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How to Take This Course

Please take a look at the steps below; these will help you to progress through the course material, complete the course examination and receive your certificate of completion.

1. **REVIEW THE OBJECTIVES**

   The objectives provide an overview of the entire course and identify what information will be focused on. Objectives are stated in terms of what you, the learner, will know or be able to do upon successful completion of the course. They let you know what you should expect to learn by taking a particular course and can help focus your study.

2. **STUDY EACH SECTION IN ORDER**

   Keep your learning "programmed" by reviewing the materials in order. This will help you understand the sections that follow.

3. **COMPLETE THE COURSE EXAM**

   After studying the course, click on the "Course Exam" option located on the course navigation toolbar. Answer each question by clicking on the button corresponding to the correct answer. All questions must be answered before the test can be graded; there is only one correct answer per question. You may refer back to the course material by minimizing the course exam window.

4. **GRADE THE TEST**

   Next, click on "Submit Test." You will know immediately whether you passed or failed. If you do not successfully complete the exam on the first attempt, you may take the exam again. If you do not pass the exam on your second attempt, you will need to purchase the course again.

5. **FILL OUT THE EVALUATION FORM**

   Upon passing the course exam you will be prompted to complete a course evaluation. You will have access to the certificate of completion **after you complete the evaluation**. At this point, you should print the certificate and keep it for your records.

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Objectives

Upon Completion of this course, the learner will be able to:

- Discuss smallpox as a weapon of biological terror.
- Identify symptoms of smallpox disease and how it manifests in the patient over a 3 week period.
- Distinguish symptoms of smallpox from other rash illnesses.
- State the process for intervention in the event of suspected smallpox.
- Describe the vaccinia vaccine.
- State the procedure for vaccination.
- Identify contraindications for vaccination with vaccinia.
- Discuss the adverse reactions that may occur, including identification of the adverse reaction and treatment.
- Describe the role of healthcare providers during the pre-event phase of possible smallpox outbreak.
- Identify local, statewide and national resources during the pre-event phase of a possible smallpox outbreak.

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Introduction

After the horror of the terrorist attacks on New York, Washington and rural Pennsylvania on September 11, 2001 and the anthrax attacks that followed, a heightened awareness of the possibility of further terrorism developed among the general population and healthcare providers in particular. Multiple governmental, educational and private agencies have responded with information for healthcare providers about the identification, prevention and treatment of a variety of biological, chemical and radiological terrorism threats.

One of the most destructive potential threats is that of smallpox, if it were to be used as a biological agent of terror. Smallpox is a serious, highly contagious, and sometimes fatal infectious viral disease. The name is derived from the Latin word for "spotted" and refers to the raised bumps that appear on the face and body of an infected person.

Smallpox outbreaks have occurred episodically for thousands of years, but the disease was considered eradicated after a successful worldwide vaccination program. The last naturally acquired case of smallpox in the United States was in 1949, and the last naturally occurring case in the world was in Somalia in 1977. The last case of smallpox, acquired from a laboratory exposure, occurred in the United Kingdom in 1978. In the United States, routine vaccination against smallpox ended in 1972 (CDC, 2001d). Smallpox was declared globally eradicated on May 8, 1980 by the World Health Assembly, the supreme decision making body of the World Health Organization. After the disease was eliminated from the world, routine vaccination against smallpox among the general public was stopped because it was no longer necessary for prevention. However, it remains a biological threat because of its potential ease of large-scale production and subsequent use in a deliberate biological attack (CDC, October, 2002).

The use of the smallpox virus as a biological weapon may be less likely than other biological agents because of its restricted availability. However, over the last several years, multiple claims have arisen about terrorist groups or foreign governments having the smallpox virus.

Even one suspected case of smallpox is an international public health emergency. It will require rapid identification, a definitive diagnosis with rapid laboratory confirmation at the Centers for Disease Control and Prevention (CDC), and vaccination to contain and prevent further smallpox transmission. In the US, in 2003, volunteer healthcare providers were vaccinated in order to have a team of healthcare providers who could rapidly begin the vaccination process among the general public, if a smallpox outbreak occurred. These immunized healthcare workers had to have been vaccinated themselves prior to being able to give the vaccination.

Currently, specific therapies with proven treatment effectiveness for smallpox are unavailable. Medical care of more seriously ill smallpox patients would be resource intensive and would include primarily supportive measures and antiviral treatment. If the patient's condition allows, medical and public health authorities should consider isolation and observation outside a hospital setting to prevent healthcare associated smallpox transmission and overburden of healthcare resources.

Government and public health officials have been working on an organized, coordinated response to the threat of smallpox as a biological weapon. In December 2002, The *CDC Smallpox Response Plan and Guidelines* was released. This document outlines the public health strategies that would guide the public health response to a smallpox emergency and many of the federal, state, and local public health activities that must be undertaken in a smallpox outbreak. It can be accessed at http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp#annex.

This course will address the pre-event information needed by healthcare providers. It will include an overview of smallpox, including identification of smallpox, distinguishing it from other rash illnesses, vaccination, adverse reactions and their management. Additionally, the process of vaccination will be covered. This course is divided into three sections: Part I provides an overview

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of smallpox including information about its use as a weapon of terror; Part II addresses smallpox immunization benefits, risks, and the vaccination procedures; and Part III includes the role of healthcare providers in preparing for the potential use of smallpox as a weapon of mass destruction. It is expected that healthcare providers will follow-up this course with a locally available experiential educational activity that will allow them the opportunity to have hands-on practice with the vaccination process.

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About the Authors

This course was developed by the New York State Nurses Association, in collaboration with the University at Albany, School of Public Health, Center for Preparedness; Columbia University Center for Public Health Preparedness; the Medical Society of New York State and the New York State Department of Health. The course is based on content provided by the Centers for Disease Control and Prevention, whose material is in the public domain and is not subject to copyright laws. CDC information is not referenced throughout the course. Additional current information was added to the course and is referenced throughout the course. All of the CDC references as well as the other references utilized can be found in the "References" section at the end of this course.

This course was reviewed by Tener Goodwin Veenema, PhD, RN, MPH, MS a nationally recognized expert on bioterrorism.

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As stated above, this course was developed utilizing the most up-to-date information available, mainly from the Centers for Disease Control and Prevention (CDC). However, the subject of smallpox disease, smallpox vaccination and bioterrorism in general is rapidly evolving. For emerging information, consult the CDC website (www.cdc.gov), the New York State Department of Health website (www.health.state.ny.us), or your state health department website for the most current changes.

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Part I. Overview of Smallpox Disease

Early History of Smallpox

Smallpox is one of the most feared biological weapons: it is contagious and disfiguring; there is no known treatment and it has a case fatality rate of approximately 30% in the unvaccinated population. Smallpox has been naturally occurring since recorded history. The book *Scourge* (Tucker, 2001) reveals the early history of smallpox.

It was mentioned in writings from ancient Egypt dating back to approximately 3700 BC. The mummified body of Ramses V, a pharaoh who died in 1157 BC, whose well-preserved remains are on display at the Cairo Museum, reveals a striking rash of yellow pustules on the face and hands - early physical evidence of the presence of smallpox. Traders carried smallpox from Egypt to India, where Sanskrit medical texts describe epidemics as early as 1500 BC. The disease arrived in China by 1122 BC, apparently imported by the Huns, since the Chinese called it "Hunpox." According to the Greek historian Thucydides, an epidemic suggestive of smallpox struck Athens around 430 BC, killing one third of the city-state's population and contributing to its defeat in the Peloponnesian War. In the 4th century BC, Alexander the Great's army suffered an outbreak of the disease in India. The Roman Emperor Marcus Aurielius died of smallpox in AD 165, accelerating the decline of the Roman Empire.

The use of smallpox as a biological weapon reportedly occurred during the French and Indian Wars 1754-1767. British troops allegedly distributed smallpox tainted blankets to Native Americans, with the intent of initiating an outbreak among them. In some of the epidemics that resulted, more than 50 percent of the infected tribes succumbed to the disease. The threat of smallpox as a bioweapon was greatly diminished with Edward Jenner's demonstration in 1796 that an infection resulting from inoculation with cowpox also provided protection against smallpox (Henderson et al., 1999).

Concerns Regarding the Use of Smallpox as a Biological Weapon

Healthcare providers should be alert to illness patterns and diagnostic clues that might indicate an unusual infectious disease outbreak associated with intentional release of any biologic agent and should report any clusters or findings to their local or state health department. The covert release of a biologic agent may not have an immediate impact because of the delay between exposure and illness onset, and outbreaks associated with intentional releases might closely resemble naturally occurring outbreaks.

Indications of intentional release of any biologic agent include

1) an unusual temporal or geographic clustering of illness (e.g., persons who attended the same public event or gathering) or patients presenting with clinical signs and symptoms that suggest an infectious disease outbreak;

2) an unusual age distribution for common diseases (e.g., an increase in what appears to be a chickenpox-like illness among adult patients, but which might be smallpox).

Smallpox used as a weapon today, would have substantial public health consequences in terms of morbidity and mortality.

Smallpox is classified as a Category A agent by the Centers for Disease Control and Prevention (CDC). Category A agents are believed to pose the greatest potential threat for adverse public health impact and have a moderate to high potential for large-scale dissemination. Other Category A agents are anthrax, plague, botulism, tularemia, and viral hemorrhagic fevers.

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In the event of an aerosol release of smallpox, all viruses will be inactivated or dissipated within one to two days. Buildings exposed to an initial aerosol release of the virus would not need to be decontaminated because by the time the first cases are identified, typically about one to two weeks after the release, the virus in the building will be gone. Infected patients, however, will be capable of spreading the virus and possibly contaminating surfaces while they are sick.

Much has been learned from previous outbreaks of naturally occurring smallpox. In 1972, in Yugoslavia, a smallpox outbreak occurred after a man who had been on Hajj, an Islamic pilgrimage to Mecca and Medina, became infected with smallpox virus while in Iraq. His infection was initially misdiagnosed as a penicillin-associated drug eruption and went undiagnosed. He brought the disease back to Yugoslavia and unknowingly infected 11 others, whose infections also went undiagnosed. It was not until the second generation of cases that the smallpox outbreak was recognized and control measures initiated. By that time there were 140 new cases of smallpox, with a transmission ratio of 1:13. Ultimately, a single index case caused 175 cases of smallpox and 34 deaths before the outbreak was brought to an end. This smallpox outbreak has been particularly instructive because it encompassed many of the concerns that would likely be expected if a smallpox outbreak occurred today:

- *A large number of susceptible people* - Since smallpox vaccination in the US was discontinued in 1972, the level of immunity, if any, among persons who were vaccinated before 1972 is uncertain; therefore, these persons are assumed to be susceptible. Some experts suspect that some level of immunity may be present although minimal, however the degree is not known. Although some healthcare workers have recently been immunized, there remains relatively few among the US population of almost 300 million people who have significant immunity to smallpox.

- *Delayed diagnosis* - Because smallpox is a threat that few healthcare providers have seen due to its eradication decades ago, it may go undiagnosed or be misdiagnosed as another eruptive illness. However, since September 11, 2001, the index of suspicion regarding possible bioterrorism related illness has increased. Additionally, diagnosis will likely be delayed because of the time it takes for the index case to develop the symptoms and seek medical care. During that time many others can be infected with the smallpox virus and include:

    - Both hospital and community transmission.
    - Wide geographic dispersion of cases - The high level of mobility of the US population will contribute to the dispersion of cases, particularly if a smallpox outbreak were calculated to start in an airport or other mass transportation area.
    - Difficulty in contact tracing - Because of the high level of mobility in the population, tracing contacts will be difficult. Other issues include fear, confidentiality and trust.

<u>Pathogenesis</u>

The viral biologic agents, variola major and variola minor, cause smallpox. Variola minor, or alastrim, is a milder form of smallpox (Henderson et al., 1999). Variola minor is a less common presentation of smallpox, and a much less severe disease, with death rates historically of 1 percent or less. Variola major is the severe and most common form of smallpox, with a more extensive rash and higher fever. This course will focus on variola major.

After smallpox virus infection, the virus remains localized and replicates for up to three days. The initial steps in viral dissemination in the body involve a primary viremia in which the virus moves to the draining lymph nodes, spleen and sometimes bone marrow. In smallpox the virus replicates further in lymphoid organs then migrates via the lymphatics to the bloodstream producing a secondary viremia followed by fever and toxemia. The secondary viremia carries the virus to the basal layer of the oropharyngeal region and epidermis by the 10th to 14th day after the initial

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infection. Just after the fever peaks, the development of oropharyngeal lesions begins (the enanthem), and is soon followed by the development of skin lesions (the exanthem). Lesions occur first on the mucous membranes of the mouth, tongue, pharynx, larynx, and upper part of the esophagus. Transmission by large-particle, airborne droplets is maximal at the time of the appearance of skin lesions. The disease can be spread by these large-particle, airborne droplets until the skin scabs fall off, however, droplet transmissibility decreases significantly after the second week of disease as the oral lesions of the enanthem heal and viral titers in the saliva decrease.

The characteristic pathologic feature of smallpox is the skin rash. Initially, the capillaries in the dermal papillae dilate, followed by swelling of the endothelium and infiltration of lymphocytes and histiocytes (macrophages present in connective tissue). Polymorphonuclear leukocytes enter skin vesicles from the dermis to produce the pustular lesions. The pustular fluid eventually dries up as the disease disappears and the lesions become filled with granular tissue, which forms scabs consisting of degenerated epithelial cells and leukocytes. Virus particles can be present in large numbers in the scabs but are generally not highly infectious because they are enclosed within the hard, dry scab. Lesion scars or pockmarks are sequelae caused mainly by destruction of infected sebaceous glands and are most prominent on the face.

Types of Smallpox Disease

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 **classic** or **ordinary smallpox**; 90% of all smallpox cases are of the classic type. This clinical manifestation will be described in the next section of this course.

Modified smallpox most often occurs in previously vaccinated individuals. Modified refers to the character of the eruption and the rapidity of its development, progression and resolution of lesions. In general, the prodrome stage may still consist of severe headache, backache, and fever, and the duration may not be shortened. However, once the skin lesions appear, they generally evolve more quickly with crusting completed within 10 days. The lesions may be fewer in number and are more superficial than those seen in ordinary-type smallpox. Fever during the evolution of the rash is also usually absent during this modified clinical course. Modified smallpox is rarely, if ever, fatal.

Flat-type smallpox is also referred to as malignant smallpox; it is a more severe form of smallpox and has a high mortality rate (97 percent in unvaccinated cases). Flat-type smallpox is so called because the lesions remained more or less flush with the skin at the time when raised vesicles formed in ordinary smallpox. It's not known with certainty why some people develop this type of disease, but many cases occur 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. 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. The prognosis for this form of 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 also a severe and uncommon form of smallpox that is almost always fatal. In patients with a highly compromised immune response**,** there is extensive multiplication of the virus in the spleen and bone marrow to produce this rare form of smallpox. It involves extensive bleeding into the skin, mucous membranes and gastrointestinal tract. Megakaryocyte destruction in the bone marrow is believed to lead to defective blood coagulation. The rare

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hemorrhagic-type smallpox is associated with petechiae in the skin and bleeding from the conjunctiva and mucous membranes.

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. Hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding and bleeding from the mouth and gums, or other mucous membranes, petechiae in the skin, epistaxis, and hematuria. Death often occurs suddenly between the fifth or sixth day of the rash, when only a few insignificant maculopapular cutaneous lesions are present. In patients who survive for eight to ten 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. Hemorrhagic-type smallpox occurs among all ages and in both sexes but is more common in adults. Pregnant women also seem to be more susceptible to developing this form of smallpox than other adults. The underlying molecular biologic reasons for the toxemia and other effects are unclear.

Clinical Manifestations of Classic Smallpox

Exposure to the smallpox virus is followed by an incubation period during which people do not have any symptoms and may feel fine. This **incubation period** averages about 12 to 14 days, but can range from 7 to 17 days. Symptoms generally begin within a 2 to 4 day **prodrome period** in which the patient experiences high fever (range of 101 to 104 degrees Fahrenheit), malaise, and prostration with severe headache and backache. Severe abdominal pain and delirium are sometimes present. Persons may be contagious in this phase. A **maculopapular rash** then appears, first on the mucosa of the mouth and pharynx, face and forearms, spreading to the trunk and legs. Within one or two days, the **rash becomes vesicular and later pustular**. The pustules are characteristically round, tense and deeply embedded in the dermis; they feel like a firm round object embedded in the skin (ACIP, 2001). By the fourth day, the pustules often have a depression in the center that looks like a bellybutton; this is a major distinguishing characteristic of smallpox.

Crusts begin to form about the eighth or ninth day. When the scabs separate, pigment-free skin remains, and eventually pitted scars form (Johns Hopkins University, 2000). The scars result from the destruction of sebaceous glands that is followed by shrinking of granulation tissue and fibrosis. Scars are most evident on the face (Henderson et al., 1999).The lesions on the mouth and pharynx ulcerate quickly, releasing large amounts of virus into the saliva. Patients are most infectious during the first week, which corresponds with the high virus titers in the saliva (Henderson et al., 1999). Patients are no longer infectious after all scabs have separated, approximately 3 to 4 weeks after the onset of the rash (ACIP, 2001).

Smallpox Disease	
Incubation Period	**Exposure to the virus** is followed by an incubation period during which people do not have any symptoms and may feel fine. This incubation period averages about 12 to 14 days, but can range from 7 to 17 days. During this time, people are not contagious.
Initial Symptoms (Prodrome)	The **first symptoms** of smallpox include fever, malaise, head and body aches and sometimes vomiting. The fever is usually high, in the range of 101 to 104 degrees Fahrenheit. At this time, people are usually too sick to carry out their normal activities. This is called the prodrome

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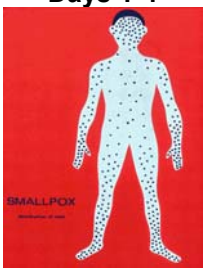
	phase and may last for 2 to 4 days.
Early Rash **Days 1-4**  **Rash Distribution**	A **rash emerges** first as small red spots on the tongue and in the mouth. These spots develop into sores that break open and spread large amounts of the virus into the mouth and throat. At this time, the person is the **most contagious**. Within 24 hours, a rash appears on the skin, starting on the face and then spreading to the arms and legs and then to the hands and feet. Usually the rash spreads to all parts of the body within 24 hours. As the rash appears, the fever usually falls and the person may start to feel better. By day three, the rash becomes raised bumps. By day four, the bumps fill with a thick, opaque fluid and often have a depression in the center that looks like a belly-button. **This is a major distinguishing characteristic of smallpox.** Fever often will rise again at this time and remain high until scabs form over the bumps.
Pustular Rash Days 5-10	Over the next 5 to 10 days, the bumps become "**pustules**" -- sharply raised, usually round and firm to the touch. They feel like there's a small round object under the skin. People often say it feels like there is a BB pellet embedded under the skin.
Pustules and Scabs Days 11-14	The pustules begin to form a crust and then **scab**. By day fourteen, most of the sores have scabbed over.
Resolving Scabs Days 15 - 21	The scabs begin to fall off, leaving marks on the skin that eventually become pitted **scars**. The person is contagious to others until all of the scabs have fallen off. Most scabs will fall off after three weeks.
Scabs Resolved After Day 21	Scabs have fallen off. Person is no longer contagious.

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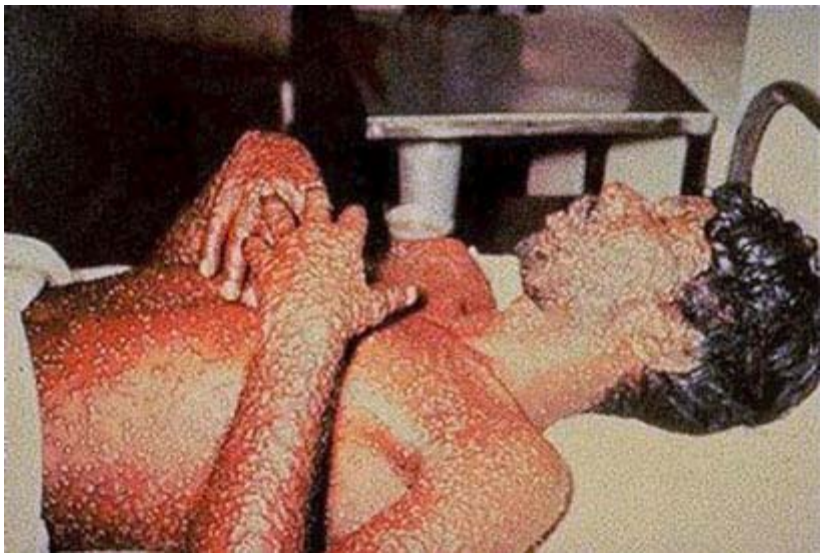
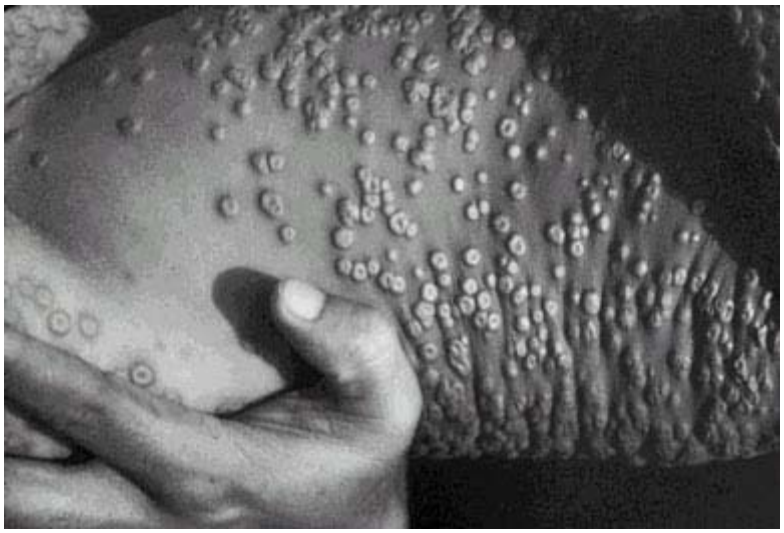


Man with smallpox. Public Health Images Library (PHIL) id# 131. Source: CDC/Barbra



Rice Smallpox lesions on skin of trunk. Picture taken in Bangladesh, 1973. Public Health Images Library (PHIL) ID # 284. Source: CDC/James Hicks.

