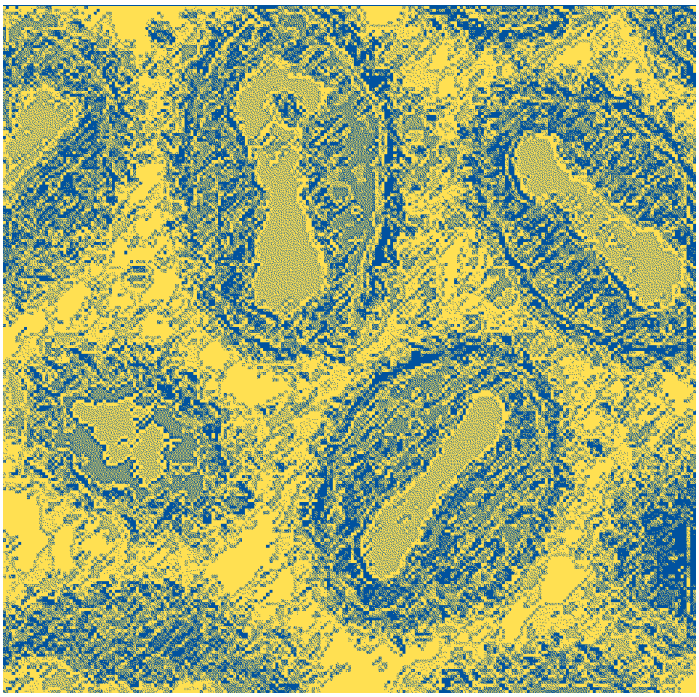
Preparing for and Responding to Bioterrorism

Information for Primary Care Clinicians



Smallpox

Developed by

Jennifer Brennan Braden, MD, MPH

Jeffrey S. Duchin, MD

Preparing for and Responding to Bioterrorism: Information for Primary Care Clinicians

Smallpox

Developed by

Jennifer Brennan Braden, MD, MPH, and Jeffrey S. Duchin, MD

Northwest Center for Public Health Practice
University of Washington

Communicable Disease, Epidemiology &
Immunization Section
Public Health – Seattle & King County
Seattle, Washington

*This manual and the accompanying MS Powerpoint® slides are current as of Dec 2002. Please refer to http://nwcphp.org/bttrain/ for updates to the material.

Last Revised December 2002

Acknowledgements

This manual and the accompanying MS PowerPoint® slides were prepared for the purpose of educating primary care clinicians in relevant aspects of bioterrorism preparedness and response. Instructors are encouraged to freely use all or portions of the material for its intended purpose. The following people and organizations provided information and support in the development of this curriculum.

Project Coordinator

Patrick O'Carroll, MD, MPH
Northwest Center for Public Health Practice, University of Washington, Seattle, Washington
Centers for Disease Control and Prevention; Atlanta, GA

Lead Developer

Jennifer Brennan Braden, MD, MPH
Northwest Center for Public Health Practice, University of Washington, Seattle, Washington

Scientific Content Development

Jennifer Brennan Braden, MD, MPH
Northwest Center for Public Health Practice, University of Washington, Seattle, Washington

Jeffrey S. Duchin, MD
Communicable Disease Control, Epidemiology and Immunization Section, Public Health – Seattle & King County
Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington

Design and Editing

Judith Yarrow
Health Policy Analysis Program, University of Washington, Seattle, Washington

Additional technical support provided by

Jane Koehler, DVM, MPH
Communicable Disease Control, Epidemiology and Immunization Section, Public Health – Seattle & King County

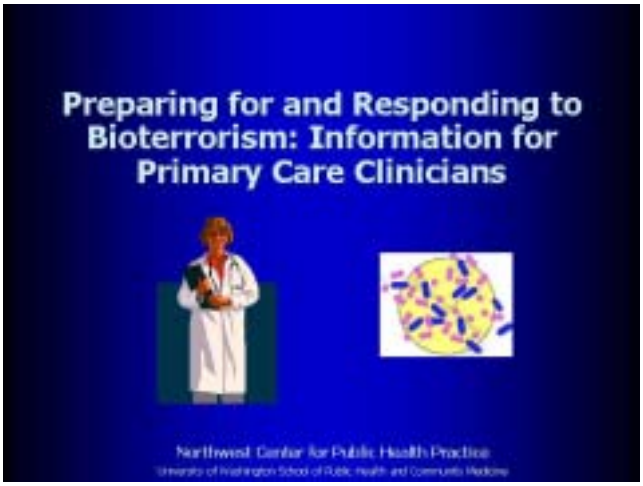
Ed Walker, MD
Department of Psychiatry, University of Washington, Seattle, Washington

Contact Information

Northwest Center for Public Health Practice
School of Public Health and Community Medicine
University of Washington
1107 NE 45th St., Suite 400
Seattle, WA 98105
Phone: (206) 685-2931, Fax: (206) 616-9415

Table of Contents

About This Course



"Preparing for and Responding to Bioterrorism: Information for Primary Care Clinicians" provides primary care clinicians with a basic understanding of bioterrorism preparedness and response, how the clinician fits into the overall process, and the clinical presentation and management of diseases produced by agents most likely to be used in a biological attack. The course was designed by the Northwest Center for Public Health Practice in Seattle, Washington, and Public Health – Seattle & King County.

The course incorporates information from a variety of sources, including the Centers for Disease Control and Prevention, the United States Army Medical Research Institute in Infectious Disease (USAMRIID), the Working Group on Civilian Biodefense, Public Health – Seattle & King County, and the Washington State Department of Health, among others (a complete list of references is given at the end of the manual). The course is not copyrighted and may created be used freely for the education of primary care clinicians.

