These are eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis. Eczema vaccinatum is the generalized spread of vaccinia on the skin of patients with eczema or a history of eczema. It occurs once per 25,000 primary vaccinations. The illness is generally mild and self—limited but could be
very severe. The most serious cases among vaccine recipients occur among primary vaccinees and are independent of the activity of the underlying eczema. Severe cases are also observed after contact of a recently vaccinated person with someone who has active eczema or a history of eczema. Eczema vaccinatum could involve either blood dissemination of vaccinia virus or by direct inoculation of vaccinia on affected skin. Vaccinia virus is readily recoverable from skin lesions.

This photograph shows severe eczema vaccinatum in a 13-month-old boy who acquired vaccinia from a recently vaccinated cousin. He died despite treatment with VIG, steroids, transfusions, and antibiotics. This is a 22-year-old woman with eczema vaccinatum acquired from her vaccinated boyfriend. She became critically ill, with nearly total involvement of her body, and required thiosemicarbazones, as well as large doses of VIG. She survived the illness but had extensive scarring of the skin.

Progressive vaccinia, also known as vaccinia necrosum, is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among persons with cellular immunodeficiency, but can occur in persons with humoral immunodeficiency. It occurs approximately once per 600,000 primary vaccinations, and was almost always fatal before the introduction of VIG and antiviral agents. Progressive vaccinia may be more common now, with HIV and post transplant immunosuppression widely prevalent.

This is a 22-month-old male child with Bruton's type hypogammaglobulinemia and vaccinia necrosum early in his illness. His lesion required more than three months hospitalization and extensive therapy including VIG, thiosemicarbazones, and topical idoxuridine. However, it eventually did heal. This is a 62-year-old woman with chronic lymphocytic leukemia who was vaccinated in a misguided attempt to alleviate facial herpes simplex four years after her leukemia was diagnosed. She died after a two month hospitalization, despite aggressive medical and surgical therapy.

A major unavoidable complication is postvaccinial encephalitis. It occurs once in about 80,000 primary vaccinations. In the majority of cases, postvaccinal encephalitis affects primary vaccinees less than one year of age or adolescents and adults receiving a primary vaccination. It presents with any of a variety of CNS signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions, similar to other postviral CNS syndromes rather than direct viral invasion of the nervous system. Approximately 15%-25% of affected vaccinees with this complication die, and 25% develop permanent neurological sequelae.

Death resulting from smallpox vaccination is rare, with approximately one death per million primary vaccinations and one death per four million revaccinations. Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

(Summary)
In summary, minor adverse events following smallpox vaccination, such as fever, erythematous rashes, and autoinoculation are frequent but generally self limited. Severe complications, such as progressive vaccinia and postvaccinal encephalitis are rare, but often fatal. Severe complications are more common in persons receiving primary vaccination compared to those being revaccinated. The risk of these rare, severe complications could be reduced by careful screening for eczema or immunodeficiency.
(Contraindications)

All vaccines have precautions and contraindications to their use. Contraindications for smallpox vaccine obviously are influenced by the live virus present, and by known risk factors for adverse reactions.

The vaccine is contraindicated for people who have experienced a serious allergic reaction to a prior dose of smallpox vaccine, or to a smallpox vaccine component. Because it's a live virus, it is contraindicated for people with significant immunosuppression, or who have an immunosuppressed household contact. Pregnant women should not be routinely vaccinated.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be routinely administered to people with eczema or a past history of eczema. It should not be given to people whose household contacts have eczema, or whose household contacts have a history of eczema because of the risk of inadvertent transmission. People less than 18 years of age should not be routinely vaccinated. Finally, vaccination should be deferred for people 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. Details of contraindications and precautions to smallpox vaccination are available in the smallpox vaccine ACIP statement.

(VIG)

Most complications of smallpox vaccination can usually be successfully treated with vaccinia immune globulin, or VIG, which is currently in very limited supply. VIG is a sterile solution of the immunoglobulin fraction of plasma from people vaccinated with vaccinia vaccine (smallpox vaccine). VIG has no role in the treatment of smallpox. CDC is currently the only source of VIG for civilians.