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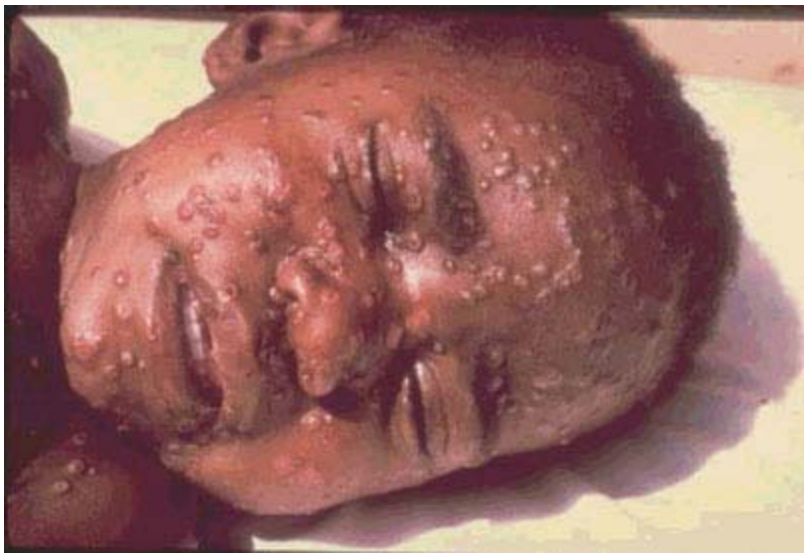

Face lesions on boy with smallpox. Public Health Images Library (PHIL) ID # 3. Source: CDC/Cheryl Tyron

Diagnosis of Smallpox Disease

The CDC has developed tools to help clinicians make the diagnosis of smallpox. The first tool, *Risk Evaluation Algorithm: Evaluate a Rash Illness Suspicious for Smallpox* (CDC, 2004), can be accessed online at http://www.bt.cdc.gov/agent/smallpox/diagnosis/index.asp#diagnosis. This online version is interactive; it allows clinicians to select answers and have the risk is evaluated, all online.

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Evaluate a Rash Illness Suspicious for Smallpox

Caution: Use this tool only when there is no release or circulation of smallpox.

Type of Rash Illness

1. Does the patient have an acute, generalized rash on the body, with vesicles or pustules?

   Yes No

   If yes, institute contact and airborne precautions.
   If no, and there is no known release or circulation of smallpox, there is no basis for calculating risk for smallpox.

Major Smallpox Criteria

2. Does the patient have classic smallpox lesions (i.e., deep-seated, firm/hard, round, well-circumscribed vesicles or pustules?

   Yes No

3. Are the vesicles or pustules all in the same stage of development? For example, on any part of the body (e.g., face, arm) are lesions all vesicles or pustules?

   Yes No

4. Did the patient develop a fever of 101 degrees Fahrenheit or greater 1-4 days before rash onset?

   Yes No High fever, not measured Unknown

5. Did the patient have any of the following symptoms 1-4 days before rash onset?

   ___ Prostration
   ___ Chills
   ___ Headache
   ___ Vomiting
   ___ Backache
   ___ Severe abdominal pain
   ___ No additional symptoms

Minor Smallpox Criteria

6. Does the patient have symptoms meeting minor criteria? Check all that apply.

   ___ Lesions are distributed centrifugally, with greatest concentration of lesions on face and distal extremities.
   ___ First lesions occurred in the oral mucosa or palate, face, or forearms.
   ___ The patient appears toxic or moribund.
   ___ Lesions evolve slowly, from macules to papules, to vesicles to pustules, with each stage lasting 1-2 days.
   ___ Lesions appear on the palms of the hands and soles of the feet.
   ___ No minor smallpox criteria.

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Another tool that the CDC developed to assist with the diagnosis of smallpox is a worksheet, Evaluating Patients for Smallpox, that can also be accessed online at http://www.bt.cdc.gov/agent/smallpox/diagnosis/index.asp#diagnosis. It appears in Appendix A The CDC also developed the Poster: Evaluating Patients for Smallpox, to be used in conjuction with the worksheet (Appendix A). The poster appears in Appendix B.

Case Definitions/Classifications

Surveillance for a disease that does not currently exist anywhere in the world presents unique challenges. The goal of pre-outbreak (pre-event) smallpox surveillance is to recognize the first case of smallpox, should it ever occur, without generating excessive numbers of false alarms, unnecessarily disrupting the health care and public health systems, or increasing public anxiety. In the absence of known smallpox disease, the predictive value of a positive smallpox diagnostic test is extremely low; therefore, testing to rule out smallpox should be limited to cases that fit the clinical case definition in order to lower the risk of obtaining a false-positive test result. It is neither feasible nor desirable, in the pre-event scenario, to perform laboratory testing for suspected cases that do not meet the clinical case definition.

Thus, in the absence of smallpox disease in the world, the suggested approach to surveillance relies on a highly specific clinical case definition, which is focused on identifying the classic case presentation (ordinary type) of smallpox. (Before eradication, classic (ordinary type) smallpox generally accounted for approximately 90 percent of smallpox cases in previously unvaccinated individuals and 70 percent of cases that occurred in previously vaccinated individuals who were no longer fully protected by vaccination.)

Smallpox clinical case definition - An illness with acute onset of fever ≥101°F (38.3°C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause.

Laboratory criteria for confirmation - Laboratory diagnostic testing for variola virus should be conducted in a CDC Laboratory Response Network (LRN) laboratory utilizing LRN-approved PCR tests and protocols for variola virus. Initial confirmation of a smallpox outbreak requires additional testing at CDC. Generic orthopox PCR and negative stain electron microscopy (EM) identification of a pox virus in a clinical specimen are suggestive of an ***orthopox*** virus infection but not diagnostic for smallpox.

- Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, **OR**
- Isolation of smallpox (variola) virus from a clinical specimen (WHO Smallpox Reference laboratory or laboratory with appropriate reference capabilities) **with** variola PCR confirmation.

The importance of case confirmation using laboratory diagnostic tests differs depending on the epidemiological situation. Because of the low predictive value of a positive lab test result in the absence of a known smallpox outbreak, in the pre-outbreak (pre-event) setting, laboratory testing should be reserved for cases that meet the clinical case definition and are thus classified as being a potential high risk for smallpox according to the rash algorithm poster (see Appendix B).

Since smallpox no longer exists as a naturally occurring disease, a single laboratory confirmed case of smallpox would be considered an outbreak. Once an outbreak of smallpox has been confirmed, the following case classifications should be used:

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- **Confirmed case -** A case of smallpox that is laboratory confirmed, or a case that meets the clinical case definition that is epidemiologically linked to a laboratory confirmed case.
- **Probable case -** A case that meets the clinical case definition, or a case that does not meet the clinical case definition but is clinically consistent with smallpox and has an epidemiological link to a confirmed case of smallpox. Examples of clinical presentations of smallpox that would not meet the ordinary type (pre-event) clinical case definition are: a) hemorrhagic type, b) flat type, and c) variola sine eruptione.
- **Suspect case -** A case with a febrile rash illness with fever preceding development of rash by one to four days.

Differential Diagnosis

There are a myriad rash illnesses; clinicians who evaluate patients with rash illnesses need to be able to determine quickly if their patient may have smallpox. An important differentiating feature between smallpox and any other rash illnesses is the presence of a prodrome: fever and other symptoms before rash onset. Patients with smallpox have a characteristic, very severe, febrile prodrome that starts one to four days before the onset of the rash. The fever is usually high, in the range of 101°F (38°C). People with varicella, or chickenpox, 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 (CDC, 2001).The most common rash illness that is likely to be confused with smallpox is varicella. However, 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. Even with this decrease, it is expected that there will be about a million and a half cases of varicella in the United States this year. There are several clinical features that distinguish smallpox from chickenpox:

- The most obvious distinction between the two infections is the period of time over which the lesions appear. In chickenpox, the lesions occur in successive "crops". Physical examination will reveal several different stages of lesion maturation and development at the same time. Smallpox lesions however, appear more or less simultaneously.
- Another diagnostic clue resides in the density and location of the lesions. Chickenpox lesions are denser over the trunk (central distribution) and smallpox lesions are denser on the face and extremities (centrifugal distribution).
- Finally, the physiology of the lesions is diagnostic as well, with chicken pox lesions being more superficial.

<u>Exposure and Transmission</u>

Healthcare providers must be prepared to recognize a vesicular exanthem as potentially variola, and to initiate appropriate countermeasures. The only known reservoir for the variola virus is humans; no known animal or insect reservoirs or vectors exist.

The most frequent mode of transmission is person-to-person, spread through direct deposit of infective droplet nuclei onto the nasal, oral, or pharyngeal mucosal membranes, or the alveoli of the lungs from close, face-to-face contact with an infectious person. Only rarely has airborne transmission been documented (ACIP, 2002a). Transmission does not occur during the prodromal period, before the rash appears. Epidemiologic studies have shown that smallpox has a lower rate of transmission than diseases such as measles, pertussis, and influenza (ACIP, 2002a). The greatest risk of infection occurs among household members and close contacts of persons with smallpox, especially those with prolonged face-to-face exposure. Vaccination and isolation of contacts of cases at greatest risk of infection has been shown to interrupt transmission of smallpox. However, poor infection control practices resulted in high rates of transmission in hospitals (ACIP, 2002a).

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Indirect spread (i.e., not requiring face-to-face contact with an infectious person) through fine-particle aerosols or a fomite containing the virus is less common (ACIP, 2001). Persons with smallpox are most infectious during the first week of illness, because that is when the largest amount of virus is present in saliva. However, some risk of transmission lasts until all scabs have fallen off. **Droplet and airborne precautions** are needed for a minimum of 17 days following exposure for all persons in direct contact with the index case, especially the unvaccinated. In the non-military setting strict quarantine of asymptomatic contacts may prove to be impractical and impossible to enforce. The United States Army Medical Research Institute of Infectious Diseases (USAMRIID, 2001) suggests that a reasonable alternative would be to require contacts to check their temperatures daily. Any fever above 38 C (101 F) during the 17-day period following exposure to a confirmed case would suggest the development of smallpox. The contact should then be isolated immediately, preferably at home, until smallpox is either confirmed or ruled out. Patients should be considered infectious until all scabs separate. Immediate vaccination or revaccination should also be undertaken for all persons exposed to either weaponized variola virus or a clinical case of smallpox.

The potential for airborne spread to other than close contacts has occurred. In general, close person-to-person contact is required for transmission to reliably occur. However, variola's potential in low relative humidity for airborne dissemination was alarming in two hospital outbreaks. Smallpox patients were infectious from the time of onset of their eruptive exanthem, most commonly from days three to six after onset of fever. Infectivity was markedly enhanced in these patients who manifested a cough which allowed for the aerosol release and transmission of smallpox. Indirect transmission via contaminated bedding or other fomites was infrequent. Some close contacts harbored virus in their throats without developing disease, and hence might have served as a means of secondary transmission (USAMRIID, 2001).Vaccination with a verified clinical "take" (vesicle with scar formation) within the past three years is considered to render a person immune to smallpox (USAMRIID, 2001).

Control of Smallpox

The primary strategy to control an outbreak of smallpox and interrupt disease transmission is surveillance and containment, which previously included ring vaccination and isolation of persons at risk of contracting smallpox (ACIP, 2002a). This strategy involves identification of infected persons through intensive surveillance, and contact tracing, isolation of infected persons, vaccination of household and other close contacts of the infected person (i.e., primary contacts), and vaccination of close contacts of the primary contacts (i.e. secondary contacts). This strategy was instrumental in the ultimate eradication of smallpox as a naturally occurring disease even in areas that had low vaccination coverage to start. Depending upon the size of the smallpox outbreak and the resources that were available for rapid and thorough contact tracing, surveillance and containment activities in areas with identified smallpox cases was sometimes supplemented with voluntary vaccination of other individuals. This was done in order to expand the ring of immune individuals within an outbreak area and to further reduce the chance of secondary transmission from smallpox patients before they could be identified and isolated. Regardless of the geographic distribution, number of cases, or number of concurrent outbreaks, surveillance and containment activities remained the primary disease control strategy. Any fever above 101° F (38°C) during the 17-day period following exposure to a confirmed case would suggest the development of smallpox**. Standard precautions** as well as **droplet and airborne precautions** for at least 17 days is required following exposure for all persons in direct contact with a confirmed case. Patients should be isolated and considered contagious until all lesion scabs separate.

Because of the problems encountered with imported cases, health officials should be diligent regarding use of adequate isolation facilities and precautions. Isolation of confirmed or suspected smallpox patients will be necessary to limit the potential exposure of nonvaccinated and, therefore, nonimmune persons. A problematic situation regarding poor infection control practices

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occurred in Germany in 1970. A German who was returning from visiting Pakistan was diagnosed with smallpox and admitted to the hospital. Nineteen subsequent cases of smallpox were diagnosed in that hospital as a result.

Since the numbers of immunized persons, at this time is very low, most of the population is at risk, and all children and infants are at risk. Although droplet spread is the major mode of person-to-person smallpox transmission, airborne transmission through fine-particle aerosol can occur. Therefore, airborne precautions using correct ventilation (e.g., negative air-pressure rooms with high-efficiency particulate air filtration) should be initiated for hospitalized confirmed or suspected smallpox patients, unless the entire facility has been restricted to smallpox patients and recently vaccinated persons.

Healthcare providers should observe standard and contact precautions (i.e., using protective clothing and shoe covers) when in contact with smallpox patients or contaminated materials to prevent inadvertent spread of variola virus to susceptible persons and potential self-contact with other infectious agents. Personnel should remove and correctly dispose of all protective clothing before contact with nonvaccinated persons. Standard hospital grade disinfectants, such as quaternary ammonias, are effective in killing the virus on surfaces and should be used for disinfecting hospitalized patients' rooms or other contaminated surfaces. Although it is less desirable because it can damage equipment and furniture, hypochlorite (bleach) is an acceptable alternative (CDC, 2001d). Contaminated clothing or bed linen could also spread the virus. In the hospital setting, patients' linens should be autoclaved or washed in hot water with bleach added. Laundry handlers should be vaccinated before handling contaminated materials. Infectious waste should be placed in biohazard bags and autoclaved before incineration. Special precautions need to be taken in the community, to ensure that all bedding and clothing of patients are cleaned appropriately with bleach and hot water. Disinfectants such as bleach and quaternary ammonia can be used for cleaning contaminated surfaces (CDC, 2001d).

Treatment

There are no proven treatments for clinical smallpox; medical care is generally supportive. Vaccination can prevent or lessen the severity of disease if given within 2-3 days of the initial exposure and decreases symptoms if given within the first week of exposure. Dehydration and electrolyte abnormalities can occur during the vesicular and pustular rash stages; supportive therapy is beneficial (e.g., intravenous fluids, good nutrition, medication to control fever or pain). Occasionally, bacterial superinfections may also occur and should be treated with appropriate antibiotic therapy.

Multiple studies of antivirals during the smallpox eradication failed to show significant benefit in the treatment of smallpox. Evaluation of modern day antivirals at CDC is ongoing. One current antiviral, Cidofovir, has shown some in-vitro and in-vivo (animal studies) activity against orthopoxviruses. However, its effectiveness for treating clinical smallpox or vaccine adverse events is not known. This medication is labeled for the treatment of CMV retinitis and has been associated with renal failure. Were an outbreak of smallpox to occur, this medication would be made available through the CDC or National Institutes of Health (NIH) under an Investigational New Drug (IND) protocol for the potential treatment of smallpox or vaccine adverse events.

Reporting Suspected Smallpox

Reporting of suspected or confirmed communicable diseases, including smallpox, is mandated under the New York State Sanitary Code (10NYCRR 2.10a). The primary responsibility for reporting rests with the physician; moreover, laboratories (PHL 2102), school nurses (10NYCRR 2.12), day care center directors, nursing homes/hospitals (10NYCRR 405.3d) and state institutions (10NYCRR 2.10) or other locations providing health services (10NYCRR 2.12) are also required to report communicable diseases. Identification of smallpox requires prompt action and should be reported immediately to local health units by phone followed by submission of the

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confidential case report form (DOH-389). Contact numbers for local agencies can be found later in this course. To access the report form (DOH-389) visit the New York State Department of Health's website at www.health.state.ny.us/nysdoh/cdc/main.htm. For states other than New York consult www.cdc.gov/other.htm#states.

Any confirmed case of smallpox should be considered an international emergency; even suspected smallpox should be reported immediately by telephone to state or local health officials and advice obtained regarding isolation and laboratory specimen collection.

Medical personnel should notify their state and local public health authorities about suspected cases of smallpox.

State or local health officials should notify the CDC immediately at: **800-232-4636, CDC's Emergency Response Hotline (24 hours)**, or at (404) 639-2184 or (404) 639-0385 if:

- A suspected case of smallpox with request for clinical specimen testing is identified;
- An outbreak of illness that is clinically compatible with smallpox;
- There is a request to test an environmental sample, package, distribution device or other device associated with potential human exposure for smallpox virus.

Clinical consultation and a preliminary laboratory diagnosis can be completed within 8 to 24 hours.

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Part II. Smallpox Vaccination

The smallpox vaccine is the only way to prevent smallpox infection. The principle behind vaccination was first determined by Jenner in 1796 following the observation that milkmaids infected with cowpox resisted smallpox infection. The smallpox vaccine is made from live vaccinia virus; it does not contain variola virus. The vaccinia virus belongs to the orthopox virus family, which includes variola (smallpox), cowpox, monkeypox, gerbilpox, camelpox and others.

The smallpox vaccine contains the "live" vaccinia virus, not dead virus like many other vaccines. Other live virus vaccinations include those for measles, mumps, rubella and chickenpox. "Live" vaccine contains "living" virus that is able to give and produce immunity, usually without causing illness. Smallpox vaccine is a highly effective immunizing agent. When the superficial layers of the skin are inoculated with the vaccinia virus, it grows and induces an immune reaction that protects against smallpox. Vaccinia vaccine enabled the global eradication of smallpox through a focused ring vaccination campaign, intensive surveillance, and contact-tracing (ACIP, 2001).

Smallpox vaccination differs from other vaccines because the "live" vaccinia virus inoculation causes a vaccinia infection on the skin surface. It is important to remember that the vaccinia virus in not the same as variola virus; the vaccine does not contain variola, or smallpox, virus. In order for the vaccination to be successful, a vaccinia infection must occur. This successful vaccination is often called a "take." The vaccination site or "take" requires specific care on the part of the person being immunized, or that person's caretaker.

A number of adverse reactions, as well as secondary infection can occur. Because of these special care requirements and possible adverse reactions, prevaccination counseling is advised prior to immunization (Sibley, 2002) (more information of prevaccination counseling and patient education appears later in this course).

The Smallpox Vaccine

The Food and Drug Administration (FDA) has licensed Wyeth Laboratories' smallpox vaccine, Dryvax®; it is Dryvax that will be covered in this course. However, the reader should note that in 2000, CDC awarded a contract to Oravax of Cambridge, Massachusetts to produce smallpox vaccine. Initially producing 40 million doses, Oravax anticipates delivery of the first full scale production lots in 2004 (UPMC, 2004).

Dryvax is prepared from calf lymph with a seed virus derived from the New York City Board of Health strain of vaccinia virus and has a minimum concentration of 108 pock-forming units (PFU)/ml. Dryvax is a lyophilized (freeze-dried), live-virus preparation of infectious vaccinia virus and must be reconstituted before use. Studies conducted among young adults with no previous smallpox vaccination history showed that a 1:5 dilution of Dryvax (Wyeth Laboratories, Inc.) produced take rates among vaccinees equivalent to those of the undiluted vaccine (Wharton, et. al., 2003). The CDC therefore recommends that the vaccine be reconstituted to a 1:5 dilution; the diluent contains 50% glycerin and 0.25% phenol. The vaccine is packaged in multiple dose vials (100 doses) which, when diluted, will yield 500 doses. The 1:5 dilution is equivalent to full strength in terms of take rates.

Contraindications to Vaccinia Vaccine

Potential vaccinees must be screened for contraindications to the smallpox vaccination. It is important that vaccinees as well their contacts who have susceptibility to complications be identified. Because the vaccinia virus used in smallpox vaccine can be spread to others from the vaccine site of an immunized person, the contraindications below apply to **both potential vaccinees and their household contacts.** "Household contacts" include persons with prolonged

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intimate contact with the potential vaccinee, including the potential for direct contact with the vaccination site, e.g., sexual contacts.

This is important in order to avoid accidental transplantation to anyone with contraindications to the vaccine. It is also important to ensure that two to three weeks, indicating a lack of infectivity. The vaccinia vaccine should not be administered for non-emergency indications if any of the conditions below are present or if the vaccinee will be in close contact with someone, either in their household, or in a healthcare setting, who has one of these conditions.

Please note however, that in the event of a smallpox outbreak where there is a high risk of contact with a patient, these contraindications would not apply. Further information will be provided in the "prevention" section of the progressive vaccinia content.

Eczema or atopic dermatitis and other acute, chronic, or exfoliative skin conditions

- Persons who have ever been diagnosed with eczema or atopic dermatitis should not be vaccinated, even if the condition is not currently active. These patients are at high risk of developing eczema vaccinatum, a potentially severe and sometimes fatal complication. Additionally, persons with household contacts that have a history of eczema or atopic dermatitis, irrespective of disease severity or activity, should not be vaccinated.
- If the potential vaccinee or any of their household contacts have other acute, chronic, or exfoliative skin conditions (e.g., burns, impetigo, chicken pox, contact dermatitis, shingles, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, or psoriasis), they are at risk for inadvertent autoinoculation of the affected skin with vaccinia virus and should not be vaccinated until the condition(s) resolves.
- Persons with Darier's disease can develop eczema vaccinatum and therefore should not be vaccinated.
- The size and extent of the skin disorder may be sufficiently small enough that vaccination can be safely performed. However, all such patients must be counseled to take great care to avoid any transfer from the primary site to the affected skin. Disruptive or eruptive, for example:

    - acne,
    - burns,
    - wounds,
    - contact dermatitis,
    - current surgical incisional wounds.

Diseases or conditions which cause immunodeficiency or immunosuppression

- If a potential vaccinee or any of their household contacts have conditions such as HIV/AIDS, solid organ or stem cell transplant, generalized malignancy, leukemia, lymphoma, or agammaglobulinemia, they should not be vaccinated. People with these conditions are at greater risk of developing a serious adverse reaction resulting from unchecked replication of the vaccine virus (progressive vaccinia).
- Before vaccination, potential vaccinees should be educated about the risk of severe vaccinial complications among persons with HIV infection or other immunosuppressive conditions; persons who think they may have one of these conditions should not be vaccinated.
- It is also reported that some patients with severe clinical manifestations of some autoimmune diseases (e.g., systemic lupus erythematosus) may have some degree of immunocompromise as a component of the disease. These patients should not receive smallpox vaccine during the pre-event vaccination program.
- ACIP does not recommend mandatory HIV testing prior to smallpox vaccination, but recommends that HIV testing should be readily available to all persons considering smallpox

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vaccination. HIV testing is recommended for persons who have any history of a risk factor for HIV infection and who are not sure of their HIV infection status. Anyone who is concerned that they could have HIV infection also should be tested. HIV testing should be available in a confidential or, where permitted by law, anonymous setting with results communicated to the potential vaccinee before the planned date of vaccination. Persons with a positive HIV test result should not receive the smallpox vaccination.