Course materials will be updated on an as-needed basis with new information (e.g., research study results, consensus statements) as it becomes available. For the most current version of the curriculum, please refer to: http://nwcphp.org/bttrain/.

How to Use This Manual

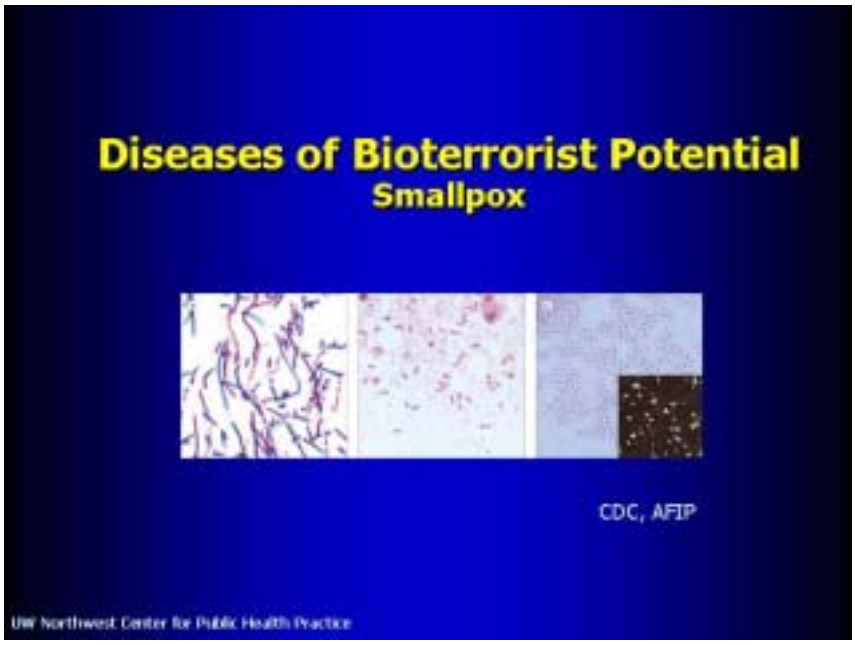
This manual provides the instructor with additional useful information related to the accompanying MS PowerPoint® slides. The manual and slides are divided into four major sections: Introduction to Bioterrorism, Bioterrorism Preparedness and Response, Diseases of Bioterrorist Potential, and Psychological Aftermath of Crisis. Learning objectives precede each section, and a list of resources is given at the end of each section. Four slide sets comprise the section on the diseases of bioterrorist potential: Anthrax, Smallpox, Plague and Botulism, and Tularemia and Viral Hemorrhagic Fevers. Each disease slide set contains the same introductory material on the critical agents at the beginning, and the same list of resources at the end. Instructors who want to skip this introductory material can use the navigation pages provided in the Plague and Botulism and Tularemia and Viral Hemorrhagic Fever modules (click the section to which you want to go), or the custom show option in the Anthrax and Smallpox modules (go to "Custom Shows" under the "Slide Show" option on the MS PowerPoint® toolbar; select "Anthrax/Smallpox, skip intro").

Links to Web sites of interest are included in the lower right-hand corner of some slides and can be accessed by clicking the link while in the "Slide Show" view. Blocks of material in the manual are summarized in the "Key Point" sections to assist the instructor in deciding what material to include in a particular presentation. A Summary of Key Points is indicated in bold, at the beginning of each section.

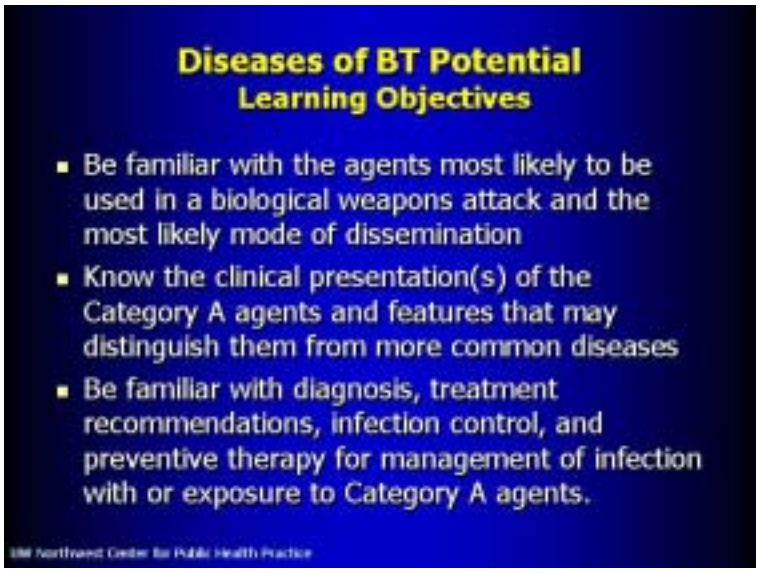
The slide set can be presented in its entirety, in subsections, or as an overview, depending on the level of detail included. The entire course was intended to be presented in a six- to seven-hour block of time or divided into one- to three-hour blocks according to instructor/audience preference. For instructors who want to present a less detailed, "overview" course, suggestions for more abbreviated presentations are incorporated into the modules. These latter options are built into the slide set and can be accessed by going to "Custom Shows" (under the "Slide Show" option on the MS PowerPoint® task bar).