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**Isolation & Management** *(slides; video)*

*William L. Atkinson, MD, MPH*

*Medical Epidemiologist*

*National Immunization Program, CDC*

(Background)

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

(Clinical case definition)

Here is the clinical case definition of smallpox. It's 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 state of development without other apparent cause.

(Isolation)
Isolation of confirmed or suspected smallpox patients is critical to limit exposure to the virus. Although droplet spread is the major mode of transmission, airborne transmission through fine particle aerosol can rarely occur. So airborne precautions using a negative air pressure room, and high efficiency particulate air filtration, if possible, should be initiated immediately for hospitalized high—risk or confirmed smallpox patients. These are similar to the isolation precaution you would take for other infectious diseases with respiratory transmission, such as varicella.

(Protective equipment)
All personnel who have contact with a suspected or confirmed case of smallpox should utilize appropriate protective equipment. This includes using properly fitted 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. 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 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.

(Medical Management)
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. But the drug must be administered intravenously, and can cause serious renal toxicity. In addition, use of cidofovir for the treatment of smallpox would be an off label use. Antiviral therapy with cidofovir or other drugs subsequently 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. Medical management of a person with suspected smallpox is otherwise supportive.

Epidemiology (slides; video)

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

(Background)
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 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. Secondary cases generally occurred in people who live in the same household as the patient and had extended close contact. People in nearby houses are rarely infected unless they enter a patient's house or otherwise have close contact.

(Infectivity)
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 rash, which is often accompanied by lesions in the mouth and pharynx. The patient 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, while most skin lesions are in the vesicular or pustular stage. 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)
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 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. But people with severe prodromal illness may seek medical attention. Consequently, hospitals could be a source of infection because of transmission from unrecognized hospitalized cases. However, implementation of appropriate isolation measures for patients with rash and fever would limit this.

(Secondary 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, 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 vaccinated people. This limited the next potential generation of cases to people who had already been exposed, such as household and other close contacts. 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.

Global Smallpox Eradication (slides; video)

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

(Background, Introduce DA Henderson)
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 on earth occurred in Somalia in October 1977.

The eradication of smallpox from the earth is one of the greatest accomplishments in human history. The methods that were used, and the lessons learned from the eradication program are still 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

(History of WHO Smallpox Eradication Program)
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 II. 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 worldwide vaccination program to be completed in a three to five year period. Some progress was made during the next seven 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 one 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 an Asia area, 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 than had been though. This proved effective 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 persons, 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 was a hospital cook in Merka, Somalia, on October 26, 1977. Searches for additional cases continued in Africa for more than two years, during which time thousands of rash illnesses were investigated. None proved to be smallpox. Although two 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, two 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 Soviet Union, and unemployment of many scientists, there is
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.

Smallpox Response Plan (slides; video)

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

(Background)
A smallpox response plan was first put in place in the United States in 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 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 smallpox response plan will change as resources and capabilities change, and additional needs are identified. 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.

(Key elements of preparedness)
The key elements of preparedness for a smallpox response are surveillance and diagnosis to achieve the early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case or cases.

(Guides, annexes, updates)
A series of chapters, or guides, give detailed information on critical aspects of the plan. Guide A contains surveillance, contact tracing, and epidemiologic investigation guidelines. This includes pre-event rash surveillance, information on differential diagnosis; case definitions; and contact identification, tracing and surveillance. In addition, there are data collection forms to support these activities.

Guide B contains details on smallpox vaccine and vaccination. This includes strategies; indications and contraindications to vaccination; and reconstitution, administration, and storage of the vaccine. It also describes recognition and surveillance of vaccine adverse events, guidelines for the use of vaccinia immune globulin, and contingencies for resterilization and re-use of needles if needed.
The current plan does NOT call for vaccination of the general public prior to the identification of a smallpox case. This is because smallpox vaccine itself has risks for side effects (as you just saw). These risks are not acceptable in the absence of smallpox disease. But the plan does describe the basic control strategy. That is, isolation of patients with smallpox, identification and rapid vaccination of contacts, and monitoring contacts for development of illness. This strategy is called surveillance and containment, or ring vaccination, and was the fundamental approach of the global eradication program.