- Information about local HIV testing options should be provided to all potential vaccinees, including sites where testing is performed at no cost.

Treatments which cause immunodeficiency or immunosuppression

- If a potential vaccinee or any of their household contacts are undergoing treatment with radiation, antimetabolites, alkylating agents, high-dose corticosteroids (i.e., $\geq$ 2 mg/kg body weight or 20 mg/day of prednisone for $\geq$ 2 weeks), chemotherapy agents, or organ transplant medications, they should not be vaccinated. People who are receiving these therapies are at greater risk of serious adverse reactions to the smallpox vaccine.
- People undergoing treatment with high dose corticosteroids, or who have household contacts undergoing such treatment, should not be vaccinated within one month of completing corticosteroid therapy. People undergoing other treatments which cause immunosuppression or who have household contacts undergoing such treatment should not receive smallpox vaccine until they or their household contacts have been off immunosuppressive treatment for three months.

Pregnancy

- Live virus vaccines are generally contraindicated during pregnancy. Pregnant women who receive the smallpox vaccine are at risk of fetal vaccinia. Although this is a very rare condition (fewer than 50 cases have ever been reported), it usually results in stillbirth or death of the infant shortly after delivery.
- Before vaccination, people should be asked if they or any of their household contacts are pregnant or intend to become pregnant in the next four weeks; those who respond positively should not be vaccinated. In addition, women who are vaccinated should be counseled not to become pregnant during the four weeks after vaccination and abstinence or highly effective contraceptive measures should be recommended to reduce the risk of pregnancy within four weeks of vaccination.
- Routine pregnancy testing of women of child-bearing age is not recommended.
- To further reduce the risk of inadvertently vaccinating a woman who is pregnant, at the time of pre-screening women of child-bearing age should be educated about fetal vaccinia. Abstinence or contraception should also be discussed to reduce the risk of pregnancy before or within four weeks after vaccination. Any woman who thinks she could be pregnant, or who wants additional assurance that she is not pregnant, should perform a urine pregnancy test with a “first morning” void urine on the day scheduled for vaccination. Such tests could be made available at the pre-screening and vaccination sites to minimize cost or access barriers to testing. However, women should be informed that a negative urine pregnancy test cannot exclude a very early pregnancy and therefore they and their healthcare providers should not base a decision about their pregnancy status solely upon a urine pregnancy test result.
- If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within four weeks after vaccinia vaccination, she should be counseled regarding the basis of concern for the fetus. However, vaccination during pregnancy should not ordinarily be a reason to terminate pregnancy.
- To expand understanding of the risk of fetal vaccinia and to document whether adverse pregnancy outcome may be associated with vaccination, a pregnancy registry should be maintained and any adverse outcomes carefully investigated.

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The following contraindications apply only to vaccinees and not to their household contacts:

Allergies to vaccine components

The current smallpox vaccine, Dryvax, contains:

- Polymyxin B sulfate,
- Streptomycin sulfate,
- Chlorotetracycline hydrochloride,
- Neomycin sulfate.

Anyone who has experienced an anaphylactic reaction to these components should not be vaccinated.

In addition, anyone who has experienced a previous allergic reaction to the smallpox vaccine should not be vaccinated.

Moderate or severe acute illness

- Moderate or severe acute illness is generally a contraindication to vaccination.
- Vaccination should be deferred until the acute illness has resolved.

Age - infants and children/geriatrics

- Smallpox vaccine is contraindicated for children under 12 months of age in a pre-event situation.
- The Advisory Committee on Immunization Practices (ACIP) advises against non-emergency use of smallpox vaccine in persons younger than 18 years of age.
- The vaccine manufacturer's package insert states that the vaccine is not recommended for use in geriatric populations in non-emergency situations. The term geriatric generally applies to people age 65 and above.

Breastfeeding

Breastfeeding mothers should not receive the smallpox vaccine. The close physical contact that occurs during breastfeeding increases the chance of inadvertent inoculation. It is not known whether vaccine virus or antibodies are excreted in human milk.

Heart disease, temporary deferral

CDC recommends that persons with known cardiac disease such as previous myocardial infarction, angina, congestive heart failure, or cardiomyopathy not be vaccinated at this time. This recommendation follows reports of cardiac events following smallpox vaccinations including myocardial infarctions and angina without myocardial infarction. It is unclear whether or not there is any association between smallpox vaccination and these cardiac events. Experts are exploring these issues more in depth. This exclusion may be removed as more information becomes available.

It was during the first phase of implementation of the Smallpox Response Plan in 2003 when healthcare workers volunteered to be immunized, so that they could be among those persons ready to immunize the population should that be needed, that the issue of cardiac problems as a contraindication first surfaced. The CDC (2004a) reports the following history relative to smallpox vaccination and cardiac illness.

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- **Past Experience -** Rare cases of heart inflammation following smallpox vaccination were reported in the 1960s and 1970s. Most of these did not occur in the United States and involved a different smallpox vaccine than is being used in the U.S. now.
- **Civilian Vaccinations -** From January 24, 2003 thru June 30, 2004, approximately 39,566 civilians received the smallpox vaccine, thirty four reported heart problems. These included problems like myo/pericarditis (heart inflammation) 21 cases, angina (chest pain caused by lack of blood flow to the heart) and heart attack, 10 cases and dilated cardiomyopathies (heart muscle weakened and cannot pump blood efficiently) 3 cases. Two people who had heart attacks died. It is not known at this time if smallpox vaccination caused these events.
- **Military Vaccinations -** Between December 16, 2002 and August 25, 2004, approximately 631,000 military personnel received the smallpox vaccine. Seventy-eight cases of heart inflammation (myocarditis or pericarditis) have been reported, mainly in the second week after vaccination, at a higher-than-expected rate among men and among people receiving smallpox vaccine for the first time. These cases have been followed carefully to evaluate their recovery, at 28 hospitals in 21 states and several countries overseas. Detailed follow-up cardiac testing is available in 46 cases: all 46 had normal electrocardiograms (ECGs), normal echocardiograms ("echos"), and normal treadmill stress test results, suggesting a high rate of recovery. [See Journal of American College of Cardiology. 2004 (Jul 7);44,1;201-5.] Another 16 cases of "ischemic" heart disease (such as heart attacks, atherosclerosis, or angina) occurred within six weeks after smallpox vaccination. This number of cases is similar to what normally occurs among unvaccinated military personnel of similar age.

General precautions

- The vaccine vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by, or when the product is administered to, persons with known or possible latex sensitivity.
- Persons with inflammatory eye diseases may be at increased risk for inadvertent inoculation due to touching or rubbing of the eye. Therefore it may be prudent to defer vaccination of persons with inflammatory eye diseases requiring steroid treatment until the condition resolves and the course of therapy is complete.

Additionally, the CDC (2003a) recommends that, at this time, those who have three or more of the following risk factors should not receive the smallpox vaccine: high blood pressure diagnosed by a doctor; high blood cholesterol diagnosed by a doctor; diabetes or high blood sugar diagnosed by a doctor; a first degree relative (for example, mother, father, brother, sister) who had a heart condition before the age of 50; and, you smoke cigarettes now.

<u>Simultaneous Administration of Smallpox Vaccine with Other Vaccines</u>

Vaccinia vaccine may be administered simultaneously with any inactivated vaccine, such as influenza vaccine, to encourage appropriate receipt of all indicated vaccines (i.e., in populations such as healthcare workers). With the exception of varicella vaccine, vaccinia vaccine may be administered simultaneously with other live virus vaccines. To avoid confusion in ascertaining which vaccine may have caused post-vaccination skin lesions or other adverse events, and facilitate managing such events, varicella vaccine and vaccinia vaccine should only be administered more than or equal to four weeks apart.

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Prevaccination Counseling/Patient Teaching

Because of the multiple factors that must be considered prior to immunization, the uniqueness of the inoculation procedure and post-vaccination care, it is important that prevaccination counseling occur prior to vaccination. Included in prevaccination counseling are: contraindications to receiving the vaccine, information regarding the immunization procedure, instructions for care of the vaccination site (which must be cared for scrupulously in order to prevent the virus from spreading) and possible adverse reactions to the vaccine.

It is important to obtain appropriate history of allergies to the antibiotics used in Dryvax and to obtain history of the conditions above. These histories may negate vaccine administration when smallpox is not present. However, as stated previously, if smallpox is present and the risk of contact great, the vaccine should be administered. It may be necessary to additionally provide an appropriate antihistamine or other medication.

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Smallpox - Cutaneous Contraindications Questionnaire (ACIP, 2002) The following questionnaire is intended to identify those individuals who have cutaneous conditions that are contraindications for smallpox vaccination. A yes response to any of the following questions may be a contraindication to vaccination if no smallpox is present.	
Are you using medications that could significantly irritate the skin or alter local immunity ? Examples include topical immunomodulators (tacrolimus, pimecrolimus), or retinoids with a potential for irritation.	You may receive the vaccine after these drugs have been discontinued and no evidence of irritation exists; you may re-institute these medications after the vaccine scab has healed.
Do you or any family members have atopic dermatitis? This particular form of eczema puts one at higher risk for adverse side effects from the vaccine. These negative side effects can occur even if your atopic dermatitis is not active. In addition, if people in your family have atopic dermatitis, they can inadvertently get inoculated from your vaccine site and also develop side effects of the vaccine, even if you don't have atopic dermatitis. Therefore, people with this form of eczema, or families who have a member with atopic dermatitis should not be vaccinated, even if the condition appears to have resolved or is inactive. Unfortunately, some people are unaware if they have this form of eczema. The following questions are intended to help you recall if you or your family members have atopic dermatitis. Have you, or your family members 1. Been told you had eczema in childhood? 2. Suffered from an itchy red rash that persists, or comes and goes, and has not been identified as another skin condition? (Atopic dermatitis generally first develops in childhood, involves the creases of the arms and legs, and may involve the cheeks in childhood. Affected individuals frequently have dry skin and a personal or family history of asthma and/or hay fever.)	You should not receive the vaccine if you answer yes to either question 1 or 2.

Additionally, patient teaching regarding the use of over-the-counter pain and antipyretic medications such as aspirin, ibuprofen and acetaminophen for soreness, aching, pain and fever should be included in prevaccination counseling as may the use of an ice-pack to reduce swelling at the site (Sibley, 2002).

Patients must be informed that they must return after seven days, so that the vaccination site can be inspected to evaluate the "take." Patients must be cautioned to inform their primary care

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provider about the vaccination site and any significant reactions that may indicate an adverse reaction. Itching is the most common complaint of vacinees and patients should be informed to contact their primary care provider in the event that it becomes intolerable. An antihistamine may be recommended (Sibley, 2002).

Patients must also be educated about the possible adverse reactions, so that they can be identified early and treated. Adverse Reactions are covered in a later section of this course.

Preventing Contact Transmission to Vaccinees and Healthcare Providers

Unlike other current immunizations, smallpox vaccination is characterized by a virus that propagates in the skin and can potentially contaminate the vaccinee's hands or the skin and mucosa of others with whom the vaccinee comes into contact. It is important to prevent dissemination of the vaccinia virus from the vaccination site to other parts of the vaccinee's body or to others. General principles for the care of vaccinees and the protection of healthcare providers and susceptible patients follow. See Appendix C for a patient information fact sheet regarding the care of the vaccination site and prevention of contact transmission.

Advise vaccinees and/or guardians that until a scab has formed:

- Keep the vaccination site covered (loosely taped sterile gauze is recommended);
- Do not touch, scratch or rub the vaccination site (this is a challenge as the site is usually itchy);
- Avoid person-to-person contact with susceptible persons (see contraindications section);
- Avoid touching, rubbing or otherwise performing any maneuvers that might transfer vaccinia virus to the eye or surrounding skin;
- Discard the vaccination site covering carefully. The cover contains viable virus and can spread the infection to others. Carefully enclose the gauze in a plastic bag that can be sealed prior to placing it in a trash receptacle;
- After handling the vaccination site covering, thoroughly wash hands with soap and running water.

Children under the age of five years old who undergo primary vaccination have had the highest rates of vaccine-related complications in earlier studies, particularly for the complications that were most severe. Children and infants are likely to scratch and pick at the vaccination site/scab and autoinnoculate other areas of the body. Special efforts should be taken to care for the "take" site in children.

In the healthcare setting, contact with vaccinees and the vaccine itself can pose a health threat to:

- Unimmunized healthcare workers
- Susceptible healthcare workers
- Susceptible patients

Great care must be taken to keep all materials that might be contaminated separate from general areas. This includes towels, gowns, instruments, etc. These materials should be placed in an appropriate biohazard container and treated as infectious waste. The role of healthcare workers in the event of widespread smallpox vaccination or in the event of smallpox outbreak is covered in Part III of this course.

Vaccination Procedure

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Because vaccination has not routinely been done for over 30 years, few healthcare providers have experience with smallpox vaccination. However, for those who do recall smallpox vaccination, caution is urged as some aspects of the vaccination procedure have changed. The vaccine must be administered with careful attention to the directions; it is not to be administered intramuscularly, subcutaneously or intravenously. Vaccination is accomplished utilizing a scarification method (described below).

Prior to administration of the vaccine, it must be reconstituted with the diluent. The diluent for Dryvax® contains 50% glycerin, and 0.25% phenol in Sterile Water for Injection, USP (Wyeth Laboratories, 2002). The following is information from Wyeth Laboratories (2002) for the reconstitution of Dryvax vaccine and the method of administration:

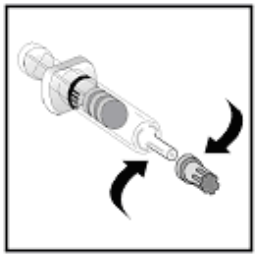
Directions for Reconstitution

When reconstituting and administering the vaccine, use protective gloves and aseptic technique. The healthcare provider must have available a sterile 21 gauge or smaller needle to release the vacuum in the vials prior to adding diluent. This needle must only be used to release the vacuum. The needle to release the vacuum is NOT included in the kit.

1. Lift up tab of aluminum seal on vaccine vial. DO NOT BREAK OFF OR TEAR DOWN TAB.

2. Wipe off vial stopper with an alcohol sponge and allow to dry.
3. Place vaccine vial upright on a hard, flat surface. Insert a sterile 21 guage or smaller needle into the rubber stopper to release the vacuum from the vaccine vial. Discard the needle in biohazard waste container.

4. To reduce viscosity of cold diluent, warm by holding diluent-cartridge in palm of hand for a minute or so.
5. Peel open the vented needle package (provided with the kit) and aseptically remove the vented needle.
6. Remove rubber cover from end of the diluent syringe.



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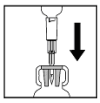
7. With a twisting motion, aseptically attach the vented needle to the hub of the diluent syringe.

8. Remove protective cover from the vented needle and expel the air from the diluent syringe.

9. Aseptically insert the needle through the rubber stopper into the vaccine vial up to the first hub.



10. Depress the plunger to ensure the entire volume of diluent is delivered into the vial.

11. Withdraw diluent syringe/vented needle and discard in biohazard waste container.
12. Allow vaccine vial to stand undisturbed for 3 to 5 minutes. Then if necessary, swirl vial gently to effect complete reconstitution.
13. Record date of reconstitution.
14. Store reconstituted vaccine at 2° to 8°C (36° to 46°F) when not in actual use. The vaccine may be stored for no more than 15 days after reconstitution.

Sites of Vaccination

The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle is the preferred site for smallpox vaccination.

Method of Vaccination

USE 2 OR 3 NEEDLE PUNCTURES FOR PRIMARY VACCINATION; 15 FOR REVACCINATION.
Reconstituted vials should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vaccine if particulate matter or discoloration is present.

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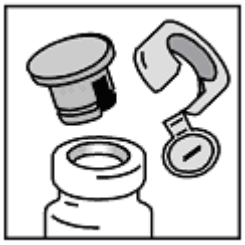
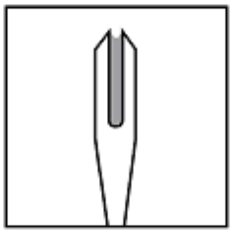
1. First pull down the “tear off” tab from the aluminum seal of the vaccine

vial.
2. Remove entire aluminum seal from the vaccine vial. Then remove rubber stopper from vaccine vial and aseptically retain stopper (set aside inverted) for



subsequent reuse.
3. The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle is the preferred site for smallpox vaccination. If alcohol is used to clean the site, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine by the alcohol.
4. Tear off a packette containing a single, sterile bifurcated vaccinating needle.
5. Peel back the packaging approximately halfway exposing the butt-end of needle.

6. Hold butt-end of needle and gently pull bifurcated point end free of packaging.
7. Carefully dip bifurcated end of needle into vaccine. Visually confirm that the needle picks up a drop of vaccine in the space between the two tips. 



8. Deposit the drop of vaccine onto clean, DRY site previously prepared for vaccination. ***Do not redip needle into vaccine if needle has touched skin.***

9. With the same needle, and using multiple-puncture technique, vaccinate through drop of vaccine. Holding the bifurcated needle perpendicular to the skin, punctures are rapidly made with strokes vigorous enough to allow a trace of

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blood to appear after 15-20 seconds. Two or 3 punctures are recommended for primary vaccination; 15 punctures for revaccination. Any remaining vaccine should be wiped off with dry sterile gauze and the gauze disposed of in a biohazard waste container.

10. Discard needle in a biohazard waste container.
11. Repeat Steps 3 through 10 for each individual to be vaccinated utilizing a new bifurcated needle for each individual vaccinated.
12. If vaccine is to be stored for subsequent use, re-stopper the vial with the rubber stopper and store at 2° to 8°C (36° to 46°F). The vaccine may be stored for no more than 15 days after reconstitution.*
13. When next needed, remove vial from refrigerator, gently swirl suspension to ensure resuspension, and then carefully take off stopper-cap.
14. Repeat Steps 3 through 10.
15. If vaccine is to be restored for subsequent use, replace stopper-cap and store at 2° to 8°C (36° to 46°F). The vaccine may be stored for no more than 15 days after reconstitution.* Wyeth Laboratories (2002). Package Insert - Dryvax, Smallpox Vaccine. Accessed December, 2004 http://www.fda.gov/cber/label/smalwye102502LB.htm#dose.

Note: *In letters to CDC from Wyeth Laboratories dated May 26, 2004, August 16, 2004 and August 26, 2004, the storage period of the vaccine after reconstitution with diluent has been increased to 90 days (http://www.bt.cdc.gov/agent/smallpox/vaccination/wyethlicense.asp).*

The current recommended method for vaccination is the multiple puncture vaccination, a process sometimes referred to as "scarification." It is achieved with a bifurcated needle. Each bifurcated needle is sterile and individually wrapped. The bifurcated needle is for single usage only and should be discarded in an appropriate biohazard container immediately after the vaccination of each patient.

The preferred site for vaccination is the deltoid area on the upper arm. In the past other sites such as the back, the inner aspects of the extremities, or the buttocks were chosen for cosmetic concerns. It is strongly recommended that the deltoid site be used. Experts cite the fact that there is differential skin sensitivity to vaccination and that most of the efficacy studies analyzed vaccinees who received deltoid vaccinations. Sibley (2002) recommends the use of the left deltoid, so that healthcare providers can quickly identify which patients have had the smallpox vaccination, and so as not to confuse the scar left by the smallpox vaccine with that left by the bacillus Calmette-Guerin (BCG) immunization used in countries, other than the US, for prevention of tuberculosis. BCG is generally administered in the right deltoid.

Smallpox Vaccination Method with Step-by Step Instructions (CDC, February 12, 2003)

During the global smallpox eradication effort, the bifurcated needle was used along with a technique called multiple puncture vaccination. Today, this is still the recommended method for administering smallpox vaccine.

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Each bifurcated needle is sterile and individually wrapped. The bifurcated needle is for one-time use only and should be discarded in an appropriate biohazard container immediately after vaccinating each patient.

1. **Review patient history for contraindications.**

2. **Choose the site for vaccination.**
   The deltoid area on the upper arm is recommended.

3. **Skin preparation.**
   No skin preparation is required. Under no circumstances should alcohol be applied to the skin prior to vaccination as it has been shown to inactivate the vaccine virus.

4. **Dip needle.**
   The needle is dipped into the vaccine vial and withdrawn. The needle is designed to hold a tiny drop of vaccine of sufficient size and strength to ensure a take if properly administered. The same needle *should never be dipped into the vaccine vial more than once*, in order to avoid contamination of the vaccine vial.

5. **Make perpendicular insertions within a 5-mm diameter area.**
   The needle is held perpendicular to the site of insertion. The wrist of the vaccinator should be maintained in a firm position by resting on the arm of the vaccinee or another firm support.

   A number of perpendicular insertions are made in rapid order in an area approximately 5 mm in diameter. The number of insertions should be in accordance with the package insert, using 3 insertions for primary vaccination and 15 insertions for revaccination with the Dryvax vaccine. A trace of blood should appear at the site of vaccination within 15-20 seconds. During primary vaccination, if no trace of blood is visible after 3 insertions, an additional 3 insertions should be made using the same bifurcated needle without reinserting the needle into the vaccine vial.

   The bifurcated needle is for one-time use only and should be discarded in an appropriate biohazard container immediately after vaccinating each patient.

6. **Absorb Excess Vaccine.**
   After vaccination, excess vaccine should be absorbed with sterile gauze. Discard the gauze in a safe manner (usually in an infection control receptacle) in order not to contaminate the site or infect others who may come in contact with it.

7. **Cover vaccination site.**
   It is important that the vaccination site be covered to prevent dissemination of virus. Recommended coverings include the following:

   Gauze loosely secured by first aid adhesive tape (taking care to obtain history of tape sensitivity).

   When working in a health care setting, vaccinees should keep their vaccination site covered with gauze or a similar absorbent material. This dressing should, in turn, be covered with a semipermeable dressing. Products combining an absorbent base with an overlying semipermeable layer also can be used to cover the vaccination site. Healthcare workers do not need to be placed on leave after receiving a smallpox vaccination. Vaccinees in settings where close personal contact is likely (such as parents of infants and young children) should cover the vaccination site with gauze or a similar absorbent

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material, wear a shirt or other clothing that would cover the vaccination site, and also make sure to practice good hand hygiene.