Diseases of Bioterrorist Potential

The photo shows, from left to right, gram stains of *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia). The source for the first two photos is CDC, and for the gram stain of *F. tularensis*, the Armed Forces Institute of Pathology



Learning Objectives (Slide 4)



The learning objectives for this session are:

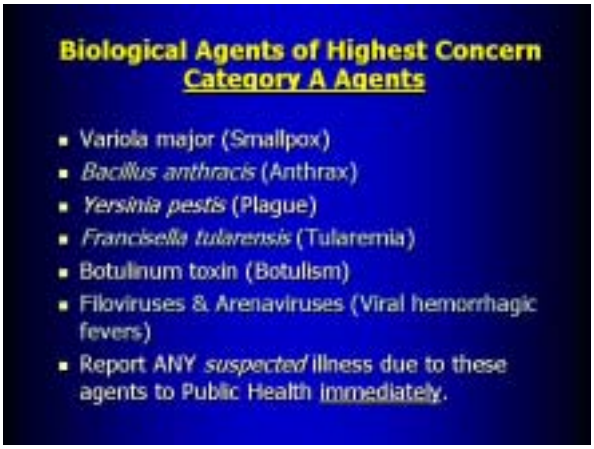
1. Be familiar with the agents most likely to be used in a biological weapons attack and the most likely mode of dissemination
2. Know the clinical presentation(s) of the Category A agents and features that may distinguish them from more common diseases
3. Be familiar with diagnosis, treatment recommendations, infection control, and preventive therapy for management of infection with or exposure to Category A agents

Section 1: Biological Agents of Highest Concern

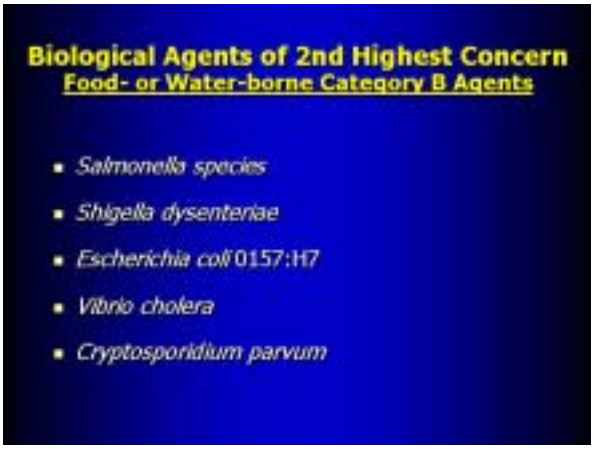
(Slides 5-9)

CDC has designated **critical agents** with potential for use as biological weapons and grouped them according to level of concern (Rotz et al., Emerging Infect Dis 2002; 8(2):225-230). Several factors determine the classification of these agents, including previous use or development as a biological weapon, ease of dissemination, ability to cause significant mortality or morbidity, and infectious nature.

Category A agents, designated as agents of highest concern, will be the focus of this session; they are listed in slide 6. Category A agents include variola major (smallpox), *bacillus anthracis* (anthrax), *yersinia pestis* (plague), *francisella tularensis* (tularemia), *clostridium botulinum* toxin (botulism), and the filoviruses and arenaviruses (hemorrhagic fever viruses).



Category B agents are of the next highest level of concern and are listed in slides 7 and 8. These agents are moderately easy to disseminate and produce lower mortality and moderate morbidity.



A subset of the Category B agents includes food- and water-borne agents. These agents more commonly produce disease outbreaks from a non-deliberate source and may also be employed in a biological attack.

The final category of agents – **Category C** – includes emerging pathogens with potential for mass dissemination based on availability, ease of production and dissemination, and potential for high morbidity and mortality. They are listed in slide 9.

The Laboratory Response Network

CDC has established a multi-level **Laboratory Response Network (LRN)** for bioterrorism. Labs are identified by increasing levels of proficiency to respond to bioterrorism, from Level A to Level D; these categories take into consideration the bio-safety level capacity of the labs, as well as other resource and capacity issues.

Level A – Most clinical labs are Level A and include public health and hospital labs with a certified biological safety cabinet as a minimum.

Level B – State and local public health labs with BSL-2 facilities that incorporate BSL-3 practices

Level C – BSL-3 facilities with the capability to perform nucleic acid amplification, molecular typing, toxicity testing (Washington Public Health Laboratories, for example)

Level D – Possess BSL-3 and BSL-4 biocontainment facilities and include CDC and USAMRIID labs. Level B/C labs can register for the LRN and then have password-protected access to information over the Web.

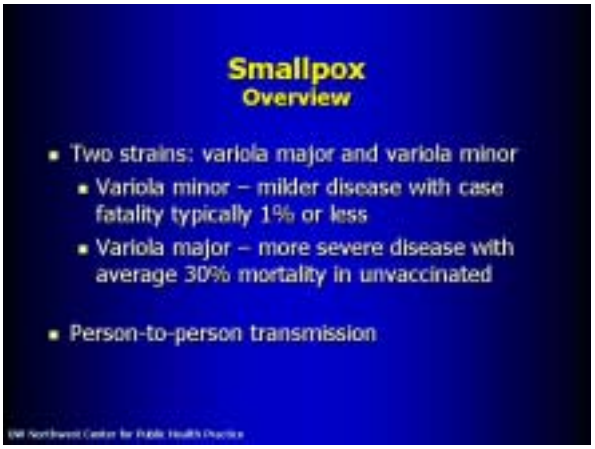
Smallpox (slides 10-64)