Guide C contains isolation guidelines for both confirmed and suspected cases. It also describes the isolation of the febrile contacts of cases, who may be developing smallpox. The issue of quarantine—that is, isolation of people before they become ill—is also discussed.

Guide D details methods specimen collection and transport. 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 decontamination guidelines for reusable medical equipment; medical waste; clothing, bedding, and linens; facilities and rooms; and vehicles used for transportation of 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, vaccine adverse event reporting. There is also a variety of forms and checklists to assist in preparing for and responding to a smallpox outbreak.

The Response Plan was released in November 2001. Over the next several months we are asking for comments from our medical and emergency response partners in state and local health departments, and professional organizations. The plan will be revised and continue to evolve as suggestions and feedback are received.

The response plan will always remain a living document that will periodically be updated as resources and capacities change. But it's an excellent starting point for response planning on all levels of public health. 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 may require adaptation.

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) 7 days  
b) 10 days  
c) 12 days  
d) 17 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

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

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

(Source: Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol)

a) chickenpox  
b) smallpox
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) can't differentiate at this stage

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

12. Refer to this photo of a Day 3 rash. This patient has
13. The patient in this photo has

a) smallpox
b) chickenpox
c) can't differentiate

14. 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
Geneva, 1988, p. 33)

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

15. 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)

16. Laboratory procedures for 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

17. 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

18. 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

e) All of the above

19. 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) disposable shoe covers
e) all of the above
20. Cidofovir has been approved by the FDA for treatment of

a) clinical smallpox
b) vaccinia vaccine adverse events
c) CMV retinitis
d) all of the above

21. Medical management of a patient with smallpox consists of all the following EXCEPT

a) isolation
b) skin care
c) high doses of corticosteroids
d) monitoring for and treatment of complications
e) monitoring and maintaining fluid and electrolyte balance

22. Examples of smallpox complications include all the following EXCEPT

a) corneal ulceration and/or keratitis
b) arthritis
c) hepatitis
d) encephalitis
e) gastroenteritis

23. 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

24. A smallpox patient can transmit the virus UNTIL

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

25. 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
26. Upon vaccination, a person is considered to be protected when a _______ develops at the vaccination site.

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

27. 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

28. The most FREQUENT complication of smallpox vaccination is

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

29. Lesions of inadvertent inoculation occur most commonly on all the following parts of the body EXCEPT

a) hands  
b) parts of the face  
c) genitalia  
d) rectum

30. 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
Patient Education Materials

- CDC Web Site for Smallpox Information (http://www.cdc.gov/nip/smallpox)
- Frequently Asked Questions About Smallpox (FAQsmallpox.pdf)
- Smallpox Fact Sheets (About.pdf)
- Smallpox Vaccination: What To Do After The Shot (AfterShot.pdf)
- Vaccine Information Statement (SmallpoxVIS.pdf)

References

Bioterrorism


Differential Diagnosis

- Illustration of Clinical Course of Ordinary-type Smallpox (clinicalchart.htm)
  - Note: This .pdf file is a reduced image of a wall poster. To get a copy of the poster, go to the online ordering system of the CDC website (http://www.cdc.gov/nip/publications) and click on "Online Order Form." Then, scroll down to the "Posters" section.

Morbidity and Mortality Weekly Reports (MMWRs)

- Epidemiologic Notes and Reports Investigation of a Smallpox Rumor - Mexico. 1985 (June 14); 34(23):343-344. EpiInvestMexico.pdf (Copy on Web: http://www.cdc.gov/mmwr/preview/mmwrhtml/00000557.htm)
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- International Notes-Smallpox Vaccination. 1982 (April 02); 31(12):159. IntlNotesSpoxVax.pdf (Copy on Web: http://www.cdc.gov/mmwr/preview/mmwrhtml/00000234.htm)
- Notice to Readers Smallpox Vaccine Available for Protection of At-Risk Laboratory Workers. 1983 (Oct. 21); 32(41):543-544. SpoxVaxLabWorkers.pdf (Copy on Web: http://www.cdc.gov/mmwr/preview/mmwrhtml/00000161.htm)
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- Vaccinia Necrosum after Smallpox Vaccination - Michigan. 1982 (Sept. 17); 31(36);501-502. VacciniaNecrosum.pdf (Copy on Web: http://www.cdc.gov/mmwr/preview/mmwrhtml/00001160.htm)