Note: The use of semipermeable dressing alone could cause maceration of the vaccination site and increased, prolonged irritation and itching at the site, thereby increasing touching, scratching, and contamination of the hands. Thus, only persons working in healthcare settings should use semipermeable dressings (over gauze or a similar absorbent material as described above).

8. **Educate vaccinee.**
   To avoid contact transmission of the virus, vaccinees must be cautioned to do the following:

   - Do not rub or scratch the vaccination site.
   - Keep the site covered and change gauze-only dressings every 1–2 days or if wet.
   - Change semipermeable dressings at least every 3-5 days.
   - Keep the vaccination site dry, covering it with a water-proof bandage while bathing.
   - Discard gauze carefully in plastic zip bags.
   - Set aside a laundry hamper for clothes, towels, sheets and other items that may come into contact with the vaccination site.
   - Wash clothing or other materials that come into contact with the vaccination site in hot water with detergent and/or bleach. Wash hands afterward.
   - Wash hands thoroughly with soap and hot water or with alcohol-based hand rubs such as gels or foams after touching the vaccination site, or bandages, clothing, towels, or sheets that have come into contact with the vaccination site.
   - When the scab falls off, throw it away in a plastic zip bag.
   - Report any problems by calling the phone number provided on the “Post-Vaccination and Follow-Up Information” sheet, calling your health care provider, or visiting and emergency room.
   - Return 7 days after vaccination for a “take” check (to see if the vaccination was successful).

9. **Record the vaccination.**
   Record vaccination information as instructed by the CDC.

<u>Normal Reactions to the Smallpox Vaccination</u>

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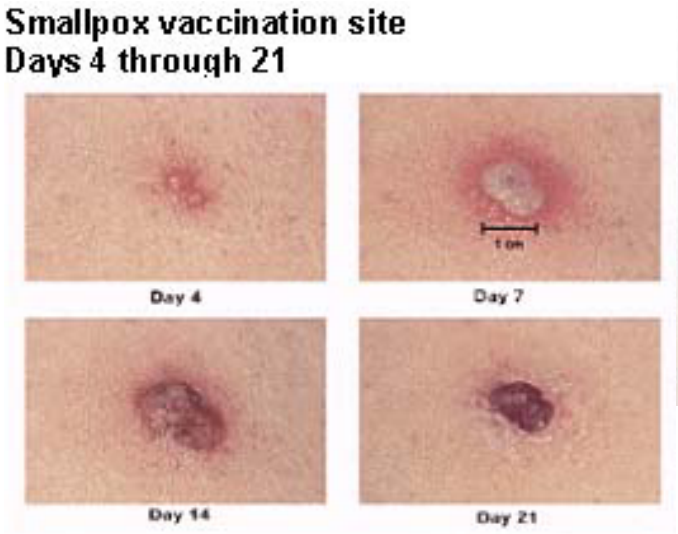

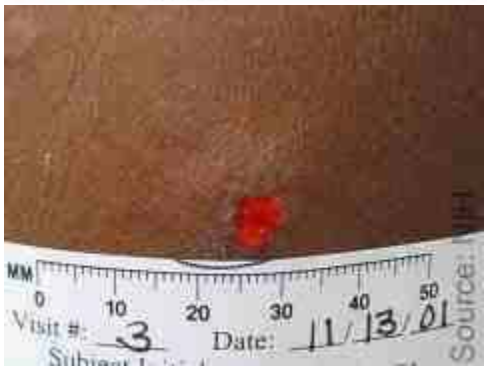

The above pictures were accessed at http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/normal.html December, 2004.

Patients must be counseled to return to have their vaccination site inspected 7 days after the vaccination. A number of potential reactions can occur.

A normal primary vaccination appears as a papule in 3 to 4 days, and rapidly progresses to a vesicle with the surrounding erythema by the fifth or sixth day. The vesicle center becomes depressed and progresses to a well-formed pustule by the eighth or ninth day. By day 12 or soon after, the pustule crusts over and forms a brown scab that progresses from the center of the pustule to the periphery. After 2 ½ to 3 weeks, the scab detaches and a well formed scar remains.

Day	Description
0	Vaccination
3-4	Papule
5-6	Vesicle with surrounding erythema, progressing to vesicle with depressed center
8-9	Well-formed pustule
12+	Pustule crusts over, progressing to scab
17-21	Scab detaches, revealing scar

Rarely, in some previously unvaccinated individuals, seemingly appropriate vaccination techniques may result in no reaction. One should assume that the individual is NOT immune and

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repeat attempts should be made to achieve a primary take. Three attempts should be made, switching skin sites after a second unsuccessful attempt.

Normal Local Reactions

Normal local reactions that are not considered adverse events can include:

- Local satellite lesions, which are normal in appearance (The frequency of satellite lesions varies fro study to study and ranges from 2.4 to 6.6%).
- Lymphagitis.
- Considerable local edema.
- What appears to be bacterial cellulitis, but is simply intense inflammation accompanying the vaccination (viral cellulitis; this is a normal consequence of vaccination but is often confused with bacterial infection).

Normal Systemic Symptoms

Some systemic symptoms are expected and usually occur about a week after vaccination. These include:

- Soreness at the vaccination site.
- Intense erythema ringing the vaccination site.
- Malaise.
- Lymphadenopathy (Local).
- Myalgia, headache, chills, nausea, fatigue.
- Fever.

The frequency of occurrence of these normal reactions varies from study to study. The following lists the symptoms covered by the studies and provides an indication of the range of results:

Lymphadenopathy	25.0 – 50.0 %
Myalgia, headache, chills, nausea, fatigue	0.3 – 37.0 %
Fever >37.7degrees C	2.0 – 16.0 %

According to the manufacturer of the vaccine, Wyeth Laboratories, a fever is common after vaccinia vaccination. Up to 70% of children have one or more days of temperature $\geq$100°F from 4 to 14 days after primary vaccination, and 15% to 20% have temperatures of $\geq$102°F. After revaccination, 35% of children develop temperatures of $\geq$100°F, and 5% have temperatures of $\geq$102°F. Fever is less common in adults than children after vaccination or revaccination (Wyeth Laboratories, 2002).

Normal Reactions: Variants

Some reactions that occur after vaccination, and differ from the above are not unexpected nor are they adverse events. They require no specific treatment; treatment for symptomatic relief and reassurance are all that is needed.

Revaccination

For those among the population who had been vaccinated against smallpox when routine immunization was still widespread, the smallpox vaccination would be considered a revaccination. The nature of the response to revaccination depends on the degree of residual immunity following previous vaccination. In general, the shorter the interval between primary vaccination and revaccination, the more likely it is that there will be no take or a major reaction.

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One of the following responses will occur:

- **Typical primary reaction** - Clear cut pustule 6-8 days after vaccination.
- **Major reaction -** Area of definite induration or congestion surrounding a central lesion that may be a scab or ulcer 6-8 days after vaccination. The evolution of the lesion is more rapid than following a primary reaction. Among those for whom 25 years or more has elapsed since last vaccination, essentially all should experience a "major reaction."
- **Equivocal reaction -** any other reaction or response including Erythema and/or a small, evanescent papule present within several days that resolves quickly. These are "sensitivity" reactions that can be evoked with vaccine virus that is no longer viable. Revaccination is indicated.
- **No reaction** – In some individuals, no take is seen after revaccination, even at long intervals after a primary vaccination. Usually this is due to poor technique, low potency vaccine, or inactivation of the virus at the skin site (e.g. if alcohol is used to prepare the site). Revaccination is indicated using vaccine of assured potency. If a patient has never had a successful take, the patient should be informed that he or she is almost certainly NOT immune.

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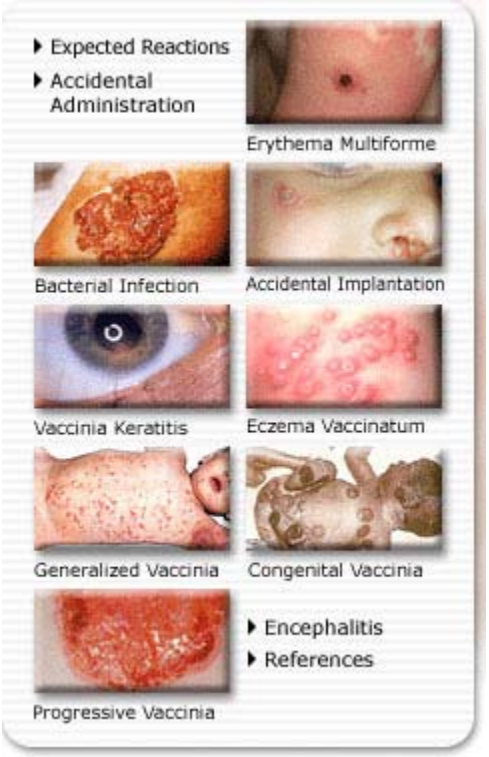
Part III: Adverse Reactions

Smallpox vaccination is a generally safe, effective preventative against smallpox. However, in a number of individuals, smallpox vaccination can result in untoward effects and adverse reactions. Most are totally benign, however frightening in appearance. Some are serious, but treatable. A few, which rarely occur, are serious, life threatening and can be fatal.
Adverse reactions that will be covered in this course are:

- Accidental implantation
- Bacterial infection
- Congential Vaccinia
- Eczema Vaccinatum
- Erythema Multiforme
- Generalized Vaccinia
- Post-Vaccinial Encephalitis
- Progressive Vaccinia
- Septic Shock
- Disseminated Intravascular Coagulation (DIC)
- Vaccinia Keratitis



All adverse reactions must be reported to the CDC; instructions and a copy of the Adverse Event Reporting System (VAERS) form can be found at: **http://vaers.hhs.gov/pdf/vaers_form.pdf.**

Immunity and Adverse Reactions

Immunity to vaccinia is dependent on both cell-mediated immune function and antibody production. In general individuals with intact cell-mediated immunity do not suffer serious consequences. Individuals with antibody-deficient states but with intact cell-mediated immunity generally handle vaccination without incident. However, there are reports of adverse events, even in this group of vaccinees.

Frequency of Adverse Events

The rates reported in the frequency tables for each adverse event were derived from two studies conducted in the 1960s, one from a 10 state survey and one from a national survey. The actual rates differ in these studies for several reasons. One is that the reports vary in the way in which data were collected. In some instances serious reactions were absent or less frequently reported than in the other study. Also the diagnoses were not uniform in definition. As a result these

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specific rates may not be as reliable as one would wish. What is apparent is that overall, less serious complications occurred at a rate of 1000 per million vaccinations. Approximately half of these were accidental inoculations occurring most frequently in children. One primary concern is the actual rates for serious adverse events. The national survey data in the tables for each adverse event appear to be more reliable. In initial vaccination programs currently only adults will be vaccinated and it is difficult to transpose data from either of these studies to form a reliable and accurate expectation of adverse event rates in that population.

Treatment of Adverse Events

Vaccinia Immune Globulin (VIG)

Studies in the 1950s and 1960s indicated that complications of vaccination appeared to occur soon after vaccination and before significant antibodies could be detected in the blood. As a result, C. Henry Kempe and others developed the concept of providing antibody in the form of gamma globulin. Empiric evidence appeared to demonstrate that patients healed when Vaccinia Immune Globulin (VIG) was administered for certain complications.

Since vaccination ceased in the early 1970s, the occurrence of complications from vaccination also ceased. Therefore no definitive studies were carried out to determine the exact efficacy of VIG. VIG was produced in the 1960s from plasma obtained from recently vaccinated donors. It contained a high titer of anti-vaccinia neutralizing antibody. Because it contained a high proportion of aggregated protein it was administered solely by the intramuscular route and could not be used intravenously. With at least some reinstitution of vaccination against smallpox, there is increased interest in the use of VIG. Vials of older VIG are stored at the CDC and are available only under Investigational New Drug (IND) protocols. An effort is underway to produce new lots that will meet the standards for intravenous immune globulin.

VIG Administration	
Indicated	• Accidental implantation (extensive lesions) • Eczema vaccinatum • Generalized vaccinia (if severe or recurrent) • Progressive vaccinia
Not Recommended	• Accidental implantation (minor instances) • Generalized vaccinia (mild or limited – most instances) • Erythema multiforme (Encephalitis post-vaccination)
Contraindicated	• Vaccinia keratitis (may produce corneal opacities)

In some instances, VIG was given concomitantly with vaccination to “prevent” complications in a susceptible person. Not enough is known about this use to recommend it. VIG is not licensed (approved) by the FDA; it is “investigational.”

When it was used in the 1950’s-1970’s, the dosage of VIG varied. In general an initial dose of 0.6 ml/kg body weight was injected intramuscularly and subsequent administration determined by the course of illness. In severe cases of eczema vaccinatum and progressive vaccinia as much as 1-10 mg/kg were used. These large doses were split into smaller units, and injected at multiple sites spread out over time.

The generally recommended dosage of VIG for treatment of complications due to vaccinia vaccination is 6000 units/kg. Dosages may vary slightly depending upon the formulation of VIG

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(intramuscular [IM] or intravenous [IV]) VIG should be administered as early as possible after the onset of symptoms. Doses may be repeated at 2 to 3 day intervals until no new lesions appear.

Postvaccination complications for which VIG may be indicated include:

1. Eczema vaccinatum;
2. Progressive vaccinia (vaccinia necrosum);
3. Severe generalized vaccinia;
4. Severe inadvertent inoculation (e.g., large number of lesions, toxicity of affected person, or substantial pain); and
5. Severe ocular complication (except isolated keratitis).

VIG is **not indicated** for the treatment of:

1. Postvaccinial encephalitis or postvaccinial encephalomyelitis.
2. Non-severe inadvertent inoculation.
3. Mild or limited generalized vaccinia.
4. Nonspecific rashes, erythema multiforme, or Stevens-Johnson syndrome.

The currently limited supplies of VIG do not allow for its concomitant administration with vaccine for the prevention of potential complications. **VIG use should be reserved for treatment of the most serious or life-threatening complications**.

Side effects of VIG include:

- VIG is made from human blood plasma. Products made from human blood may contain infectious agents, such as viruses, that can cause disease. To decrease the chance that such products carry viruses, plasma donors are checked for prior contact with certain viruses, the collected plasma is treated for the presence of certain viruses, which are killed and/or removed from the plasma.
- Immune globulin products like VIG may cause allergic reactions that can be mild or may be serious and cause life-threatening breathing and heart problems. If you have a serious or life-threatening reaction, medical care and drugs are available to treat you.
- People who have a problem making a certain antibody called IgA or who have had a serious allergic reaction to human antibody products before are at risk for an allergic reaction to VIG.
- Most side effects from similar products are mild and do not last for very long. You may experience back pain, chills, headache, muscle pain, joint pain, itching, weakness, fever, nausea, vomiting, abdominal cramps, flushing, tightness of the chest, sweating, changes in blood pressure, dizziness, paleness, shortness of breath, and wheezing. Rashes occur rarely.
- Some people experience pain and soreness at or near the site where VIG is given. While this is unpleasant, it is not serious and can be treated with common pain relievers.

Cidofovir

In addition to VIG, the CDC recommends that **cidofovir**, an antiviral drug marketed as Vistide, as another medication that may be used to treat certain serious smallpox vaccine reactions. Cidofovir is currently licensed for the treatment of cytomegaloviral retinitis and has demonstrated antiviral activity against poxviruses in vitro, and against cowpox and vaccinia viruses in mice. However, its use for the treatment of vaccinia adverse reactions is restricted under an IND protocol. Under the IND, cidofovir would only be used when VIG was not efficacious.

Cidofovir is administered intravenously. Side effects can include:

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- Kidney toxicity, kidney failure.
- Low white blood cells.
- Pressure in the eye.
- Swelling and tenderness of the eye.
- Build up of acid in the body that can result in liver problems and inflammation of the pancreas that can result in death.
- fever, infection, pneumonia, shortness of breath and nausea with vomiting.
- headache, weakness, rash, hair loss, diarrhea, pain, lowered number of red blood cells, loss of appetite, chills, coughing, and infections in the mouth.

Reporting Adverse Events

To report adverse events or request consultation about an adverse event, please call your state or local public health authorities (see Resources). For general vaccine questions (not adverse event reporting), please email the National Immunization Program at nipinfor@cdc.gov.

The Vaccine Adverse Event Reporting System (VAERS)

The Food and Drug Administration (FDA) has recommended that the Vaccine Adverse Event Reporting System (VAERS) be used to report adverse events. The VAERS, established in 1990, is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of US licensed vaccines.

The National Childhood Vaccine Injury Act (NCVIA-1986) requires health professionals and vaccine manufacturers to report to the Department of Health and Human Services (DHHS) specific adverse events following the administration of specific licensed vaccines. Reports may be submitted by mail, fax and the Internet (see http://vaers.hhs.gov/ for details). All reports enter the VAERS database.

Forms have been developed for consistent reporting and include identifying information about the patient, the vaccination given, the reported adverse event, and the person reporting the event. Visit http://vaers.hhs.gov/pdf/vaers_form.pdf to open a PDF version of the VAERS form.

Serious reports include hospitalization, prolongation of hospitalization, death, life-threatening illness or permanent disability. In order to provide as full a picture as possible, all serious reports are followed up by a team of nurses to obtain additional information (such as medical records and autopsy reports). The data are subsequently analyzed.

All personal information is confidential. Medical records are protected by confidentiality requirements.

Accidental Implantation

The florid vaccination site contains high titers of vaccinia virus. Transfer of this virus from the primary site to other parts of the body, or to other individuals, is a constant threat. Accidental implantation varies from single lesions to massive involvement of disruptive skin disorders (e.g., eczema).

The degree of skin involvement appears to parallel the risk and severity of accidental implantation. Slight lesions, such as superficial wounds, burns and those seen in skin diseases may pose less of a risk than massively involved skin areas. Nevertheless, any disrupted skin can lead to implantation, although the consequences may be less for minor lesions.

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Adequate screening of vaccinees and contact information may assist in preventing such transmission. Careful history should be taken to rule out susceptibility to complications in the vacinee or his or her contacts. The degree of skin disruption should be taken into account before vaccination is denied. Small areas of involvement accompanied by adequate instruction to the patients and suggested coverage of the area to avoid implantation may be sufficient to permit vaccination. Careful patient teaching regarding the care of the affected areas in order to avoid further transfer to themselves or to others is needed and may also assist in lowering the risk.

Accidental implantation can be by autoinoculation or contact inoculation. As indicated from the data below, accidental implantation is one of the most common adverse events following primary vaccination. It is far less common after revaccination, but the threat of transfer to contacts remains.

As described earlier, although no age group is spared, infants and children are most susceptible to more extensive inoculations because of their tendency to scratch an itching vaccination site. Older individuals may be able to control scratching, despite the itching, but younger individuals most often cannot. Older persons tend to have fewer lesions but they are seen more frequently. Older individuals implant virus frequently on the face as a result of inadvertent contamination of the hands or via fomites. Minute injuries, such as occur in shaving, establish the potential for implantation.

Accidental Implantation Frequencies (*) per 1,000,000 Primary Vaccinations

Age in Years	1968 National Survey (**)	1968 Ten State Survey (++)
1-4	33	577
5-19	18	371
20+	14	606
Total (1+)	26	497

*Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.
** Case sources include: American Red Cross Vaccinia Immune Globulin (VIG) distribution system, Red Cross VIG consultants, State and Territorial Epidemiologists, Burroughs-Wellcome Thiosemicarbazone distribution list, smallpox vaccine manufacturers complication reporting files, state reports to the Encephalitis Surveillance Unit of the National Communicable Disease Center (NCDC), and specimen submissions for vaccinia testing to the Viral Exanthems Unit of NCDC.
++ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (progressive vaccinia) reports.

Individuals who are particularly susceptible to accidental implantation, either by autoinoculation or contact inoculation include those with:

- Eczema.
- Skin disorders with open lesions.
- Inflammatory eye disease.

These individuals are more susceptible to serious disease as a consequence.

Following primary vaccination, high titers of vaccinia virus are extruded onto the surface of the site. After revaccination, less virus is present on the skin. This surface virus is easily transferred to the hands and to fomites. Either may be the source of inoculation elsewhere, but most implantations occur as a result of transfer from hand to skin or to mucosa.

The vaccination site is pruritic and many vaccinees, particularly children, tend to scratch, pick, or otherwise contact the site. Virus is then transferred to normal skin by touch or scratch. Minor breaks in the skin provide a fertile field for implantation. Virus is more easily transferred to abnormal skin or mucosa. Since the virus is highly dermatotrophic, a primary vaccination

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reaction occurs at the site of implantation. In normal individuals, each lesion will follow the same course as the primary vaccination.

If the individual has a cell-mediated immune defect, however, the implantation can be serious and life threatening. (Please see the section on Progressive Vaccinia later in this Adverse Reactions section of the course.) Lesions on eczematous skin, in disrupted skin and in the eye pose special hazards, as the infection can be extensive in skin lesions and a threat to eyesight in the eye.

Clinical Manifestations for Patients with Pre-Existing Conditions	
Condition	**Notes**
Cell-mediated immune dysfunction	Each lesion progresses without an inflammatory response, does not heal, and expands.
Eczema or disrupted skin	Lesions tend to be confluent and massive in extent.
Prior inflammatory eye disease	Periorbital, conjunctival and corneal lesions are seen in those with prior inflammatory eye disease. The periorbital and conjunctival lesions undergo the same evolution as the primary in skin and mucosa, whereas the corneal infection causes ulceration and ultimate cloudiness.

Diagnosis of accidental implantation is easily made, because in normal persons, the primary and implanted lesions are characteristic of a normal vaccination and easily identified. In most instances, laboratory testing is unnecessary (see Laboratory Testing later in this course). If the lesions are extensive, immunologic investigation is warranted in addition to virologic studies. In some cases, particularly in individuals who lack specific contact information, it may be necessary to establish the etiology of a give lesion by viral study to differentiate it from other diseases.

Management of Accidental Implantation	
Number of Lesions	**Treatment**
One or a few	No specific treatment is required
Multiple (especially if the lesions are confluent and cover large portions of the body) See the section of the course on Eczema Vaccinatum and Vaccinia Keratitits for management of these specific autoinoculations.	Vaccinia Immune Globulin (VIG): 0.6 ml/kg **Except in Vaccinia Keratitis, where VIG is contraindicated.**

Bacterial Infection of the Vaccination Site

Today, staphylococci and streptococci would be the most likely organisms to be encountered in normal individuals. Occasionally, enteric or anaerobic organisms are the cause of bacterial superinfection of vaccinations. Normal skin flora includes staphylococcal species and streptococcal organisms. In addition, in infants, fecal contamination of skin is not uncommon. Thus disruption of the skin by vaccination may provide a fertile field for bacterial superinfection and multiplication. In the immunodeficient person, particularly those with antibody or polymorphonuclear white blood cell (WBC) deficiency as a component, bacterial infection is common and may be due to unusual organisms.