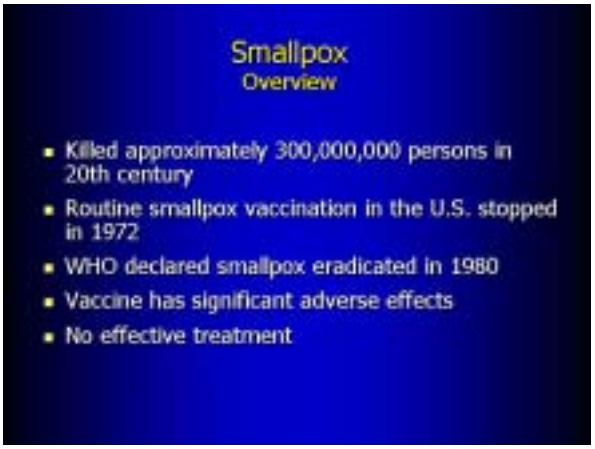
Summary of Key Points:

(Listed in slides 63-64)

1. The clinical diagnosis of smallpox is a public health emergency; the local or state health department and hospital infection control should be notified immediately for suspected cases, including cases that meet criteria of CDC smallpox case definition.
2. Smallpox is transmitted person to person; standard contact and air-borne precautions should be initiated in all suspected cases until smallpox is ruled out.
3. Vaccine-induced immunity wanes with time; therefore most people today are considered susceptible to infection.
4. CDC criteria for determining the risk of smallpox can help differentiate smallpox from varicella and other rash illnesses.

Overview (Slides 10-12)





Smallpox is caused by variola virus, a member of the Orthopoxvirus family. There are two strains: variola minor and variola major. Variola major had an average mortality rate of 30%; variola minor produced a much milder form of smallpox in unvaccinated individuals (fatality rate 1% or less). In the context of biological weapons attack, we are concerned only with variola major, and all discussion of smallpox in this course refers to variola major.

Variola major is thought to be much less accessible to potential terrorists than the other agents discussed in this course: All known stocks are located either at CDC in Atlanta, Georgia, or at the Institute for Viral Preparations in Moscow; the extent of clandestine stockpiles elsewhere is unknown.

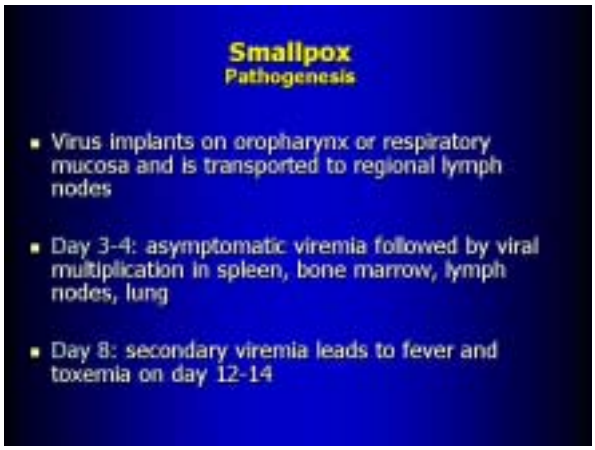
Smallpox is of concern, however, because of its high mortality (averages 30%, but is significantly higher in unimmunized older adults, infants, and persons with underlying immune system compromise), person-person transmission, lack of effective treatment, and lack of immunity among the general population.

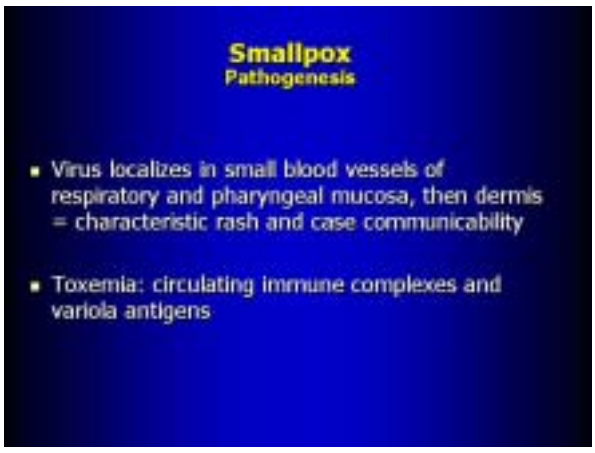
Key Points, Slides 13-29

1. Smallpox is transmitted primarily via respiratory droplets, similar to varicella.
2. Airborne transmission is uncommon but possible, particularly in severe cases and cases with cough.
3. Smallpox is characterized by a febrile prodrome, followed by a rash with firm, deep-seated vesicles or pustules in the same stage of development on any given area of the body.
4. Smallpox patients are considered infectious from the onset of rash, until all scabs have separated.

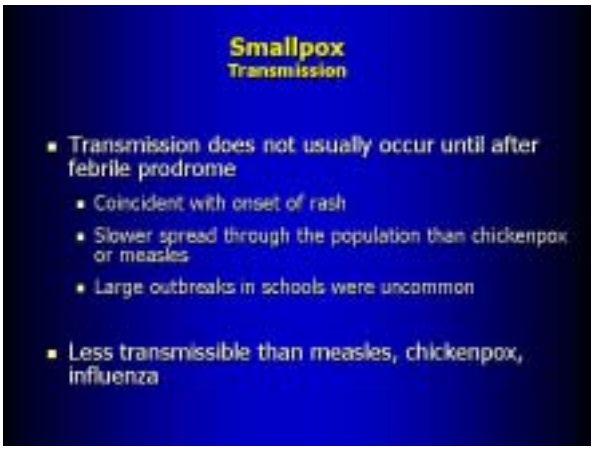
Pathogenesis and Transmission (Slides 13-17)