Safety Surveillance


Smallpox as a Weapon

**Smallpox Overview**

- CDC Web sites on smallpox, updated regularly:
  - 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.
  - CDC National Immunization Program
    Information for health care providers includes a poster presentation for evaluating patients for smallpox, training opportunities, and links to additional resources.
    [http://www.cdc.gov/nip/smallpox](http://www.cdc.gov/nip/smallpox)
  - Smallpox Information for Health Care Providers
    Contains information on evaluating patients for smallpox, training opportunities and additional resources.
    [http://www.cdc.gov/nip/smallpox/Providers.htm](http://www.cdc.gov/nip/smallpox/Providers.htm)
To ask smallpox-related questions via telephone, call:

**CDC Public Response Hotline:**

(888) 246-2675 (English)
(888) 246-2857 (Spanish)

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

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

- Smallpox Reference Photos
- Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2001 (June 22); 50(RR10):1-25. [rr5010.pdf](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm) (Copy on Web: [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5010a1.htm))
- WHO Web site on smallpox. [http://www.who.int/EMC/diseases/smallpox/](http://www.who.int/EMC/diseases/smallpox/)

**Smallpox Vaccine Adverse Reactions**


**Supplemental Video Segments**


**History of Smallpox-the Disease** ([Slides](http://www.sph.unc.edu/about/webcasts/2001-12-13_smallpox/); [Video](http://www.sph.unc.edu/about/webcasts/2001-12-13_smallpox/))

*Lisa D. Rotz, MD*
*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. 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.

Two forms of smallpox are recognized. Variola major was the only form known until the end of the nineteenth century. This 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 higher. 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.

Variola minor was first described in South Africa in 1904, and in the United States in 1913. Variola minor is a 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.

- Smallpox as a Biological Weapon ([Slides; Video])

Lisa D. Rotz, MD
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 distributed blankets to the Indians that had been used by smallpox patients. Smallpox outbreaks resulted, killing more than 50% 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 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.

Variola virus is classified as a Category A bioterrorism agent. Other category A 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. Most agents in category A 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 health care providers today have seen a case of smallpox. This is the reason for this program - to familiarize providers with the disease and its epidemiology, the vaccine to prevent it, and the action to take should a case be suspected.
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.

(Strategy)
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.

(Components)
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.

(Effectiveness in US)

**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.

(Would surveillance and containment be effective 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.
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 Orthopox virus. 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.

Four ortho poxviruses are known to infect humans - variola, vaccinia, cowpox, and monkeypox. Variola virus is strictly a human virus, although primates and other animals could be infected with variola virus 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. 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.

Variola virus can remain viable for several days in a controlled environment. In temperate climates, scabs 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 low 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 major virus have particularly severe illness. This suggests that there could be differences in the virulence of strains of the virus. But no laboratory test correlates with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

NOTE: The verification code for this self-study is NT013F.

At the time you complete the online evaluation for this activity you will be required to provide this verification code for continuing education credit. Be
sure to write down this code for later reference. For more information about receiving continuing education credit for this training, see "Continuing Education Credit Information."

About This Training

*Program Purpose*

The purpose of Smallpox: What Every Clinician Should Know is to present information to clinicians on clinical features, diagnosis and treatment of smallpox, and the characteristics and use of smallpox vaccine. The factual information presented about smallpox comes directly from the live satellite broadcast that was first aired on December 13, 2001 by the National Immunization Program (NIP) and the Public Health Training Network (PHTN) of the Centers for Disease Control and Prevention (CDC). This training has been developed as another medium for clinicians to learn about smallpox.

*Goal*

To improve health care providers' ability to recognize, diagnose, treat, and prevent smallpox.