The use of occlusive dressings, especially those tightly bound to the skin, may result in increased maceration of the skin. Occlusive dressings may also lead to more frequent occurrence of infection, the possibility of anaerobic infection, and more serious disease.

The frequency of bacterial infections is unknown. Infants and young children experience bacterial infections post vaccination more frequently because of scratching of the vaccination site, and in

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some instances, unsanitary behavior. In some of the more serious vital complications, bacterial superinfection may also occur as a consequence of both the necrotic tissue and the immune deficiency of the vaccine.

Staphylococcal infection is most often due to S. Aureus or related species. This results in a vesiculo-pustular lesion at the site of vaccination, often spreading peripherally in circumferential fashion, with clearing behind the advancing border. Bacterial lymphangitis and regional lymphadenitits may occur, but most often the lesions are solely superficial infections.

Streptococcal infection may result in lesions similar to staphylococcal impetigo, but more commonly one sees a piled up eschar, heaping at the vaccination site. Lymphangitis occurs commonly as does edematous painful regional lymphadenitis.

Occasionally, streptococci and staphylococci may coinfect the vaccination site.

Enteric and anaerobic infections may present with purulence or with extensive necrosis at the vaccination site. Necrotic fasciitis has also been encountered in some cases.

Diagnosis is made through clinical recognition, confirmed by appropriate bacterial cultures. Purulent lesions should be swabbed, and if vesicular or pustular, aspirated specimens obtained. If septic symptoms accompany local infection, blood should be cultured. In individuals suspected of immunodeficiency, it is prudent to examine antibody and polymorphonuclear white blood cell numbers and function.

Appropriate antimicrobial therapy is required, selected on the basis of anticipated etiology and the results of culture and sensitivities. The area should be kept clean and debrided as appropriate. A loose dressing and topical antimicrobials may prevent spread and potentially hasten healing.

In the immunologically deficient, appropriate replacement therapy should be used. For antibody deficiencies, immune globulin is appropriate and current therapy for phagocytic disorders is indicated. Consultation with infectious diseases and immunology experts is advised. Notification to CDC is required.

Local use pf prophylactic antimicrobials without evidence of infection is not recommended as resistant organisms may then dominate.

Congenital Vaccinia

Congenital vaccinia is infection of the last trimester with evidence of the disease in the newborn infant. No proven instance of congenital abnormalities has been attributed to vaccination during any stage of pregnancy. Some have postulated that vaccination in the first trimester results in some fetal loss but this has not been substantiated.

Congenital vaccinia is a very rare event. Despite large-scale vaccination campaigns in the past that undoubtedly resulted in inadvertent vaccination of many pregnant women, fewer than 50 cases of congenital disease have been recorded in the literature.

The third trimester of pregnancy appears to be a critical time for the risk to the fetus of congenital vaccinia, although there have been rare reports of vaccination earlier in pregnancy resulting, at birth, in evidence of disease having been present.

Viremia in the vaccinated pregnant female is thought to either directly infect the fetus, or infect the fetus secondarily following placental or amniotic membrane infection. Whether virus infects the skin from the blood or by direct contact with infected amniotic fluid is unknown.

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The affected infant is often premature. The lesions in the newborn infant may be typical of generalized vaccinia or may be progressive in nature (See Generalized Vaccinia and Progressive Vaccinia sections of this course). Lesions are often confluent and extensive. Death almost always occurs before birth or shortly thereafter.

In the absence of natural smallpox, a history of vaccination and typical lesions in the infant suffice to establish the diagnosis. Virologic studies are confirmatory. If smallpox is extant, differential diagnosis is based on virus isolation from the lesions.

There is no experience in treating the fetus or newborns for congenital vaccinia. If an infant is born with lesions and is viable, then use of VIG is warranted and the dosage is empiric.

In order to prevent congenital vaccinia, avoid vaccination of pregnant women unless they have been exposed to a smallpox patient or are a household member of a smallpox case.

Eczema Vaccinatum

Individuals with eczema (more correctly termed atopic dermatitis) are at special risk from implantation of vaccinia virus into the diseased skin, sometimes with a fatal outcome. Atopic dermatitis implies both a skin abnormality and an immunologic difference, ill defined, in individuals subject to this disease.

If smallpox is not an immediate risk, vaccination should **not** be performed in these patients and they should not be in contact with vaccinees. If there is smallpox in the community with potential exposure, or if the patient is a household contact of a case, then vaccination must be performed.

Transfer of vaccinia virus can occur from autoinoculation or from contact with a vaccinee whose lesion is in the florid stages. With early recognition and appropriate use of Vaccinia Immune Globulin (VIG), mortality can be reduced to zero, and morbidity alleviated.

It is estimated that there are 27 million individuals in the United States in 2002 who have atopic dermatitis, many of whom would be susceptible to eczema vaccinatum if vaccinated or in contact with a vaccinee.

Further, it appears that even healed skin is not normal and eczema vaccinatum has occurred in the skin of such individuals at the sites of prior florid eczema.

Eczema Vaccinatum Frequencies(*) per 1,000,000 Primary Vaccinations		
Age in Years	**1968 National Survey(†)**	**1968 Ten State Survey(§)**
1-4	11	44
5-19	7	35
20+	24	30
Total (1+)	10	40

* Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.
† Case sources include: American Red Cross Vaccinia Immune Globulin (VIG) distribution system, Red Cross VIG consultants, State and Territorial Epidemiologists, Burroughs-Wellcome Thiosemicarbazone distribution list, smallpox vaccine manufacturers complication reporting files, state reports to the Encephalitis Surveillance Unit of the National Communicable Disease Center (NCDC), and specimen submissions for vaccinia testing to the Viral Exanthems Unit of NCDC.

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§ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (progressive vaccinia) reports.

Disrupted skin in patients with atopic dermatitis permits viral implantation. Once the virus is implanted (and it may be implanted at multiple sites) it spreads from cell to cell producing extensive lesions dependent only on the extent of the abnormal skin.

An underlying T-cell immunologic defect is suspected in some patients with atopic eczema on the basis of their propensity to develop cutaneous viral and fungal infections and a decreased sensitivity to contact dermatitis which is T-cell mediated. Some patients with T-cell immune deficiencies have atopic dermatitis as a feature, also suggesting a link between the two. Laboratory findings support this hypothesis. The T-cell defects are a contributory factor to the severity of vaccinia infection and help explain lesions in “healed” skin.

If early diagnosis is not established and treatment with VIG is delayed, viremia ensues allowing the spread of virus to other parts of the body, including skin that is not affected by eczema. Bacterial and fungal invasion may occur as a late stage of untreated eczema vaccinatum.

The individual lesions appear identical to a primary vaccination and undergo identical evolution. Because most individuals have large contiguous patches of skin in the affected areas, confluent lesions are the rule. These often cover the entire face, antecubital fossa or behind the knee in the popliteal fossa. Confluent lesions may also appear on other areas of the body. Individual lesions may occur as a result of autoinoculation after the initial transfer, or by viremic spread.

Untreated patients become quite ill and evidence systemic symptoms. If unrecognized and untreated, the patient will manifest severe systemic symptoms resembling septic shock, and death ensues.

Bacterial infection of the lesions may occur. The lesions will appear similar to those described under Bacterial Infection of Site, but will be more extensive and necrotic. Bacteremia and septicemia may result from local contamination or frank infection of the site, at which time the patient will experience fever, chills, obtundation, and even coma. Abscesses may occur by extension from infected sites.

Successfully treated individuals will heal as with normal primary vaccinations, with evolution of the individual lesions through the scarring phase. Scarring may be extensive depending on extent of the infected area and the normal tendency for the body to clear the lesions by scar formation.

The clinical appearance of lesions together with a primary vaccination site usually establishes the diagnosis. Diagnosis may be more difficult in contact cases, because history of contact with a vaccinee may be unknown or unappreciated as to risk.

Laboratory confirmation may be indicated in cases where distinction from herpes virus infection or other pox diseases may be necessary. Immunologic studies, particularly of T-cell function and IgE levels, are recommended and should be performed in consultation with either the CDC or an established immunologist familiar with atopic dermatitis. In this way, the subtle immunologic differences that contribute to the occurrence and morbidity of this condition may be better understood.

Appropriate bacterial and/or fungal cultures of the skin or blood may be indicated if there is evidence of contamination or symptoms suggesting bacteremia or septicemia. If abscesses occur, treat appropriately by incision and drainage.

Eczema vaccinatum demands urgent treatment with Vaccinia Immune Globulin. Mortality has generally been prevented if patients are treated promptly and adequately. However, even if there

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is a delay in recognition, prompt institution of VIG should be undertaken.

Normally, the initial dose of intramuscular VIG (IM-VIG) is 0.6-1.0 ml per kg body weight. However, if the lesions are extensive when first seen, as much as 5-10 ml per kg of IM-VIG, divided into multiple doses, and given over several days should be administered.

The current IM-VIG is an experimental drug and is only available under the IND protocol. Intravenous VIG (IV-VIG) may be available in the near future. Specific recommendations for its use should be followed.

With bacterial infection, appropriate antibiotic treatment should be guided by most probable organisms (staphylococcus aureus, streptococci, and enteric bacteria) and subsequently by results of culture and sensitivity. Fungal infections should be treated by the appropriate antifungal agent. It is recommended that an infectious disease specialist be consulted. For treatment of the underlying atopic dermatitis, a dermatologist should be consulted.

If septic shock supervenes then all appropriate measures should be employed based on clinical observations and laboratory data.

The most effective preventive measure is the identification of susceptibles by a careful history of prior or current atopic dermatitis in the vaccinee or potential contact of the vaccinee with such persons.

Individuals with current or prior eczema should **not** be vaccinated. Normal candidates for vaccination who have contact with persons with eczema should **not** be vaccinated unless they can avoid person-to-person contact with the susceptible person or persons until the scab separates from the vaccination lesion.

In established eczema vaccinatum, appropriate skin care is recommended to diminish bacterial contamination of the vaccination sites. Consultation with a dermatologist familiar with this disease may assist in developing appropriate measures to accomplish this goal.

Erythema Multiforme

Many vaccinees develop skin rashes after vaccination, almost all of which are benign, if occasionally frightening in appearance. The rashes are collectively termed erythema multiforme. These rashes are either toxic or allergic and require only symptomatic therapy. Rarely, a more serious eruption, Stevens Johnson Syndrome may occur, requiring more aggressive steroid therapy.

A variety of rashes occur in a large number of vaccinees 1-2 weeks after vaccination.

Erythema Multiforme Frequencies(*) per 1,000,000 Primary Vaccinations

Age in Years	1968 National Survey(†)	1968 Ten State Survey(§)
1-4	N/A	158
5-19	N/A	87
20+	N/A	30
Total (1+)	N/A	250

* Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.

† Erythema multiforme case rates not reported in this study.

§ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (progressive vaccinia) reports.

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Recent studies indicate that 5.6-14.3 percent of adult vaccinees develop rashes at sites other than the vaccination.

In general, the rashes are benign, with the exception of the rarely encountered Stevens-Johnson Syndrome. The underlying mechanism is uncertain and may be either allergic or toxic or both.

There appears to be no predilection for these rashes, although some believe that allergic persons may be more likely to develop them. Immunologic data on affected vaccinees is lacking. Some investigators believe that a concurrent enterovirus infection causes the rash but data are insufficient to determine if this is a true association.

As the local lesion matures, a variety of different rashes are observed beginning 1-2 weeks after vaccination:

Severity	Description

Age in Years	1968 National Survey+	1968 Ten state Survey++
1-4	17	233
5-19	13	140
20+	45	212
Total (1+)	17	195

Mild	The mildest form consists of a few papules or erythematous blotches. Some patients manifest urticaria, vesicles, or even pustules.
Extensive	A few patients have extensive rash covering most of their bodies.
Severe	Rarely, one sees the desquamating Stevens-Johnson Syndrome with full body involvement and conjuctival and corneal inflammation.

The rash is erythematous and pruritic in most instances and is most intense surrounding the vaccination site. The degree of erythema is intense and the rash may be raised or flat, with an urticarial border. The rash tends to be symmetrical and often involves the palms and soles.

Intense itching may accompany the rash and scratching can lead to bacterial superinfection. In general, the presence of a vaccination and the appearance of the rash suffice to make a clinical diagnosis and no further studies are required.

The vesicular and papular eruptions may be diagnostically problematic, depending on the extent and evolution of the individual lesions, as they may be mistaken for generalized vaccinia or accidental autoinoculation. The lesions of generalized vaccinia and accidental implantation tend to occur later and to be devoid of massive erythematous reactions and each evolves in a manner similar to primary vaccinations.

Occasionally, virologic studies may be required to rule out viral infection.

Appropriate allergic and immunologic studies may help to gain a better understanding of their pathogenesis.

Most of these rashes will resolve on their own and require no specific therapy.

Since pruritus is constant, an appropriate antihistamine or antipruritic is indicated and measures should be taken to reduce scratching. For infants, swathing of the hands with cotton has proved useful. Older children and adults should wash their hands frequently and keep their fingernails closely trimmed.

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The skin requires no special care in uncomplicated erythema multiforme. If Stevens-Johnson Syndrome is encountered, hospitalization and supportive care may be indicated depending on the degree of body surface and mucosal involvement.

There are no known methods to predict or prevent these reactions.

Generalized Vaccinia

Generalized vaccinia is the result of the systemic spread of virus from the vaccination site. Despite the appearance of the lesions, it is a totally benign complication of primary vaccination. Its frequency is not known but it is believed to be rare.

The literature is confusing as this term has been used to describe this benign event as well as more serious and even lethal complications (eczema vaccinatum, other implantations, and progressive vaccinia). The term "generalized vaccinia" as used here will refer **only** to the rare, benign complication itself.

Generalized Vaccina Frequencies* per 1,000,000 Primary Vaccinations		
Age in Years	1968 National Survey +	1968 Ten State Survey + +
1-4	17	233
5-19	13	140
20+	45	212
Total (1+)	17	195

* Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.
+ Case sources include: American Red Cross Vaccinia Immune Globulin (VIG) distribution system, Red Cross VIG consultants, State and Territorial Epidemiologists, Burroughs-Wellcome Thiosemicarbazone distribution list, smallpox vaccine manufacturers complication reporting files, state reports to the Encephalitis Surveillance Unit of the National Communicable Disease Center (NCDC), and specimen submissions for vaccinia testing to the Viral Exanthems Unit of NCDC.
++ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (progressive vaccinia) reports.

The 1968 Ten State Survey rates may be over estimates as generalized vaccinia was often confused with other, non-specific immune mediated rashes, such as erythema multiforme, that can occur following vaccination.

Since most of these individuals are children, and most were seen and studied at a time when immunologic knowledge was less complete than at present, characteristics that enhance susceptibility are not known for certain. It is likely that many of these children had subtle and minor immunologic abnormalities that permitted some extension of virus spread, but not morbid or lethal disease.

The mechanisms underlying apparent viremic spread from a primary vaccination site to other parts of the body are not known. Virus is present in the blood, but clinically only the skin appears to be a target for implantation. Subtle minor immunologic abnormalities, particularly of the immunoglobulin B-cell system, are suspected to be present but such studies were not available at the time this complication was observed.

The fact that recurrent episodes are seen in some individuals lends credence to an immunologic defect. Antibody deficiency is likely because the lesions result from viremia, which is normally controlled by antibodies. Also, each of the lesions, as well as the primary, heals without incident and in normal fashion, suggesting that cell-mediated immunity is intact.

Within a week after the onset of a vaccination reaction, lesions appear on unimmunized skin and appear to derive from viremia, not inoculation by transfer. Each takes the form of a primary vaccination, but is usually much smaller in size, and undergoes rapid evolution to scarring.

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Lesions may occur on any part of the body, most often on the trunk and abdomen, less commonly on the face and limbs. Lesions may occur on the palms and soles. In rare cases, a profuse rash occurs and may be confluent in nature. Rarely, lesions may recur at 4-6 week intervals for as long as one year.

Exact diagnosis can be difficult and this disorder must be differentiated from:

- Erythema multiforme – Lesions of these diseases are not umbilicated and do not resemble mature vaccinations.
- Eczema vaccinatum – Usually differentiation is not difficult because of the patient's history but can be difficult if the eczema is healed and history is not elicited. However, the distribution of the lesions in the usual sites of atopic dermatitis (eczema) is helpful.
- Progressive vaccinia (early stages) – The primary lesion in progressive vaccinia presents without inflammation and has a characteristic appearance.
- Severe chickenpox – Chickenpox lesions are superficial vesicles and do not resemble vaccination lesions.

If smallpox is endemic, differentiation between smallpox and generalized vaccinia may be very difficult. Vaccinia lesions will occur after vaccination, but if the patient has been exposed to smallpox, he/she may have modified smallpox. Virologic differentiation is mandatory in this instance. Notify and consult your state and local health departments.

Virologic diagnosis is seldom needed. On occasion, isolation of vaccinia virus will be helpful in differentiating generalized vaccinia from some of the other disorders that may be confused with it. For further information on laboratory testing, see that section of this course.

Consultation with an immunologist is strongly recommended in order that appropriate studies, particularly of the B-cell immune system, are undertaken to determine whether an immunologic deficiency is present. This will be of importance to the patient as well as to expanding our knowledge of the cause of this particular complication.

Most instances of generalized vaccinia, particularly if the lesions are few, require no specific therapy. In some cases, with extensive lesions, or in recurrent disease, Vaccinia Immune Globulin (VIG) should be administered in an initial dose of 0.6 ml per kg body weight. Rarely is it necessary to administer more than one course with recurrent disease.

If an antibody (B-cell) deficient state or another immunologic abnormality is diagnosed, then both VIG therapy for the viral disease and appropriate therapy for the immunologic deficiency must be decided in consultation with an immunologist.

Until the precise underlying cause is identified, it is not possible to predict which patients will be affected, and no preventive measures are known. If an individual has a history suggestive of, or an established diagnosis of an antibody (B-cell system) immunodeficiency, they should not be vaccinated.

Post Vaccinial Encephalitis

Encephalitis or meningoencephalitis following vaccination has been reported among vaccinees in the U.S. and from many other countries, but how many such cases are coincidental in time and how many are related to the vaccination itself is impossible to know. A number of different infectious agents and non-infectious processes can be responsible and it is often impossible to establish the etiology.

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In general, this is a severe disease with high mortality and morbidity.

Post-Vaccinial Encephalitis Frequencies * per 1,000,000 Primary Vaccinations

Age in Years	1968 National Survey+	1968 Ten State Survey++
1-4	2	10
5-19	3	9
20+	4	0
Total (1+)	2	9

* Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.
+ Case sources include: American Red Cross Vaccinia Immune Globulin (VIG) distribution system, Red Cross VIG consultants, State and Territorial Epidemiologists, Burroughs-Wellcome Thiosemicarbazone distribution list, smallpox vaccine manufacturers complication reporting files, state reports to the Encephalitis Surveillance Unit of the National Communicable Disease Center (NCDC), and specimen submissions for vaccinia testing to the Viral Exanthems Unit of NCDC.
++ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (Progressive vaccinia) reports.

European data indicate a higher incidence than in the US, but whether this reflects the use of different vaccine strains or differences in diagnostic methods is unknown. There are no known predictive antecedents.

The mechanisms for this form of encephalitis are unknown. Various hypotheses have been advanced but the one that is deemed most likely is that it represents an autoimmune process. Midbrain, cerebral and medullary lesions have been observed, and in 1/5th of cases myelitis is predominant. Increases in cerebrospinal fluid (CSF) pressure, CSF lymphocytosis, and increases in CSF protein content all represent non-specific findings.

One-third of all cases have proved fatal and half of all survivors have had some residual neurologic defect, ranging from a convulsive disorder to profound neurologic deficit.

Encephalitis usually occurs 10-14 days after vaccination. It is difficult to delineate the clinical spectrum because of the potential confusion with other causes of encephalitis in reported cases.

Headache, vomiting, drowsiness and fever are the first symptoms observed and may be all that is seen in mild cases with rapid recovery. In more severe cases, symptoms progress to include paralysis, incontinence, urinary retention, and various forms of convulsions.

Death can occur suddenly, usually within a week of onset of symptoms.

Many patients recover completely without discernible residual difficulties. Some patients experience a variety of neurologic sequelae.

A variety of encephalitic syndromes can mimic those attributed to vaccination. The possible causes are numerous and include, but are not limited to, Epstein-Barr Virus (EBV), herpes viruses, enteroviruses, measles, mumps, Mycoplasma pneumoniae, varicella-zoster virus, and arboviruses. In addition a variety of encephalopathies can produce identical symptoms.

Studies should be undertaken to rule out other causes, as this diagnosis is ultimately one of exclusion. Polymerase chain reaction (PCR) testing of spinal fluid for a range of agents normally causing meningo-encephalitis should be performed. Bacterial infection should also be ruled out by examination of the cerebrospinal fluid, and other appropriate cultures. The peripheral white blood cell count and in the CSF are non-specific, showing an increase in mononuclear cells. Cerebrospinal fluid protein and glucose may be slightly elevated.

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Typically, temporal association with vaccination (10-14 days to onset on the average) and meningo-encephalitic symptoms suggest this entity.

There is no specific therapy. Supportive care, anticonvulsants and intensive care may be required in individual cases.

Vaccinia Immune Globulin is **not** effective and is **not** recommended.

There are no specific indicators of susceptibility. Any patient with an evolving central nervous system disorder should not receive a vaccination. It is not known if a prior history of convulsions is associated with a higher frequency of post-vaccination encephalitis. Stable Central Nervous System disorders should not be a contraindication to vaccination.

Progressive Vaccinia

Progressive vaccinia is the most severe complication of smallpox vaccination. It is almost always life threatening.


Progressive Vaccinia

Progressive vaccinia is the preferred designation for this complication although, in the past, it has sometimes been termed: Vaccinia necrosum, Vaccinia gangrenosa, Disseminated vaccinia.

Rare in the past, it may be a greater threat today, given the larger proportion of susceptible persons in the population.

Progressive Vaccinia Frequencies * per 1,000,000 Primary Vaccinations

Age in Years	1968 National Survey+	1968 Ten State Survey++
1-4	1	3
5-19	1	0
20+	7	0
Total (1+)	1	2

* Numbers rounded to the nearest whole number, total number of vaccinations estimated in both studies.
+ Case sources include: American Red Cross Vaccinia Immune Globulin (VIG) distrivution system, Red Cross VIG consultants, State and Territorial Epidemiologists, Burroughs-Wellcome Thiosemicarbazone distribution list, smallpox vaccine manufacturers complication reporting files, state reports to the Encephalitis Surveillance Unit of the National Communicable Disease Center (NCDC), and specimen submissions for vaccinia testing to the Viral Exanthems Unit of NCDC.
++ Case sources include: Physician reporting via survey in 10 states with active case information follow-up and chart review for post-vaccinial encephalitis and vaccinia necrosum (progressive vaccinia) reports.