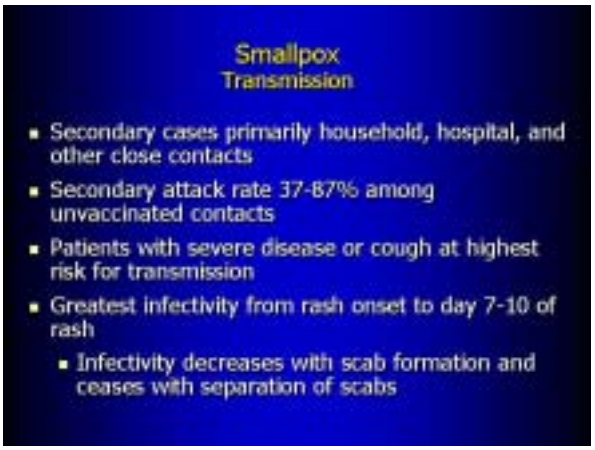
The primary mode of transmission of variola is through respiratory droplets. Aerosol transmission occurs but is uncommon. Contact with virus-contaminated clothing or bed linens is the least frequent route of transmission. An initial asymptomatic viremia is followed by viral multiplication in the spleen, bone marrow, lymph nodes, and lung. Symptoms follow the development of a secondary viremia on approximately day eight of infection.





The toxemia of smallpox is not well understood, but is probably secondary to circulating immune complexes and viral antigens. With the onset of fever and toxemia, virus localizes in the small blood vessels of the dermis and respiratory and pharyngeal mucosa.





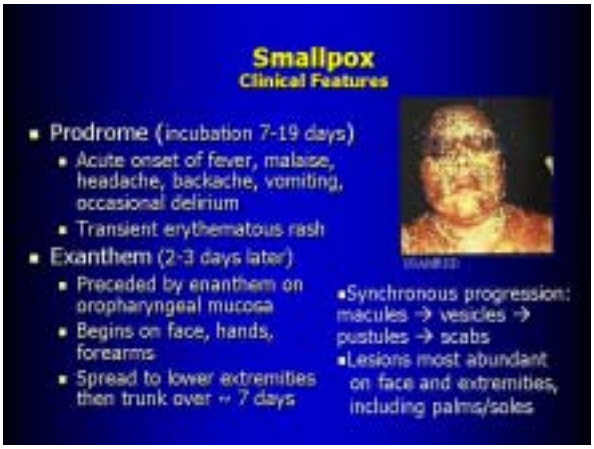
The onset of communicability coincides with the development of lesions on the oral and pharyngeal mucosa, which rupture, releasing large quantities of virus, and precedes the onset of the characteristic rash by a day. Thus transmission is possible when the skin lesions are in an early, difficult to recognize stage. Examining the oral mucosa and throat is important in the evaluation of persons suspected of having early-stage smallpox

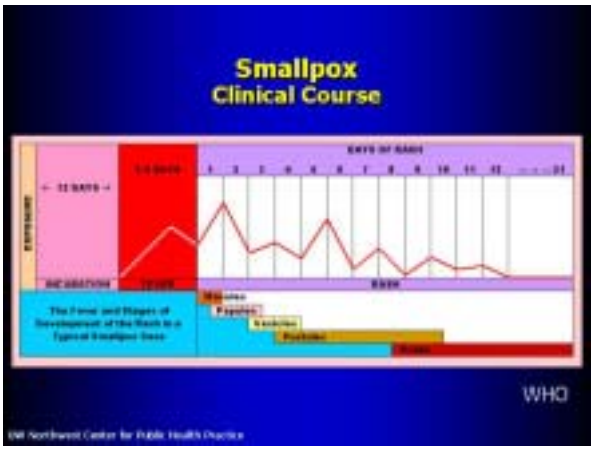
Despite the low infectious dose, the virus historically spread relatively slowly through the population: By the time patients were infectious (i.e., when the rash appeared), they were sick enough to remain confined to bed, thus limiting the number of contacts outside the home.

Viable virus was noted to be present in scabs, but scabs were not very infectious, probably because the tight fibrin matrix of the scab impeded virus transmission.

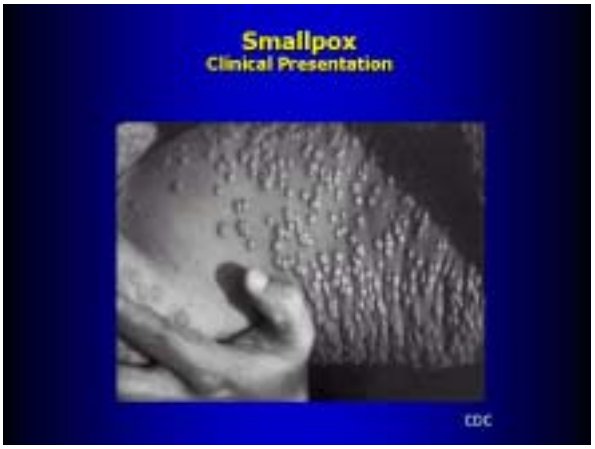
Clinical Features (Slides 18-25)

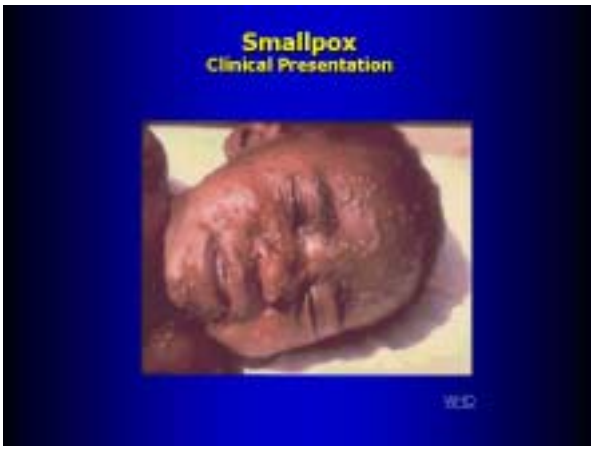
Symptomatic smallpox begins suddenly with a febrile prodrome one to four days before the onset of the rash and may include headache, backache, malaise, vomiting, and delirium.. The rash is characterized by firm, deep-seated vesicles or pustules in the same stage of evolution on any given area of the body. The rash begins on the face, hands, and forearms and spreads to the lower extremities and trunk over several days. The progression of smallpox lesions from macules to papules to vesicles to pustules to scabs occurs relatively slowly, each stage lasting approximately one or two days. The lesions of chickenpox typically evolve from macules to papules to crusts in <24 hours. In addition, fever occurs with the onset of rash in chickenpox, lesions are more superficial, and are not deep-seated.