*Objectives*

After completing this training, you should be able to:

- Describe the clinical characteristics and pathogenesis of smallpox;
- Differentiate between smallpox and other rash illnesses;
- Describe the characteristics, administration, indications, contraindications, and adverse events for smallpox vaccine.

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

Audience

The intended audience for this training is: physicians, nurses, health educators, immunization program managers, pharmacists, and other health care 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.

Continuing Education Credit Information

How to Register

To register for the course and receive continuing education credit:

- Go to www.phppo.cdc.gov/phtnonline
- Login as a participant (the first time you use this online learner support system you will need to login as a new participant and create a participant profile).
- Find the course by searching the catalog for course number: CB 3062.
- Select the type of credit you want 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 online evaluation/post-test.

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

For assistance using the online registration system, call 1 (800) 41-TRAIN, Monday through Friday, 8:00 AM to 4:30 PM Eastern Standard Time.

General Information

Smallpox: What Every Clinician Should Know is accredited for continuing medical education (CME), continuing nursing education (CNE), continuing education contact hours in health education (CHES), and continuing education units (CEU).

The content for this course was finalized April 3, 2002 and is valid for continuing education credit until March 31, 2005.

Credit

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

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

CHES: CDC is a designated provider of continuing education contact hours 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 continuing education contact hours in health education.

CEU: CDC 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:

NIPINFO@CDC.GOV

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) 7 days
   b) 10 days
   c) 12 days
   d) 17 days

   Correct Answer: c) 12 days

   Explanation: The average incubation period is 12 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

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

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

Correct Answer: c) pustule  

Explanation: Papules are seen on days 3 and 4; vesicles on day 5; pustules on days 7 and 9; and scabs on day 13.

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?

a) the patient has chickenpox
b) the patient has smallpox
c) can't 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. Refer to this photo of a Day 3 rash. This patient has
13. The patient in this photo has

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

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

14. The patient in this photo has
15. 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.

16. Laboratory procedures for 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: A suspected case of smallpox is a public health and medical emergency. The physician will work with the local and state health department to determine the risk of smallpox. Only cases that the state health department classifies as high risk will involve the CDC.
17. 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.

18. 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.

19. 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) disposable shoe covers  
e) all of the above

Correct Answer: e) all of the above

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

20. Cidofovir has been approved by the FDA for treatment of

a) clinical smallpox  
b) vaccinia vaccine adverse events  
c) CMV retinitis  
d) all of the above

Correct Answer: c) CMV retinitis
Explanation: Cidofovir has never been used as a treatment for smallpox. Use of cidofovir for the treatment of smallpox would be an off label use. Recent studies suggest that it might be useful as a therapeutic agent, but it must be administered intravenously, and it can cause serious renal toxicity.

21. Medical management of a patient with smallpox consists of all the following EXCEPT

a) isolation  
b) skin care  
c) high doses of corticosteroids  
d) monitoring for and treatment of complications  
e) monitoring and maintaining fluid and electrolyte balance

Correct Answer: c) high doses of corticosteroids

Explanation: Administering corticosteroids is NOT a recommended treatment for a smallpox patient. The CDC Smallpox Response Plan provides more information on medical management.

22. Examples of smallpox complications include all the following EXCEPT

a) corneal ulceration and/or keratitis  
b) arthritis  
c) hepatitis  
d) encephalitis  
e) gastroenteritis

Correct Answer: c) hepatitis

Explanation: Hepatitis in NOT a complication of smallpox. The CDC Smallpox Response Plan provides more information on smallpox complications.

23. 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.

24. 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.

25. 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.

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

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

Correct Answer: d) pustule

Explanation: The pustule appears by 7 to 11 days after vaccination.

27. 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.
28. 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.

29. Lesions of inadvertent inoculation occur most commonly on all the following parts of the body EXCEPT

a) hands  
b) parts of the face  
c) genitalia  
d) rectum

Correct Answer: a) hands

Explanation: Lesions of inadvertent inoculation could occur anywhere on the body, but the most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum.

30. 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.