Cases among young children in 1968 were due to congenital immune deficiency, the condition only being identified when their vaccinial infection failed to heal.

Adults experienced progressive vaccinia almost always as a result of an immunosuppressive disease (e.g. leukemia, lymphoma). Those who experienced progressive vaccinia secondary to immunosuppressive therapy generally had a milder form of the disease, which was often treatable.

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Susceptible individuals today include those with the conditions in the accompanying table:

Susceptible Populations

Condition	Size of the Population
Immunodeficiency (congenital or acquired, particularly of cell-mediated immunity; although antibody-deficient individuals may also be at some risk)	Unknown
HIV or AIDS (it is not known if susceptibility correlates with T-cell counts)	900,000
Cancer (particularly those that impair cell-mediated immune function such as lymphomas, leukemia and lymphosarcomas)	Approx. 8 million
Organ transplantation with immunosuppressive therapy	184,000 (US)
High dose corticosteroid treatment (a variety of diseases are treated with high doses of corticosteroids)	Unknown
Other immunosuppressive therapy (patients with a variety of disease that require immunosuppressive therapy of a type that suppresses cell-mediated immune function)	Unknown

Progressive vaccinia occurs because of an immune defect in the vaccinated individual or in a susceptible contact of a vaccinee.

Nearly all instances have been in those with a defined cell-mediated immune (CMI) defect (T-cell deficiency).

In patients with CMI deficiency but intact antibody (B-cell) function, progressive vaccinia occurs, but is a less extensive disease, often limited to progression in the skin without viremic spread. In these latter patients, antibody presumably neutralizes virus in the blood preventing skin dissemination. Other subtypes of CMI deficiencies were not studied at the time progressive vaccinia was seen.

The virus multiplies by cell-to-cell spread at the primary vaccination site causing the lesion to expand circumferentially. Necrotic skin remains in the central lesion behind the advancing edge.

Virus gains entry into the blood at an early stage in patients with nearly totally deficient immune systems and implants in distant skin sites and in multiple organs. Secondary skin lesions follow the same pattern as the primary vaccination, each expanding in situ.

Local and systemic bacterial infection can ensue with progressive disease. Untreated or unsuccessfully treated patients succumb in what appears to be toxic or septic shock.

In addition to bacterial infections, patients with T-cell immunodeficiencies are also susceptible to fungal and parasitic infections. Patients with progressive vaccinia have had systemic fungal infections and *Pneumocystis carinii* infection during the course of their progressive viral disease.

Patients with antibody deficiency but intact cell-mediated immunity (e.g., Bruton-type hypogammaglobulinemia) usually underwent vaccination without incident, healing the local lesion as in normal individuals. The lesions often evolved in slower fashion, but did resolve in most. In one case, a patient with hypogammaglobulinemia of the Bruton-type who experienced progressive vaccinia after a mumps or mumps-like infection. It is likely that the viral infection

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depressed cell-mediated immunity and allowed a lingering vaccinia infection to become extensive. That patient survived only after massive surgical reduction of the vaccination masses and extensive treatment with VIG and other modalities available at the time. Reports in the literature of hypogammaglobulinemia and progressive vaccinia are clouded by the lack of immunologic understanding at the time that these patients were reported. Many probably had unknown or undiagnosed CMI deficiencies.

Death occurred in nearly all individuals with profound CMI defects. Some individuals survived when their immune function improved coincident with the withdrawal of immunosuppressive therapy or spontaneous improvement in their underlying disease. Aggressive administration of VIG then resulted in cures. Patients with milder degrees of depression of CMI responded to aggressive VIG therapy.

Evolution of Progressive Vaccinia

1.	Primary vaccination site does not heal.
2.	Lesion is • Ulcerative or • Vesiculo-pustular with central necrosis
3.	Lesion expands circumferentially with extensive necrosis
4.	Viremic or secondary inoculation lesions undergo same evolution with massive involvement
5.	Coalescent lesions cover large portions of body with extensive destruction of normal tissue
6.	Normally, there is no: • Lymphadenopathy, • Splenomegaly, or • Other signs of inflammatory response.
7.	If allowed to progress, patient may experience: • Toxic or septicemic shock/disseminated intravascular coagulation. • Superimposed systemic fungal symptoms. • Parasitic infection symptoms. • Bacterial infections, bacteremia, septicemia.
8.	If viable unmatched lymphocytes have been administered, graft-versus-host disease may occur, with splenomegaly, hepatomegaly, skin rash, DIC and signs of inflammatory response to vaccination sites.

Progressive vaccinia is diagnosed clinically by the typical appearance of the vaccination site. This disease is suspected in patients with underlying CMI defects.

Progressive Vaccinia Differential Diagnosis

Condition	Notes
Severe bacterial infection	Differentiate by: • Vigorous inflammatory response.

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	• Lack of history compatible with immune defect.
Severe cases of smallpox	Smallpox might be confused with progressive vaccinia in an individual who has been vaccinated and exposed
Severe chickenpox	Differentiate by: • Lack of a primary vaccination site. • If vaccinated, the character of the lesions (superficial vesicles, in varying stages, with typical distribution).
Disseminated herpes simplex infections	Differentiate by: • Lack of a primary vaccination site. • If vaccinated, the character of the lesions (superficial vesicles, in varying stages, with typical distribution).

Virologic and immunologic laboratory testing is **MANDATORY** and should be accomplished after consultation with CDC or Infectious disease of immunology experts with experience in complications of vaccination.

Rapid viral diagnostic tests can determine the exact etiologic agent, confirmed by more definitive testing later.

Aggressive use of Vaccinia Immune Globulin (VIG) is the mainstay of treatment for Progressive Vaccinia.

Managing Progressive Vaccinia

VIG	Massive doses of VIG are necessary to control viremia. Up to 10 ml per kg of intramuscular VIG has been used. Plasma from recently vaccinated donors, irradiated blood, and platelet infusions has occasionally been administered. A few patients received exchange transfusions in an effort to supply immunologic factors as well as to counteract anemia and the metabolic defects resulting from organ failure. Caution: Graft-versus-host disease must be avoided. Viable lymphocytes, even from a single unit of blood, can cause GVHD in patients with profound CMI defects.
Surgery followed by VIG	Surgical removal of massive lesions has been performed to reduce viral mass. In a few patients, this has been the turning point in treatment after which VIG administration resulted in eventual cure.
Antiviral therapy	There is no proven antiviral therapy. Preliminary studies with cidofovir show some effect in vitro; studies in animals are pending. Immediate consultation with the CDC is recommended to determine if any experimental antiviral drugs are available.
Future Therapy	In the future, therapy might include immunologic replacement, provided graft-versus-host disease can be eliminated or minimized.

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Bacterial, Fungal or Parasitic Superinfections – Patients with bacterial, fungal or parasitic superinfections should receive appropriate antimicrobial therapy.

Toxic or Septic Shock – Patients with toxic or septic shock should receive current intensive care and appropriate toxic or septic shock therapy.

The exact cause for death from smallpox and certain life-threatening complications of vaccination is uncertain. Symptom complexes characteristic of toxic or septic shock were observed in the 1960s and before, but little could be done to counteract the symptoms with the modalities available in those times. Other patients appeared to suffer hemorrhagic complications that were characteristic of Disseminated Intravascular Coagulation (DIC). Again, little could be done as therapy for this condition was in its infancy.

Significant gain in decreased morbidity and prevention of mortality could result from aggressive application of modern intensive-care level of treatment. Every effort should be made to apply such modalities to patients with complications of vaccination that appear to have as a component toxic or septic shock, or DIC.

This section is not meant as a definitive guide to the diagnosis and treatment of these shock conditions, but to serve as a reminder that a major effort should be made in seriously ill patients with complications of vaccination to apply the best modern technology and care to reduce morbidity and mortality.

Septic Shock

The symptom complex of the usually sudden onset of fever, chills, myalgias, and change in mental status (agitation, irritability, restlessness, delirium, confusion, or even stupor or coma) should lead to the diagnosis of septicemia. Tachycardia, tachypnea, hypotension establish impending or actual shock. End organ failure may supervene as evidenced by cyanosis (pulmonary), jaundice (hepatic), anuria (renal) and congestive heart failure (cardiac). With infection of the central nervous system, convulsions, meningeal signs and focal neurologic signs occur. Adult respiratory distress syndrome may intervene.

The laboratory findings include positive cultures from blood and other sites (in the case of vaccinia, virus or viral antigens may be detected), leukocytosis with shifts to the left, thrombocytopenia, hypoxemia, alterations in electrolytes, and reduction in serum concentrations of iron, glucose, and calcium. Hyperbilirubinemia will be seen in hepatic failure and signs of renal failure will be detected in the urine and by azotemia. Imaging studies may be necessary with pulmonary, central nervous system or abdominal findings.

Consultation with intensivists is strongly advised to establish the diagnosis and to institute appropriate ICU-level treatment.

Therapeutic Principles

First, use VIG aggressively to reduce the virus load and potentially to reduce circulating “toxins” of the virus or induced by the virus as it infects other sites from viremia. Having accomplished that, the principles of treatment include:

- Maintenance of vascular competence by adequate fluid replacement to ensure blood flow to vital organs.
- Use of vasopressors to support blood pressure.
- Maintenance of the airway and provision of adequate oxygenation.

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- Appropriate use of antimicrobial agents to treat potential and/or identified bacterial infection.
- Management of multiple organ failure.
- Treatment of congestive heart failure.
- Dialysis p.r.n.
- Use of agents to reduce intracranial pressure.
- Appropriate antibiotics if bacterial infection is present.
- Treatment of anemia, if present.
- Counteraction of toxin presence with appropriate anti-toxin medications, as available at the time (e.g. anti-endotoxin antibody, anti-tumor necrosis factor).

In effect, a major intensive care effort should be undertaken in consultation with appropriate specialists.

Disseminated Intravascular Coagulation (DIC)

Hemorrhagic forms of smallpox and in some cases, progressive vaccinia may engender consumption of coagulation factors. Fibrinolytic activity increases, pro-coagulants are activated, hematologic inhibitors are consumed, platelets decrease, often dramatically, and ultimately end-organ failure supervenes. Both acute DIC and chronic forms have been described. Tissue injury, probably directly caused by virus, or by viral antigens, results in endothelial damage, releasing procoagulant materials that start the cascade into DIC.

Generalized bleeding is the first sign of established DIC. Petechiae, skin hemorrhages, and massive bleeding may be observed. Thrombosis of small and large vessels follows with hypoperfusion of organs or frank infarction that result in end-organ damage in the kidneys, liver and other vital organs. Shock, as described above, occurs rapidly. In the chronic forms, a slower process is observed, characterized mainly by subacute bleeding and diffuse evidence for microthrombosis.

Fibrin split products may be detected in laboratory testing; elevated levels are present in almost all patients. The presence of D-dimer is the most definitive test for DIC. Antithrombin III, platelets and fibrinogen are all decreased. The coagulation profile may be disordered, but consistent findings are not always present. Anemia, azotemia, elevated liver enzymes, decrease in specific coagulation factors, hemoglobinuria, hematuria, and hematochezia may be detected. Clinical symptoms and signs should guide imaging studies.

All life-threatening symptoms or signs should be counteracted by appropriate life-support measures as described for septic shock. Specific measures for DIC include:

- Anticoagulant therapy.
- Blood product replacement.
- Correction of anemia.
- Platelet replacement.
- Use of fresh frozen plasma and cryoprecipitate to replace coagulation factors.
- Administration of antithrombin III concentrate.

Immediate consultation with a hematologist and intensivist is mandatory to ensure that modern methods of diagnosis and treatment are provided to the patient.

In the absence of smallpox, patients with T-cell abnormalities should not receive smallpox vaccine. Not all patients suffering from immune defects, cancer, HIV or receiving immunosuppressive therapy are T-cell deficient. Consultation with an immunologist is advised for

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patients in these categories, but prudence would dictate they not receive vaccine in non-emergent situations. Patients in these categories should also be cautioned not to come in contact with vaccinated individuals.

If a smallpox outbreak occurs, the ACIP and CDC have recommended that all patients in these categories that have been exposed to smallpox be vaccinated. That recommendation is likely to be reviewed as deliberations about smallpox vaccine policy continue. For further information, please visit the Advisory Committee on Immunization Practice (ACIP) web site and the CDC Public Health Emergency Preparedness & Response Smallpox web site.

An appropriate history suggestive of T-cell immunodeficiency, either on a congenital basis or secondary to some other disease or treatment identifies a person as potentially susceptible to progressive vaccinia.

The following areas should be explored with the potential vaccinee. These potential susceptibilities apply to the vaccine and his/her contacts.

Potential Susceptibiities

Condition	Notes
Immunodeficiency, congenital or acquired	Is there a known immunodeficiency, congenital or acquired? • Family history • History of prior infections compatible with CMI deficiency
Disease associated with immunodeficiency	• HIV • AIDS • Many cancers
Immunosuppressive therapy	Is the patient or the contact receiving any immunosuppressive therapy? • For cancer • For maintenance of an organ or other transplant • Steroid therapy equivalent to 2mgm per kg of prednisone daily • For any disorder that requires the use of immunosuppressive therapy, especially that which reduces T-cell immune function

Vaccinia Keratitis

Lesions of the cornea secondary to implantation of vaccinia are potentially threatening to eyesight. Corneal abrasion, ulceration and subsequent clouding may result in significantly impaired vision.

The frequency of vaccinia keratitis is unknown. From the experience of those who cared for patients with vaccinia keratitis and from published reports, it is not a common occurrence.

There are two categories of susceptible persons:

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1. Those with pre-existing eye disease
2. Those who have normal eyes

In both cases, the transfer of vaccinia virus from the hands to the eyes can result in keratitis. Those with pre-existing eye disease, particularly inflammatory diseases of the lids, conjunctiva and cornea, are particularly prone to implantation from contact with contaminated hands. Caretakers who bath or otherwise handle children with vaccinations are the most likely to experience such transfer.

Vaccinia virus can be implanted to diseased or injured onjunctiva and cornea resulting initially in viral replication with ulceration and ultimately in an antigen-antibody interaction leading to corneal cloudiness. Ten days after transfer the clinical signs of infection appear.

Untreated there may be considerable scarring as the lesion heals with significant impairment of vision.

VIG is contraindicated for use in vaccinial keratitis. If VIG is administered, an antigen-antibody reaction is accentuated in the cornea and may result in significantly more cloudiness than in the normal health process.

One week to 10 days after implantation, a central, grayish, disciform corneal lesion can be seen. (Often there are accompanying or preceding palpebral or peri-orbital vaccinations). With periorbital or mucosal involvement there may be considerable pruritus, leading to further rubbing of the eye and continued spread of the virus.

Slit-lamp examination is best for defining the early stages, as well as following the course of disease and response to treatment. As the infection progresses a deep ring-like lesion appears in the cornea. There may be uveal involvement and Descemet's membrane may be infected. In some instances, more distal parts of the cornea may be involved. The corneal lesions appear crater-like and are indurated, edematous and infiltrated.

A late manifestation, occurring as a result of natural healing, or because of the administration of VIG (which is contraindicated), is extensive cloudiness in the region of the original lesion.

Consultation with an experienced ophthalmologist is strongly recommended. Slit-lamp examination provides more definitive information of the anterior segments of the eye than does usual ophthalmoscopic study.

Diagnosis is made on the basis of typical clinical findings. Usually it is not necessary to undertake viral studies, unless there is confusion with herpes virus keratitis or some other eye disease.

Topical antiviral agents are the treatment of choice. The best agent to use should be determined in immediate consultation with an experienced ophthalmologist. Current information suggests that a combination of an antiviral nucleotide and interferon topically speeds healing. Agents such as vidarabine, trifluridine or acyclovir have been used. Some ophthalmologists recommend concurrent debridement or other physical or physicochemical methods of treatment, but these methods have not been adequately investigated to make firm recommendations.

VIG should NOT be used in vaccinia keratitis. There is some evidence in humans and animal models that more extensive corneal clouding can occur following VIG therapy.

The only effective preventive measures are:

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- Avoidance of vaccination in individuals with inflammatory eye or periorbital disease.
- Careful instruction to vaccinees and contacts of vaccinees about the necessity to avoid touching, rubbing or otherwise performing any maneuvers that might transfer vaccinia virus from a vaccination site to the eye or surrounding skin.

Benefit of Vaccine Following Exposure to Smallpox

Vaccination within 3 days of exposure will completely prevent or significantly modify smallpox in the vast majority of persons. Vaccination 4 to 7 days after exposure will also likely offer some protection from disease or modify the severity of disease.

After the events of September and October 2001, the U.S. government took further actions to improve its level of preparedness against terrorism. One of many such measures – designed specifically to prepare for an intentional release of the smallpox virus - included updating and releasing a smallpox response plan. In addition, the U.S. government ordered production of enough smallpox vaccine to immunize the American public in the event of a smallpox outbreak.

Strategic National Stockpile

An act of terrorism targeting the U.S. civilian population will require rapid access to large quantities of pharmaceuticals and medical supplies. It is not generally possible to anticipate exactly where a terrorist will strike and few state or local governments have the resources to create sufficient stockpiles on their own. Therefore a national stockpile has been created as a resource for all (CDC, 2003c).

In 1999 Congress charged the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) with the establishment of the National Pharmaceutical Stockpile (NPS). The mission was to provide a re-supply of large quantities of essential medical materiel to states and communities during an emergency within twelve hours of the federal decision to deploy (CDC, 2003c).

The Homeland Security Act of 2002 tasked the Department of Homeland Security (DHS) with defining the goals and performance requirements of the Program as well as managing the actual deployment of assets. Effective on March 1, 2003, the NPS became the Strategic National Stockpile (SNS) managed jointly by DHS and HHS (CDC, 2003c).

The SNS is a national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, IV administration, airway maintenance supplies, and medical/surgical items. The SNS is designed to supplement and re-supply state and local public health agencies in the event of a national emergency anywhere and at anytime within the U.S. or its territories (CDC, 2003c).

The SNS is organized for flexible response. The first line of support lies within the immediate response 12-hour Push Packages. These are caches of pharmaceuticals, antidotes, and medical supplies designed to provide rapid delivery of a broad spectrum of assets for an ill defined threat in the early hours of an event. These Push Packages are positioned in strategically located, secure warehouses ready for immediate deployment to a designated site within 12 hours of the federal decision to deploy SNS assets (CDC, 2003c).

If the incident requires additional pharmaceuticals and/or medical supplies, follow-on vendor managed inventory (VMI) supplies will be shipped to arrive within 24 to 36 hours. If the agent is well defined, VMI can be tailored to provide pharmaceuticals, supplies and/or products specific to the suspected or confirmed agent(s). In this case, the VMI could act as the first option for immediate response from the SNS (CDC, 2003c).

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The SNS has developed protocols to allow for the rapid, simultaneous delivery of smallpox vaccine to every state and US territory within 12-24 hours. State and local bioterrorism response plans should provide for the rapid distribution of vaccine within their jurisdiction. For information on New York State's bioterrorism response plans visit their Web site at http://www.health.state.ny.us/nysdoh/bt/bt.htm.

According to the National Immunization Program (NIP) (2001), any vaccination strategy for containing a smallpox outbreak should utilize the ring vaccination concept. This includes isolation of confirmed and suspected smallpox cases with tracing, vaccination and close surveillance of contacts to these cases as well as vaccination of the household contacts of the contacts. Vaccinating and monitoring a "ring" of people around each case and contact will help to protect those at the greatest risk for contracting the disease as well as form a buffer of immune individuals to prevent the spread of disease.

In a smallpox outbreak, the following are considered high risk groups and should be prioritized for vaccination (NIP, 2001):

- Face to face close contacts (6.5 feet or less).
- Persons exposed to the initial release of the virus (if the release was discovered during the first generation of cases and vaccination may still provide benefit).
- Household members of contacts to smallpox patients.
- Persons involved in the direct medical care, public health evaluation or transportation of confirmed or suspected smallpox patients.
- Laboratory personnel involved in the collection and/or processing of clinical specimens.
- Other persons with a high likelihood of exposure to infectious materials, such as those responsible for hospital waste disposal and disinfection.
- Personnel involved in contact tracing and vaccination, or quarantine/isolation or enforcement.
- Persons permitted to enter any facility designated for the evaluation, treatment, or isolation of smallpox patients (only essential personnel should be allowed to enter such facilities).

Anyone exposed to the variola virus should be vaccinated or revaccinated immediately. Intradermal inoculation of the smallpox vaccine, preferably within four days after exposure, may prevent or ameliorate disease (CDC, 2001d).

While vaccination in a pre-event smallpox situation is contraindicated for those previously mentioned, there are no absolute contraindications to post-exposure vaccination of a person who experiences bona fide exposure to variola.

Concomitant VIG is recommended for pregnant and eczematous persons and is generally indicated for treatment of complications to the smallpox vaccine (NIP, 2001).

Immunity

Both antibody and cell-mediated immunity result from successful vaccination; greater than 95% of primary vaccines have detectable neutralizing antibody at a titer of 1:10 or more within 1-2 weeks following immunization.

Evidence for a brisk cell-mediated immune response has also been detected. It is believed that healing of the vaccinia infection is associated with intact cell-mediated or T-cell and cytokine immune competence, and that viremia is defended by an intact antibody or B-cell immune competence.

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Protection against disease following primary vaccination begins to fade after 5 years and is probably negligible after 20 years. In individuals who have been successfully revaccinated one or more times, it has been found that residual immunity may persist for 30 years or longer.

Past experience indicates that the first dose of the vaccine offers protection from smallpox for three to five years, and sometimes as long as 10 years or more. If a person is vaccinated again later, immunity lasts even longer. Historically, the vaccine has been effective in preventing smallpox infection in 95 percent of those vaccinated. In addition, the vaccine was proven to prevent or severely lessen infection when given within a few days of exposure. It is important to note, however, that at the time when the smallpox vaccine was used to eradicate the disease, testing was not as advanced or precise as it is today, so there may still be things to learn about the vaccine and its effectiveness and length of protection.

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Part IV. Role of Healthcare Providers in the Pre-event Smallpox Preparedness

The CDC has developed Emergency Preparedness Competencies that are applicable for all public health workers. In addition, there are specific competencies for leaders/administrators, professionals and technical and support staff. Healthcare professionals such as nurses, regardless of their current practice setting will be focused on the public health in the event of an intentional release of smallpox.