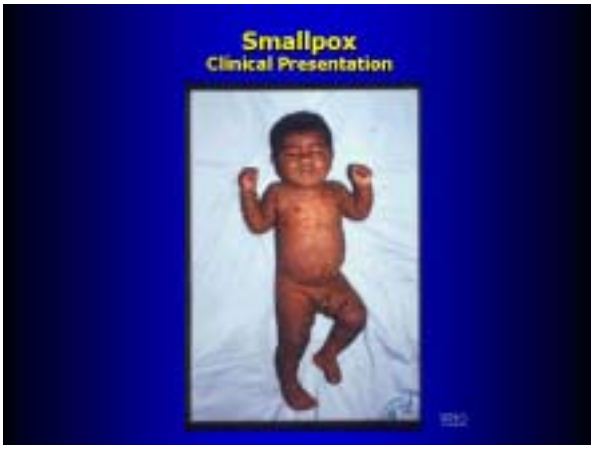




Slide 19 is a graphical representation of the clinical course of smallpox. The incubation period is indicated in pink, the prodromal febrile stage in crimson, the rash in lavender, and fever throughout the course of disease by the line graph. The colored boxes below the line graph indicate the progression of lesions: macules –> papules –> vesicles –> pustules –> scabs.



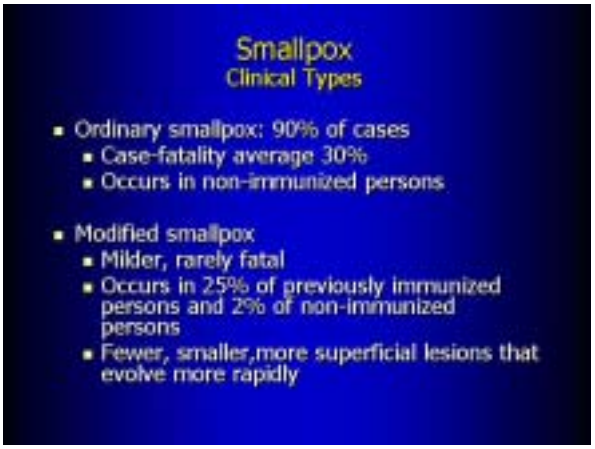




Slides 20-22 illustrate the clinical presentation of a typical "ordinary" smallpox case. Note the umbilicated and well demarcated appearance of the mature lesions, the heavy distribution on the face and extremities (but lighter on the trunk), and the presence of all lesions in the same stage of development on a given area of the body. Lesions are deeply imbedded in the dermis, and scarring is evident after scabs separate. Scarring is usually not permanent, however, except sometimes on the face due to destruction of sebaceous glands.

Slide 23 shows the progression of smallpox lesions from macules to vesicles to pustules. The clinical progression is continued on slides 24 and 25. Note the presence of scabs on the girl's face and the de-pigmentation that has occurred on the arm after scabs have separated.

Clinical Types (Slides 26-29)



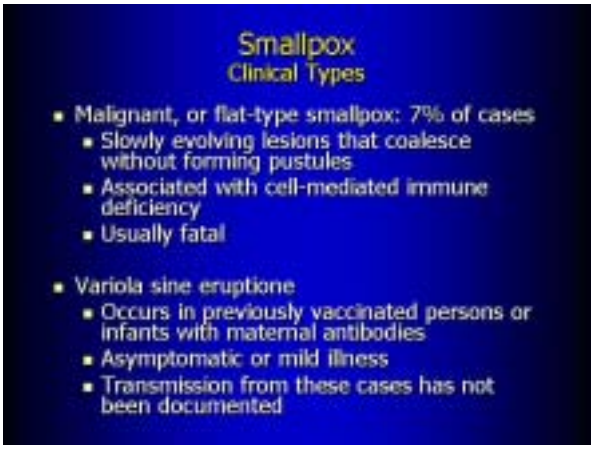
Five types of smallpox have been identified, based on a study by the World Health Organization of 3544 patients in India.

"Ordinary" smallpox is the typical type in non-immunized persons and accounts for approximately 90% of cases.

"Modified" smallpox is a milder, rarely fatal illness that occurs in 25% of previously immunized and 2% of unimmunized persons. Modified smallpox cases are characterized by fewer, smaller, more superficial lesions, which evolve more rapidly.

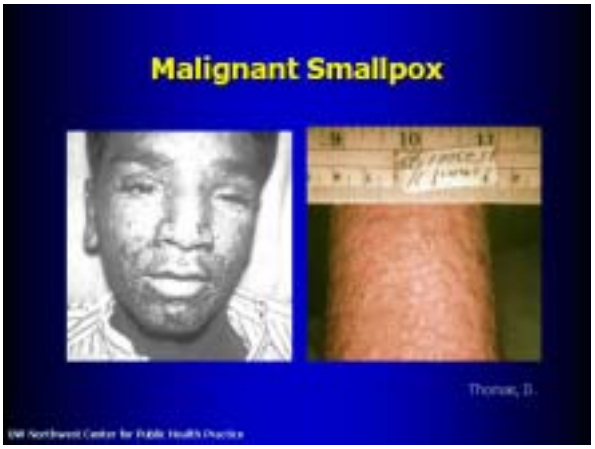
"Hemmorhagic" smallpox (<3% of cases) occurs in persons with immune compromise (pregnant women are also at increased risk) and is associated with extensive viral multiplication and coagulopathy, possibly secondary to megakaryocyte destruction in the bone marrow. Patients develop cutaneous petechiae and bleeding from the conjunctiva and mucous membranes. The incubation period is shortened, and the prodromal illness is severe and almost uniformly fatal within seven days of onset.

"Flat-type," or "malignant," smallpox is a usually fatal illness that occurs in a minority (7% in the WHO study) of cases. Lesions evolve more slowly and coalesce, remaining flat and soft, without forming pustules. Malignant smallpox is thought to be associated with a deficient cell-mediated immune response.

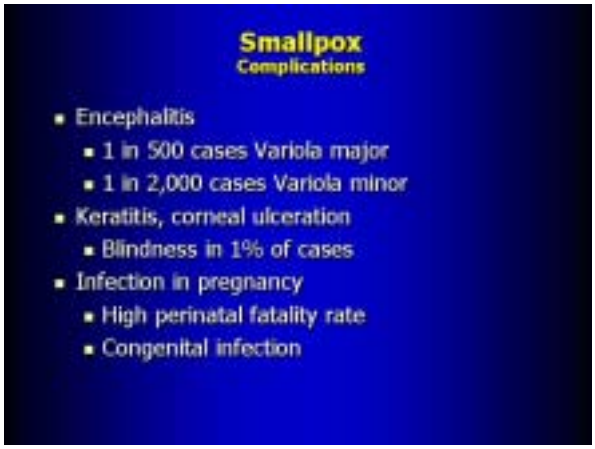


"Variola sine eruptione," or smalllpox without rash, occurs in previously vaccinated persons and infants with maternal antibody. Cases are asymptomatic or have a mild febrile illness with influenza-like symptoms. Transmission of smallpox from these cases has not been documented.

Slide 29 shows a patient with malignant smallpox. Note the flat, confluent appearance of the lesions.



Hemorrhagic and malignant smallpox are difficult to recognize as smallpox and may be mistaken for viral hemorrhagic fever, meningococcemia, acute leukemia, or other infections with disseminated intravascular coagulation (DIC). In an outbreak in Yugoslavia in 1972 (Fenner et al., Smallpox and Its Eradication, Breman & Henderson, New Engl J Med 2002;346(17):1300-1308), a case of hemorrhagic smallpox was misdiagnosed as a penicillin-associated drug eruption. Hemorrhagic and malignant smallpox cases are highly infectious and present the greatest risk for airborne transmission.



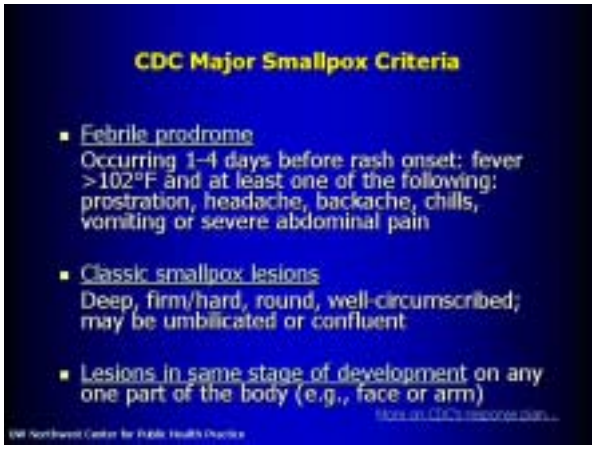
Potential complications of smallpox infection are listed in slide 30.

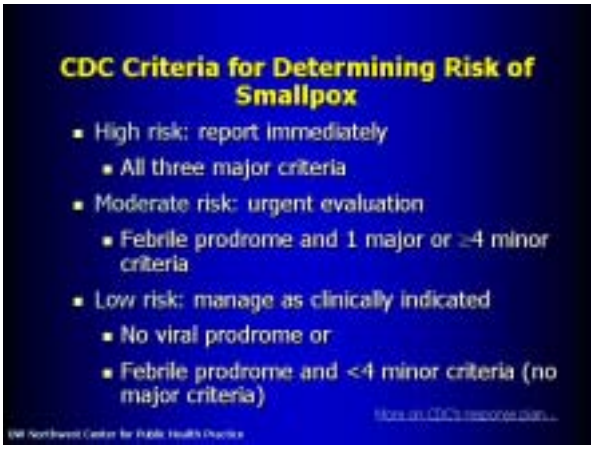
Major and Minor Criteria, and Risk Categories (Slides 31-36)

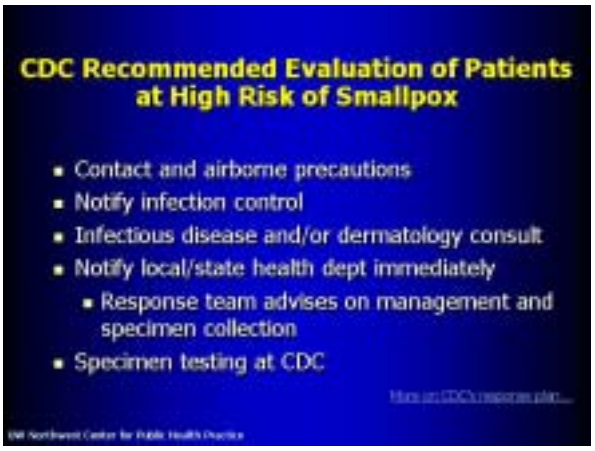
Key Points

1. CDC criteria can help to determine a patient's likelihood (risk) for having smallpox.
2. High-, medium-, and low-risk categories require contact and airborne precautions until smallpox is ruled out.
3. High- and medium-risk categories require notification of local public health.