The Emergency Preparedness Competencies for professionals include:

- Demonstrate readiness to apply professional skills to a range of emergency situations during regular drills. (For example: access, use and interpret surveillance data; access and use lab resources; access and use science-based investigation and risk assessment protocols; identify and use appropriate personal protective equipment.)

- Maintain regular communication with partner professionals in other agencies involved in emergency response. (This includes contributing to effective community-wide response through leadership, team building, negotiation and conflict resolution.)

- Participate in continuing education to maintain up to date knowledge in areas relevant to emergency response. (For example: emerging infectious diseases, hazardous materials, and diagnostic tests, as well as taking this course.)

In September 2002 the CDC issued the *Smallpox Response Plan and Guidelines*. This is a document that outlines pre and post-event activities that need to be undertaken in response to a smallpox emergency. These activities include:

Surveillance and Epidemiological Investigations:

- Pre-event rash surveillance
- Smallpox clinical presentations and differential diagnosis guidelines
- Smallpox case definitions
- Notification procedures for suspected smallpox cases
- Case and outbreak investigations

General Vaccination activities:

- CDC vaccine deployment
- Clinic vaccination procedures and adverse event reporting
- Rapid identification and vaccination of all priority groups (non-contact and contact)
- Evaluation of vaccine responses (takes) with revaccination when needed
- Recognition and treatment of vaccine adverse events
- Decontamination guidelines
- Monitoring of vaccine utilization and supplies

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Quarantine/Isolation related activities:

- Fever/rash surveillance and education of contacts (vaccinated and unvaccinated)
- Isolation and care of smallpox patients during the infectious period
- Quarantine guidelines and considerations

Surveillance activities:

- Identification and reporting of suspected smallpox cases through active surveillance at the local, state, national, and international levels
- Surveillance of vaccine adverse events

Epidemiology:

- Epidemiological investigation of the outbreak to determine at-risk populations (contacts), source of outbreak, and risk factors for illness
- Specimen collection and transportation guidelines

Public/Media Communications:

- Communications principles and guidelines
- Pre-event communication education and information
- Smallpox emergency communication operations and activities

These interrelated, multifaceted activities are discussed in the document and the reader is urged to consult the CDC website at http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp#annex. This plan identifies and provides examples of many of the specific activities, forms, and procedures that should be followed in preparation for and in response to a smallpox emergency.

It is important to remember that the *CDC Smallpox Response Plan and Guidelines* is a draft document that will be updated as needed to reflect changes in capacities and resources for responding to a smallpox emergency. Public health authorities will be notified when updated drafts are available.

Vaccination of Smallpox Vaccinators

Part of the CDC *Smallpox Response Plan and Guidelines* were guidelines for state or local public health agencies to address:

1. Establishment of an Executive Planning Committee, including identification and involvement of key partners, stakeholders, and local elected officials.
2. Command, control, and management procedures.
3. Mobilization of necessary staff, resources, and their availability.
4. Surveillance and epidemiologic investigation procedures, including contact identification and tracing; vaccination of contacts; mobilizing laboratory resources; and alerting and training of health care providers about the identification and reporting of suspected cases of smallpox.
5. Vaccine management, including storage, distribution, protection procedures, and vaccination of essential personnel.
6. Adverse events monitoring.
7. Legal powers for quarantine and selection of isolation sites and plans for how they will be used.

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8. Decontamination of smallpox-contaminated equipment, waste, rooms, and vehicles.
9. Plans for communications with healthcare providers, the public and the media.
10. Training identified healthcare staff and other first responders (e.g., police and firemen) for outbreak control.
11. Establishment of security procedures in conjunction with local police and other law enforcement agencies, including operational procedures for essential functions including the maintenance of essential systems such as water, electricity, and waste disposal.

Smallpox Response Teams

This *Smallpox Response Plan* includes the creation of preparedness teams on the state and local level that are ready to respond to a smallpox attack on the United States (NYSDOH, 2003). Members of these teams - healthcare and public health workers - are being vaccinated so that they might safely protect others in the event of a smallpox outbreak (NYSDOH, 2003).

Smallpox vaccination is recommended for persons designated by appropriate terrorism and public health authorities to conduct investigations and follow-up of initial smallpox cases that might necessitate direct patient contact. Additionally, persons responsible for administering smallpox vaccine in the pre-event vaccination program should be vaccinated. The Advisory Committee on Immunization Practices (ACIP) (Wharton et al., 2003) recommends that persons who will be handling and administering smallpox vaccine in the proposed pre-event smallpox vaccination program be vaccinated in order to minimize the clinical impact of inadvertent inoculation, should it occur. Vaccination of this group will also contribute to preparedness for smallpox response, should a smallpox release occur, with development of a cadre of vaccinated, experienced vaccinators who could immediately be deployed for outbreak response.

To enhance public health preparedness and response for smallpox control, specific teams at the federal, state, and local levels have been established to facilitate diagnostic evaluation of initial suspected cases of smallpox and to initiate control measures. These smallpox response teams might include persons designated as medical team leaders, public health advisors, medical epidemiologists, disease investigators, diagnostic laboratory scientists, nurses, personnel who could administer smallpox vaccines, security or law enforcement personnel, and other medical personnel to assist in evaluating suspected smallpox cases. ACIP recommends that each state and territory establish and maintain one or more smallpox response teams. Considerations for additional teams should include population and geographic concerns, and should be developed in accordance with federal, state, and local terrorism-response plans.

This first phase of the *Smallpox Response Plan* was initiated in 2003 with the immunization of volunteer healthcare providers. This has been a controversial issue, with fewer healthcare providers volunteering to be immunized and some healthcare facilities refusing to offer the vaccine to employees. It was expected that 500,000 healthcare providers be immunized in this phase, however only approximately 40,000 have been immunized (Connelly, 2003). APIC recommended against expanding the immunization to include first responders due to the occurrence of cardiac complications among some of those who were immunized. These cardiac issues also prompted the warning, at least temporarily, to exclude persons who had diagnosed cardiac problems from receiving the smallpox vaccination.

Smallpox Healthcare Teams

ACIP and HICPAC (Wharton et al., 2003) recommended that in the first stages of the response plan, smallpox healthcare teams be identified. The size and composition of smallpox healthcare teams will vary according to the institutions and their patient populations, but each hospital should ideally have enough vaccinated personnel from each occupational category to ensure continuity of care. Pre-event smallpox vaccination of these smallpox healthcare team would be a component of the response plan. When feasible, the first-stage vaccination program should

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include previously vaccinated healthcare personnel to further decrease the potential for adverse events, because adverse events occur less commonly among previously vaccinated persons.

Each acute care hospital should also identify a group of healthcare workers who would be vaccinated and trained to provide in-room medical care for the first few smallpox patients requiring hospital admission and to evaluate and manage patients who present to the Emergency Department with suspected smallpox. For the first 7-10 days after patients with smallpox have been identified, this team would be hospital-based and provide care 24 hours a day, using 8-12 hour shifts. Non-essential workers would be restricted from entering into the rooms of patients with smallpox.

The ACIP and HICPAC (Wharton et al., 2003) recommends that Smallpox Healthcare Teams include:

1. Emergency Room Staff, including both physicians and nurses.
2. Intensive Care Unit staff, including physicians, nurses, and in hospitals that care for infants and children, this encompasses pediatricians, pediatric intensivists, and pediatric emergency room physicians and nurses.
3. General Medical Unit staff, including physicians, internists, pediatricians, obstetricians, and family physicians in institutions where these individuals are the essential providers of primary medical care.
4. Medical house staff (i.e., selected medical, pediatric, obstetric, and family physicians).
5. Medical subspecialists including infectious disease specialists may also involve the creation of regional teams of subspecialists, such as local medical consultants with smallpox experience, dermatologists, ophthalmologists, pathologists, surgeons, anesthesiologists in facilities where intensivists are not trained in anesthesia. These regional teams would deliver consultative services.
6. Infection control professionals (ICPs).
7. Respiratory therapists.
8. Radiology technicians.
9. Security personnel.
10. Housekeeping staff (e.g., those staff involved in maintaining the health care environment and decreasing the risk of fomite transmission).

Overall, each Smallpox Healthcare Team might include about 15 emergency room doctors and nurses, 15 intensive care unit doctors and nurses, and a total of 10-15 personnel from the other areas. It is anticipated that the size and composition of a smallpox medical care team will vary according to the individual institutions and their patient populations. Each hospital should have enough teams to ensure continuity of care. Smallpox vaccination would be voluntary.

Adherence to Infection Control Recommendations

Healthcare workers must adhere to infection control recommendations this includes topics such as vaccination site care, precautions and hand hygiene.

Following smallpox vaccination, ACIP and HICPAC (Wharton et al., 2003) recommends that healthcare workers involved in direct patient care should keep their vaccination sites covered with gauze or a similar absorbent material in order to absorb exudates that would develop. This dressing should, in turn, be covered with a semi-permeable dressing to provide a barrier to vaccinia virus. Use of a semi-permeable dressing alone could cause maceration of the vaccination site as well as increased prolonged irritation and itching at the site, thereby increasing touching, scratching and contamination of the hands.

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Products combining an absorbent base with an overlying semi-permeable layer can be used to cover the vaccination site. The vaccination site should be covered during direct patient care until the scab separates.

Vaccinia is generally transmitted by direct person-to-person and close contact (within 6 feet), and infection control precautions should be taken to reduce this likelihood. The most critical measure in preventing inadvertent implantation and contact transmission from the vaccinia vaccination site is thorough hand-hygiene after changing the bandage or after any other contact with the vaccination site. Hospitals should include a site-care component to their smallpox vaccination programs in which designated, vaccinated staff would assess dressings for all vaccinated healthcare workers daily (whether involved in direct patient care or in other duties), determine if dressings needed changing, and then change the dressing if indicated. This designated staff would assess the vaccination site for local reactions and for vaccine take. They should also use the opportunity to reinforce messages to vaccinees about the need for meticulous hand-hygiene.

Transmission of vaccinia is also a concern in other settings when close personal contact with children or other persons is likely—for example, parenting of infants and young children. In these situations, the vaccination site should be covered with gauze or a similar absorbent material, and a shirt or other clothing should be worn, and careful attention to hand hygiene (hand washing) practiced.

Administrative Leave for Vaccinated Healthcare Workers

Administrative leave is not required routinely for newly vaccinated healthcare personnel unless they:

1) are physically unable to work because of systemic signs and symptoms of illness;

2) have extensive skin lesions that cannot be covered adequately; or

3) are unable to adhere to the recommended infection-control precautions.

The close contact required for transmission of vaccinia to household contacts is unlikely to occur in the healthcare setting.

ACIP and HICPAC (2003) recommended that vaccination of Smallpox Healthcare Team members be phased in, starting with a small number of hospitals. Within a single institution, it would be prudent to designate a small proportion, e.g. 20-30% of the candidate healthcare workers, for the first phase of vaccinations to allow institutions to gain experience in post-vaccination management. The ACIP recognizes that the incidence of adverse events following vaccination of previously vaccinated persons is substantially less than in primary vaccinees, and therefore recommends that when feasible, previously vaccinated healthcare workers be included in this stage 1 vaccination program. It is also advisable to stagger vaccination of healthcare workers within an individual patient care unit by three weeks in order to minimize the number of vaccinated individuals who would be on sick leave concurrently in association with systemic effects of the vaccine, which usually occur at days 8-10 after inoculation.

In addition to care of the site of vaccination, healthcare workers must utilize consistent performance of hand hygiene before and after each patient contact and after touching vaccination sites and handling dressing materials. The CDC issued updated Guidelines for Hand Hygiene in Healthcare Settings – 2002 (Boyce & Pittet, 2002). This guideline focuses on the use of alcohol-based antiseptic handrubs and antimicrobial soaps. Although not entirely abandoning soap and

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water, the CDC identified the use of alcohol based products with a 60-90% concentration as having a 4+ ranking ("excellent") against viruses. Additionally, they are fast acting.

Hand-hygiene technique (Boyce & Pittet, 2002):

1. When decontaminating hands with an alcohol-based hand rub, apply product to palm of one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry. Follow the manufacturer's recommendations regarding the volume of product to use.
2. When washing hands with soap and water, wet hands first with water, apply an amount of product recommended by the manufacturer to hands, and rub hands together vigorously for at least 15 seconds, covering all surfaces of the hands and fingers. Rinse hands with water and dry thoroughly with a disposable towel. Use towel to turn off the faucet. Avoid using hot water, because repeated exposure to hot water may increase the risk of dermatitis.
3. Liquid, bar, leaflet or powdered forms of plain soap are acceptable when washing hands with a non-antimicrobial soap and water. When bar soap is used, soap racks that facilitate drainage and small bars of soap should be used.
4. Multiple-use cloth towels of the hanging or roll type are not recommended for use in healthcare settings.

In the pre-smallpox vaccination process, there will be no known smallpox virus in the environment, so there is no threat of smallpox infection. However, healthcare providers who will be immunizing others with the vaccinia vaccine need to follow standard precautions during the immunization process. Other than standard precautions, during the pre-smallpox phase, no specific infection control precautions need be utilized.

<u>In the Event of a Case of Smallpox</u>

However, in a smallpox outbreak significant precautions must be utilized. Symptomatic patients with suspected or confirmed smallpox should be managed according to current guidelines (these are outside the scope of this course). Healthcare workers must utilize airborne, contact and standard precautions when coming into contact with suspected or confirmed smallpox.

Standard Precautions:

- Wash hands after patient contact.
- Wear gloves when touching blood, body fluids, secretions, excretions and contaminated items.
- Wear a mask and eye protection, or a face shield during procedures likely to generate splashes or sprays of blood, body fluids, secretions or excretions
- Handle used patient-care equipment and linen in a manner that prevents the transfer of microorganisms to people or equipment.
- Use care when handling sharps and use a mouthpiece or other ventilation device as an alternative to mouth-to-mouth resuscitation when practical.
- <u>Standard precautions are employed in the care of ALL patients</u>

Airborne Precautions:

- Airborne Precautions are used for patients known or suspected to be infected with microorganisms transmitted by airborne droplet nuclei (small particle residue, 5μ or smaller in size) of evaporated droplets containing microorganisms that can remain suspended in air and can be widely dispersed by air currents. Airborne precautions require the healthcare providers and others to wear respiratory protection when entering

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the patient room. The appropriate respiratory protection is based on facility selection policy and must meet the minimal NIOSH standard for particulate respirators, N95.

Standard Precautions plus:

- Place the patient in a private room that has monitored negative air pressure, a minimum of six complete air exchanges/hour, and appropriate filtration of air before it is discharged from the room.
- Wear respiratory protection when entering the room.
- Limit movement and transport of the patient. Place a mask on the patient if they need to be moved.

Contact Precautions:

Contact precautions are used for patients known or suspected to be infected or colonized with epidemiologically important organisms that can be transmitted by direct contact with the patient or indirect contact with potentially contaminated surfaces in the patient's care area. Contact precautions require healthcare providers and others to:

- Wear clean gloves upon entry into the patient room.
- Wear a gown for all patient contact and for all contact with the patient's environment. Based on local infection control policy, some healthcare facilities require a gown to be worn to enter the room of any patient on Contact Precautions. Gowns must be removed before leaving the patient's room.
- Wash hands using an antimicrobial agent.

Standard Precautions plus:

- Place the patient in a private room or cohort them with someone with the same infection if possible.
- Wear gloves when entering the room. Change gloves after contact with infective material.
- Wear a gown when entering the room if contact with a patient is anticipated or if the patient has diarrhea, a colostomy or wound drainage not covered by a dressing.
- Limit the movement or transport of the patient from the room.
- Ensure that patient-care items, bedside equipment, and frequently touched surfaces receive daily cleaning.
- Dedicate use of noncritical patient-care equipment (such as stethoscopes) to a single patient, or cohort of patients with the same pathogen. If not feasible, adequate disinfection between patients is necessary.

<u>Decontamination Guidelines</u>

Only vaccinated personnel should perform the following decontamination procedures. Protective clothing including gowns, gloves, shoe covers, caps and masks should be worn. Although it is not considered a common mode of transmission during the smallpox era, infection with smallpox via contaminated bedding or fomites did occur rarely. Ideally, all disposable protective clothing worn by decontamination personnel should be place in biohazard bags and autoclaved or incinerated before disposal. However, if needed because of shortages of protective clothing, reuseable protective clothing that can be laundered may be transported to the laundry in biohazard bags, then laundered using hot water (71° C) and bleach according to the standard proportions recommended by the manufacturer. The contaminated clothing should be wetted before sorting by laundry personnel as this should help prevent the aerosolization of contaminated particles during sorting). Reuseable materials should be laundered on site and all

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personnel handling laundry must be recently vaccinated (within 3 years). Decontamination personnel should immediately shower with soap and water after the contaminated protective clothing is removed.

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Conclusion

The possibility of smallpox used as a weapon of terror is a very frightening prospect. Preparations for response to the deliberate use of smallpox as a bioweapon, or for the likelihood of mass vaccination of the US population, prior to a smallpox outbreak, will require tremendous effort on the part of healthcare providers. Rapid identification of symptoms characteristic to smallpox, distinguishing smallpox from other rash illnesses and immediate treatment and reporting of possible smallpox is critical. Equally important is knowledge regarding the smallpox vaccine, including contraindications for its use, the procedure for vaccination, possible adverse reactions and their treatment.

Healthcare providers will play a significant role in the event of a smallpox outbreak. The health of the population rests with knowledgeable providers who can provide the best available information and care.

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Appendix A – Worksheet: Evaluating Patients for Smallpox

http://www.bt.cdc.gov/agent/smallpox/diagnosis/index.asp#diagnosis

WORKSHEET: EVALUATING PATIENTS FOR SMALLPOX

Identification Number _____
Person Completing Form _____
Date of Contact with Case _____
Today's Date (mo/da/yr) _____

PATIENT INFORMATION

Name:
LAST FIRST MIDDLE INITIAL

Date of Birth: ___/___/___ **Age:** ___ **Sex:** ☐ Male ☐ Female

Telephone:
Home _____ Other _____

Address: _____
CITY STATE ZIP

Where is the patient now? ☐ Home ☐ Doctor's Office
☐ Emergency Room *(if checked, continue below)*
☐ Hospital *(if checked, continue below)*
☐ Other *(specify)* _____

Hospital Name _____
City/State _____
Admission Date ___/___/___ Discharge Date ___/___/___
Hospital Telephone Number ( ) _____

Race: ☐ White ☐ Black ☐ Asian ☐ Other **Ethnicity:** ☐ Hispanic ☐ Non-Hispanic **Country of Birth:** _____

PROVIDER INFORMATION

Name: _____
Patient Population: ☐ Adult ☐ Peds ☐ Both
Specialty: _____
Telephone:
Type _____ ( ) _____
Type _____ ( ) _____
E-mail Address: _____

Name: _____
Patient Population: ☐ Adult ☐ Peds ☐ Both
Specialty: _____
Telephone:
Type _____ ( ) _____
Type _____ ( ) _____
E-mail Address: _____

CLINICAL INFORMATION

PRODROME / SYMPTOMS 1-4 DAYS BEFORE RASH ONSET

Did the patient have a fever and other illness 1-4 days before rash onset? ☐ Yes ☐ No ☐ Unknown

Date of prodrome onset ___/___/ 200__

Date of first fever ≥101° F: ___/___/___

What was the highest temperature? _____ °F or _____ °C

On what date? ___/___/___

Check all features of the prodrome that apply:
☐ No/Mild prodrome (<1 day)
☐ Headache
☐ Backache
☐ Chills
☐ Vomiting
☐ Abdominal pain
☐ Sore throat*
☐ Other *(specify)* _____

*In infants, this may manifest as drooling or refusing to eat or drink.

Was the patient toxic or seriously ill? ☐ Yes ☐ No ☐ Unknown

Was the patient able to do most normal activities? ☐ Yes ☐ No ☐ Unknown

RASH

Date of rash onset ___/___/ 200__

Was the rash acute (sudden) in onset? ☐ Yes ☐ No ☐ Unknown

Was a black scar (eschar) present before or at the time of appearance of the rash? ☐ Yes ☐ No ☐ Unknown

Is the rash *generalized* (i.e., multiple parts of the body) or *focal* (i.e., only one part of the body)? ☐ Generalized ☐ Focal

Where on the body were the first lesions noted?
☐ Face
☐ Trunk
☐ Inside the mouth
☐ Other *(specify)* _____
☐ Arms
☐ Legs
☐ Unknown

Since rash onset, where on the body was the rash most dense?
☐ Trunk
☐ Face or scalp
☐ Distal extremities (arms, legs)
☐ Equally distributed everywhere
☐ Other *(describe)* _____

Are there any lesions on the palms or soles? ☐ Yes ☐ No ☐ Unknown

What kind of lesions does the patient have now? *(check all that apply)*
☐ Macules (flat spots)
☐ Papules (solid bumps)
☐ Vesicles (fluid-filled blisters)
☐ Pustules (blisters filled with pus)
☐ Crusts
☐ Other _____

If more than one kind of lesion, which kind of lesion is now the most common? _____

Are the lesions now:
☐ Superficial (on top of the skin)
☐ Deep (feel embedded deeply in the skin)
☐ Neither *(describe)* _____

How many lesions are present? (in total) _____

If no precise count is available, please estimate:
☐ <20
☐ 20-50 (able to count in less than a minute)
☐ 51-499 (typically an average case of varicella has 200-400 lesions)
☐ >500 (lesions confluent in some places, can't see normal skin between)

On any one part of the body (e.g., face or arm), are all the lesions in the same state of development? ☐ Yes ☐ No ☐ Unknown

How big are most of the lesions? *(Do not measure superinfected lesions.)*
☐ Small (1-5 mm)
☐ Large (5-10 mm)
☐ Neither *(describe)* _____

Have any lesions crusted? ☐ Yes ☐ No ☐ Unknown
If *Yes*, how many days did it take for the first lesions to crust? _____

How itchy is the rash? ☐ Not at all ☐ Somewhat ☐ Very ☐ Unknown

Does the patient have lymphadenopathy? ☐ Yes ☐ No ☐ Unknown
If *Yes*, describe: _____

Is the patient toxic or moribund now? ☐ Yes ☐ No ☐ Unknown
If *Yes*, describe: _____

Continues

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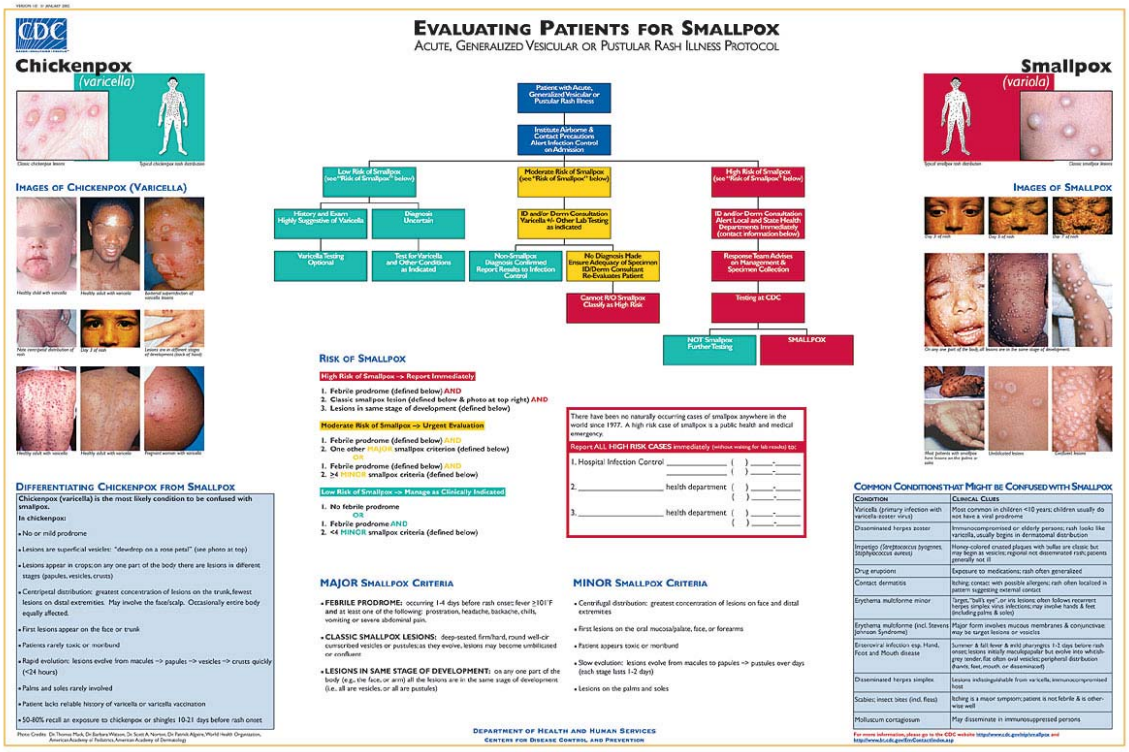
Appendix B – Poster: Evaluating Patients for Smallpox

http://www.bt.cdc.gov/agent/smallpox/diagnosis/evalposter.asp



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Appendix C

Patient Information: What to Do After You've Gotten the Smallpox Vaccine (CDC, 2003b)

The smallpox vaccine contains a **live** virus called vaccinia. After vaccination, this live virus is present at the vaccine site and can be spread to other parts of the body or to other individuals through contact. To avoid this, the vaccination site must be cared for carefully until the scab that forms after vaccination falls off on its own (in 2 to 3 weeks). Follow these instructions:

WHAT YOU SHOULD DO:

- ***Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep it in place.*** Keep it covered until the scab falls off on its own. This bandage will provide a barrier to protect against spread of the vaccinia virus. (When involved in direct patient care, healthcare workers should cover the gauze with a semipermeable (semiocclusive) dressing as an additional barrier. A semipermeable dressing is one that allows for the passage of air but does not allow for the passage of fluids.)

- *Wear a shirt that covers the vaccination site* **as an** *extra* **precaution to prevent spread of the vaccinia virus. This is particularly important in situations of close physical contact.**

- ***Change the bandage every 1 to 3 days.*** This will keep skin at the vaccination site from softening and wearing away.

- ***Wash hands with soap and hot water or with alcohol-based hand rubs such as gels or foams after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with virus from the vaccination site.*** This is vital in order to remove any virus from your hands and prevent contact spread.

- ***Keep the vaccination site dry.*** Cover the vaccination site with a waterproof bandage when you bathe. Remember to change back to the loose gauze bandage after bathing.

- ***Put the contaminated bandages in a sealed plastic bag and throw them away in the trash.***

- Keep a ***separate laundry hamper*** for clothing, towels, bedding or other items that may have come in direct contact with the vaccine site or drainage from the site.

- ***Wash clothing or other any material that comes in contact with the vaccination site***, using hot water with detergent and/or bleach. ***Wash hands afterwards.***

- When the scab falls off, ***throw it away in a sealed plastic bag*** (remember to wash your hands afterwards).

DO NOT:

- ***Don't use a bandage that blocks all air from the vaccination site.*** This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.

- ***Don't put salves or ointments on the vaccination site.***

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- ***Don't scratch or pick at the scab.***

Resources

For more information on disease reporting, call your local health department or the New York State Department of Health Bureau of Communicable Disease Control at (518) 473-4439. In New York City, 1 (866) NYC-DOH1. To obtain reporting forms (DOH-389), call (518) 474-0548.

Local Health Units	Phone Number
Albany County Health Department 175 Green Street Albany, New York 12201-0678	(518) 447-4640
Allegany County Health Department County Office Building, 7 Court Street Belmont, New York 14813	(716) 268-9250
Broome County Health Department 225 Front Street Binghamton, New York 13901-2795	(607) 778-2804
Cattaraugus County Health Department 1701 Lincoln Avenue Olean, New York 14760-1154	(716) 373-8050
Cayuga County Health Department 160 Genesee Street Auburn, New York 13021	(315) 253-1469
Chautauqua County Health Department Hall & R. Clothier Building 7 North Erie Street Mayville, New York 14757-1027	(716) 753-4491
Chemung County Health Department 103 Washington Street P.O. Box 588 Elmira, New York 14902-0588	(607) 737-2028
Chenango County Health Department County Office Building 5 Court Street Norwich, New York 13815	(607) 337-1660
Clinton County Health Department 133 Margaret Street Plattsburgh, New York 12901	(518) 565-4848
Columbia County Health Department 71 North Third Street Hudson, New York 12534	(518) 828-3358
Cortland County Health Department 60 Central Avenue Cortland, New York 13045-2746	(607) 753-5036
Delaware County Public Health Nursing Service	(607) 746-3166

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99 Main Street Delhi, New York 13753	
Dutchess County Health Department 387-391 Main Mall Poughkeepsie, New York 12601-3316	(845) 486-3452
Erie County Health Department Rath Office Building 95 Franklin Street Buffalo, New York 14202	(716) 858-6150
Essex County Public Health Nursing Service 100 Court Street, P.O. Box 217 Elizabethtown, New York 12932-0217	(518) 873-3514
Franklin County Public Health Nursing Service 63 West Main Street Malone, New York 12953	(518) 891-4471
Fulton County Public Health Department 2714 State Highway 29 P.O. Box 415 Johnstown, New York 12095-0415	(518) 736-5720
Genesee County Health Department County Office Building #2 3837 West Main Street Road Batavia, New York 14020-9406	(716) 344-8506
Greene County Public Health Nursing Service 159 Jefferson Heights Suite A-201 P.O. Box 771 Catskill, New York 12414	(518) 943-6591
Hamilton County Public Health Nursing Service P.O. Box 250 White Birch Lane Indian Lake, New York 12842-0250	(518) 648-6141
Herkimer County Public Health Nursing Service 301 North Washington Street Suite 2355 Herkimer, New York 13350	(315) 867-1430
Jefferson County Public Health Service 531 Meade Street Watertown, New York 13601	(315) 786-3720
Lewis County Public Health Agency 7785 North State Street Lowville, New York 13367	(315) 376-5449
Livingston County Health Department 2 Livingston County Campus Mt. Morris, New York 14510	(716) 243-7299
Madison County Public Health Department County Office Building P.O. Box 605	(315) 363-5490

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Wampsville, New York 13163	
Monroe County Health Department Disease Control Unit, PO Box 92832 111 Westfall Road, Room 870 Rochester, New York 14692	(716) 274-6080
Montgomery County Public Health County Annex Building #2 20 Park Street, P.O. Box 1500 Fonda, New York 12068-1500	(518) 853-3531
Nassau County Health Department 240 Old Country Road Mineola, New York 11501	(516) 571-3258
New York City Health Department 125 Worth Street, Room 331, Box 28 New York, New York 10013	(212) 788-4202 (212) 788-9830
Niagara County Health Department 5467 Upper Mountain Rd. Suite 100 Lockport, NY 14094-1894	(716) 439-7430
Oneida County Health Department 520 Seneca Street, 2nd Floor Utica, New York 13502	(315) 731-3465
Onondaga County Health Department 421 Montgomery Street 9th Floor Civic Center Syracuse, New York 13202	(315) 435-3236
Ontario County Community Health Service 3019 County Complex Drive Canandaigua, New York 14424	(716) 396-4343 (800) 299-2995
Orange County Health Department 124 Main Street Goshen, New York 10924-2199	(845) 291-2332
Orleans County Health Department 14012 Route 31 West Albion, New York 14411	(716) 589-3269
Oswego County Health Department 70 Bunner Street P.O. Box 3080 Oswego, New York 13126-0780	(315) 349-3547
Otsego County Public Health Nursing Service 197 Main Street County Office Building Annex Cooperstown, New York 13326	(607) 547-4230
Putnam County Health Department 1 Geneva Road Brewster, New York 10509	(845) 278-6558
Rensselaer County Health Department	(518) 270-2643

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1600 Seventh Avenue Troy, New York 12180	
Rockland County Health Department 50 Sanatorium Road, Building D Pomona, New York 10970	(845) 364-2663 (845) 364-2525
St. Lawrence County Public Health Department VanHoesen Hall P.O. Box 5157 Potsdam, New York 13676-5157	(315) 265-3768
Saratoga County Public Health Nursing Service 31 Woodlawn Avenue Saratoga Springs, New York 12866	(518) 584-7460
Schenectady County Health Department 107 Nott Terrace - Room 304 Schenectady, New York 12308	(518) 386-2824
Schoharie County Health Department Main Street P.O. Box 667 Schoharie, New York 12157-0667	(518) 295-8474
Schuyler County Home Health Agency 105 Ninth Street, Unit 34 Watkins Glen, New York 14891	(607) 535-8140
Seneca County Health Department 31 Thurber Drive Waterloo, New York 13165	(315) 539-1939
Steuben County Public Health Nursing Services 3 East Pulteney Square Bath, New York 14810	(607) 776-9631
Suffolk County Health Services Division of Public Health 225 Rabro Drive East, Room #12 Hauppauge, New York 11788-4290	(631) 853-3057
Sullivan County Public Health Nursing Service Infirmary Road P.O. Box 590 Liberty, New York 12754	(845) 292-0100
Tioga County Health Department 231 Main Street Owego, New York 13827	(607) 687-8600
Tompkins County Health Department 401 Harris B. Dates Drive Ithaca, New York 14850-1385	(607) 274-6604
Ulster County Health Department 300 Flatbush Avenue Kingston, New York 12401-2740	(845) 340-3090
Warren County Health Services	(518) 761-6415

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Warren County Municipal Center 1340 State Route 9 Lake George, New York 12845	
Washington County Public Health Nursing Services County Annex Building 415 Lower Main Street Hudson Falls, New York 12839	(518) 746-2400
Wayne County Public Health Nursing Services 1519 Nye Road, Suite 200 Lyons, New York 14489	(315) 946-5749
Westchester County Health Department 145 Huguenot Street, 8th Floor New Rochelle, New York 10801	(914) 637-4910 (315) 637-4943
Wyoming County Health Department 338 North Main Street Warsaw, New York 14569	(716) 786-8890
Yates County Public Health Nursing Services 431 Liberty Street Penn Yan, New York 14527	(315) 536-5160

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New York State Department of Health
Regional Epidemiology Staff

BUFFALO	COUNTIES SERVED
Western Regional Office NYS Department of Health 584 Delaware Avenue Buffalo, New York 14202-1295 Phone: (716) 847-4503 FAX: (716) 847-4333	Buffalo and Rochester Area: Allegany, Cattaraugus, Chautauqua, Chemung, Erie, Genesee, Livingston, Monroe, Niagara, Ontario, Orleans, Schuyler, Seneca, Steuben, Wayne, Yates, Wyoming

ALBANY	
NYS Department of Health Capital District Field Office #2 Third Street Troy, New York 12180-3281 Phone: (518) 271-2728 FAX: (518) 271-2629	Albany Area: Albany, Clinton, Columbia, Delaware, Essex, Franklin, Fulton, Greene, Hamilton, Montgomery, Otsego, Rensselaer, Saratoga, Schenectady, Schoharie, Warren, Washington

NEW ROCHELLE	
NYS Department of Health Metropolitan Regional Area Office 145 Huguenot Street New Rochelle, NY 10801-5228 Phone: (914) 654-7000 FAX: (914) 654-7169	New Rochelle & Long Island: Dutchess, Nassau, Orange, Putnam, Rockland, Suffolk, Sullivan, Ulster, Westchester

SYRACUSE	
NYS Department of Health Herkimer District Office 5665 State Route 5 Herkimer, New York 13350 Phone: (315) 866-6879 FAX: (315) 866-8192	Syracuse Area: Broome, Cayuga, Chenango, Cortland, Herkimer, Jefferson, Lewis, Madison, Oneida, Onondaga, Oswego, St. Lawrence, Tioga, Tompkins

Statewide

ALBANY - CENTRAL OFFICE	NEW YORK CITY
Regional Epidemiology Program NYS Department of Health Bureau of Communicable Disease Control ESP Corning Tower, Room 651 Albany, New York 12237-0627 Phone: (518) 473-4439 FAX: (518) 474-7381	New York City Health Department 125 Worth Street, Room 300 New York, New York 10013 Phone: (212) 295-5668 FAX: (212) 295-5421

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New York State Department of Health:
Ten Critical Steps for Handling Possible Bioterrorist Events (October, 2001)

<table>
<tr><td>1. Maintain an index of suspicion.</td><td>In an otherwise healthy population, some associations are very suggestive, especially when seen in clusters, high numbers, or unusual presentations: Hemoptysis, Plague, Flaccid Paraysis, Botulism, Purpura, Viral Hemorrhagic Fevers (VFH), Wide Mediastinum, Anthrax Centripetal Rash, Smallpox</td></tr>
<tr><td>2. Protect yourself and your patients.</td><td>Use appropriate personal protection equipment (PPE). Prophylaxis: vaccines, if available, or antibiotics if risks are known.</td></tr>
<tr><td>3. Adequately assess the patient.</td><td>Review and assess the patient's history. Also ask:
Are others ill?
Were there any unusual events?
Was there an uncontrolled food source or other environmental factor?
Was there vector exposure?
Has the patient been traveling?
What is the patient's immunization record?
Perform a physical examination with special attention to the respiratory system, nervous system, skin condition, and hematologic and vascular status.</td></tr>
<tr><td>4. Decontaminate as appropriate.</td><td>Do not use bleach on exposed people. Soap, water and shampoo are perfectly adequate for all biological and most chemical agents. Chemically contaminated clothes should be removed and discarded safely. Biologically contaminated clothes can be laundered with soap, water, and perhaps bleach.</td></tr>
<tr><td>5. Establish a diagnosis.</td><td>Think clinically and epidemiologically; always send specimens for culture.<table><tr><td>Symptom (individuals)</td><td>Possible Diagnosis</td></tr><tr><td>Pulmonary</td><td>Tularemia, plague, staph enterotoxin B (SEB)</td></tr><tr><td>Neuromuscular</td><td>Botulism, Venezuelan equine encephalitis (VEE)</td></tr><tr><td>Bleeding/purpura</td><td>VHF, ricin, plague (late)</td></tr><tr><td>Rash (various types)</td><td>VHF, T2 mycotoxin, smallpox, Plague</td></tr><tr><td>Flu-like symptoms</td><td>Varies</td></tr><tr><td>Immediate Symptoms (large #s)</td><td>Possible Diagnosis</td></tr><tr><td>Pulmonary</td><td>SEB, mustard, Lewisite, phosgene, cyanide</td></tr><tr><td>Neurologic</td><td>Nerve gases, cyanide</td></tr><tr><td>Delayed Symptoms (large #s)</td><td>Possible Diagnosis</td></tr><tr><td>Pulmonary</td><td>Biologic agents, mustard, Phosgene</td></tr><tr><td>Neurologic</td><td>Botulism, VEE, other encephalitis</td></tr></table></td></tr>
<tr><td>6. Render prompt treatment.</td><td>Doxycycline can be used to treat virtually everything (except virals or toxins) while awaiting lab results. Observe pediatric precautions as appropriate.</td></tr>
</table>

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<table>
<tr><td>7. Provide good infection control.</td><td>Gown, gloves, mask and handwashing, and eyewear if necessary are sufficient.
Recommended isolation precautions for biologic agents include:

Standard Precautions — For all exposed individuals/patients
Contact Precautions (herpes) — Viral Hemorrhagic Fevers
Droplet Precautions — Pneumonic Plague
Airborne Precautions — Smallpox</td></tr>
<tr><td>8. Alert the proper authorities.</td><td><table>
<tr><th>Agency</th><th>Telephone Number</th></tr>
<tr><td>FBI</td><td>518-465-7551 (Albany)
212-384-1000 (NYC)
716-856-7800 (Buffalo)</td></tr>
<tr><td>Municipal Police/County Sheriff</td><td>*</td></tr>
<tr><td>New York State Police</td><td>*</td></tr>
<tr><td>County Health Unit</td><td>*</td></tr>
<tr><td>New York State Health Dept.</td><td>518-473-1730 or
518-465-9720 (after hours)</td></tr>
<tr><td>Local Emergency Medical Services Unit</td><td>*</td></tr>
<tr><td>Local Hospitals</td><td>*</td></tr>
<tr><td>Centers for Disease Control And Prevention</td><td>770-488-7100</td></tr>
</table>*Check your local telephone directory for numbers in your area.</td></tr>
<tr><td>9. Assist in the epidemiologic investigations so as to determine who else may be at risk.</td><td>Steps in an epidemiological investigation:

• Count cases
• Relate to the at-risk population
• Make comparisons
• Develop hypotheses
• Make inferences
• Conduct studies
• Interpret and evaluate</td></tr>
<tr><td>10. Know and spread this information.</td><td></td></tr>
</table>

(Oct. 2001)

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Smallpox as a Biological Agent of Terror: Pre-event Information

Course Exam

***NOTE**: After studying the downloaded course and completing the exam, you need to enter your exam answers **ONLINE**; answers cannot be answered and graded on this downloadable version of the course. To enter your answers return to e-leaRN's Web site, www.elearnonline.net and click on "Login/My Account." Next, login using your username and password, select the course and proceed to the course exam.

1. Smallpox, used as a bioterrorist weapon, is particularly fearsome because of the large number of susceptible persons due to the discontinuation of vaccination decades ago; the likelihood of delayed diagnosis and subsequent infection of others in the community and healthcare facilities; wide geographic dispersion of cases; and difficulty in contact tracing.

   A. True.
   B. False.

2. Smallpox, caused by the variola virus, includes an incubation period of from 7 to 17 days, wherein those infected may have few, if any symptoms.

   A. True.
   B. False.

3. Patients with smallpox are most infectious during the first week after rash appears. This is due to

   A. Quick ulceration of the lesions on the mucosa of the mouth and pharynx.
   B. High virus titers in the saliva.
   C. Both A and B.
   D. Neither A or B.

4. An important differentiating feature between smallpox and other rash illnesses is the presence of a prodrome. This period which generally lasts from one to four days before the onset of the rash, includes the following symptoms:

   A. Fever, often ranging 101-104 degrees.
   B. Malaise.
   C. Head and body aches.
   D. All of the above.

5. The smallpox lesions begin as a maculopapular rash. After 1 to 2 days the rash becomes vesicular, with a depression in the center. Between 5 and 10 days, the rash becomes pustular and feels round, firm and deeply embedded in the skin. The pustules began to scab over. It generally takes about 3 weeks for scabs to fall off. Then the person is no longer contagious.

   A. True.
   B. False.

6. Flat-type smallpox and hemorrhagic smallpox are the most common and are considered to be milder versions of the smallpox disease.

   A. True.
   B. False.

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7. The most frequent mode of transmission of smallpox is person to person spread through direct deposit of infective droplet nuclei onto the nasal, oral or pharyngeal mucosal membranes or the alveoli of the lungs from close, face to face contact with an infected person.

    A. True.
    B. False.

8. In addition to standard precautions, droplet and airborne precautions are needed in the treatment of all suspected cases of smallpox.

    A. True.
    B. False.

9. The primary strategy for controlling an outbreak of smallpox has previously included:

    A. Ring vaccination
    B. Isolation of persons at risk of contracting smallpox
    C. Surveillance.
    D. All of the above.

10. There is no current FDA approved treatment for smallpox.

    A. True.
    B. False.

11. Prevaccination counseling includes:

    A. Contraindications to receiving the vaccine.
    B. Information about the vaccination procedure.
    C. Instructions for care of the vaccination site.
    D. Possible adverse reactions.
    E. All of the above.

12. Contraindications to the vaccinia vaccine include: allergy to vaccine components, pregnancy, immunodeficiency states, immunosuppressive therapy, eczema, skin disorders and diseases of the conjunctiva or cornea of the eye.

    A. True.
    B. False.

13. The vaccination site should be

    A. Kept loosely covered with sterile gauze.
    B. Not touched, scratched or rubbed.
    C. The site should be avoided, so as to prevent transfer of the vaccinia virus to the eye or surrounding skin.
    D. All of the above.

14. Vaccination with the vaccina virus is accomplished through the scarification method, which entails utilizing a bifurcated needle to vigorously puncture the skin 3 times for primary vaccination; 15 times for revaccination.

    A. True.
    B. False.

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15. Normal primary vaccination reaction include: Between days 3 and 21 a papule develops, then a vesicle with surrounding erythema, progressing o a vesicle with a depressed center, then a well-formed pustule, to a crusting pustule, progressing to a scab, then the scab detaches, revealing a scar.

    A. True.
    B. False.

16. Normal systemic reactions to vaccination include:

    A. Chills and nausea.
    B. Fever, malaise and fatigue.
    C. Myalgia and headache.
    D. All of the above.

17. Adverse reactions to the vaccine include:

    A. Accidental implantation.
    B. Eczema Vaccinatum.
    C. Progressive vaccinia.
    D. All of the above.

18. The CDC recommends that serious smallpox adverse reactions be treated with the use of

    A. Vaccinia Immune Globulin (VIG) for select adverse reactions.
    B. Cidofovir, an antiviral drug marketed as Vistide.
    C. Both A and B.
    D. There is no current treatment for serious smallpox adverse reactions.

19. Vaccination within 3 days of exposure will completely prevent or significantly modify smallpox in the vast majority of persons. Vaccination within 4 to 7 days post exposure will also likely offer some protection from the disease or modify severity of the disease.

    A. True.
    B. False.

20. The Center for Disease Control and Prevention Emergency phone number is 800-232-4636.

    A. True.
    B. False.

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