CDC has developed major and minor criteria for smallpox to assist in diagnosis and management. The criteria are listed in slides 31 and 32, the associated risk categories in slide 33, and the management of patients in different risk categories in slides 34-36.

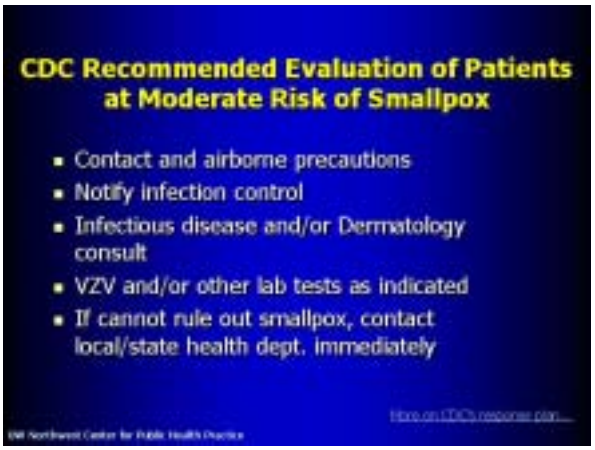




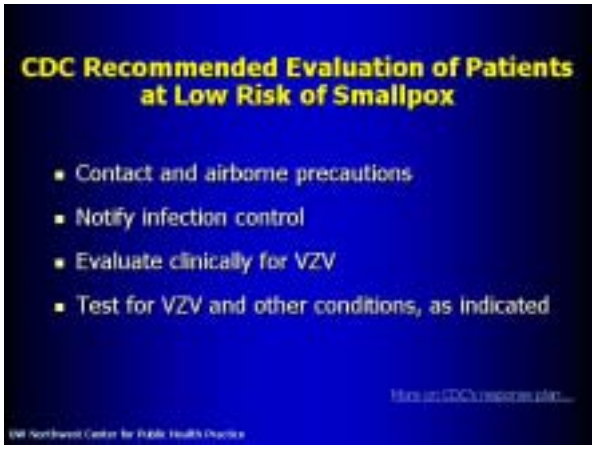


Any suspicion of smallpox in a patient should be followed by the institution of contact and airborne precautions and notification of the health care facility's infection control officer.

The practice, hospital, or institution's plan for management of smallpox cases should be implemented. If the patient is deemed to be high or moderate risk for smallpox, the local or state health department should be notified immediately. The health department will provide instruction on specimen collection and transportation for testing.



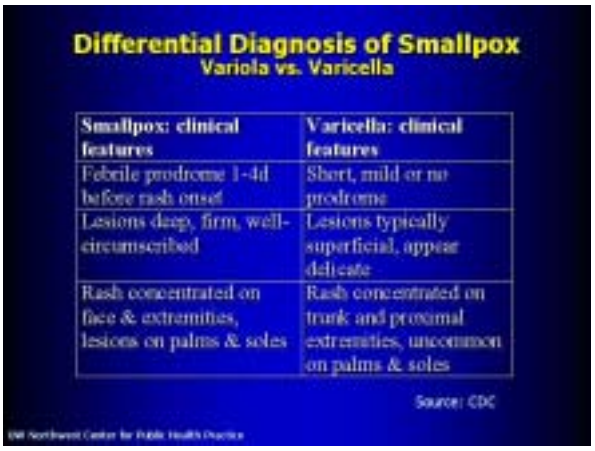
Whenever possible, only recently successfully vaccinated medical personnel or persons without contraindication for vaccination and with appropriate barrier protection should obtain specimens. If the patient is deemed to be of low risk for smallpox, the clinician should evaluate the patient for varicella infection and other illnesses in the differential diagnosis of smallpox. If recently vaccinated health care personnel are not available, only persons without contraindications for smallpox vaccine (see below) should come in contact with potential smallpox cases.

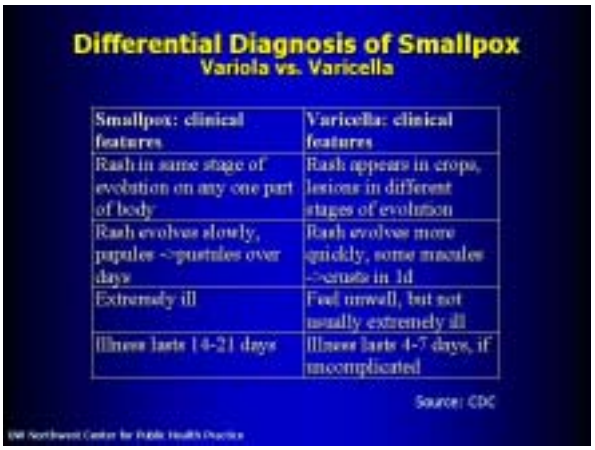

CDC Recommended Evaluation of Patients at Low Risk of Smallpox
Contact and airborne precautions
Notify infection control
Evaluate clinically for VZV
Test for VZV and other conditions, as indicated

Key Points, Slides 37-47

1. Smallpox can be differentiated from chickenpox (varicella) by clinical history and presentation.
2. Culture of vesicular or pustular fluid in a BSL-4 laboratory provides confirmatory diagnosis of smallpox.
3. Treatment of smallpox is supportive.

Differential Diagnosis (Slides 37-41)





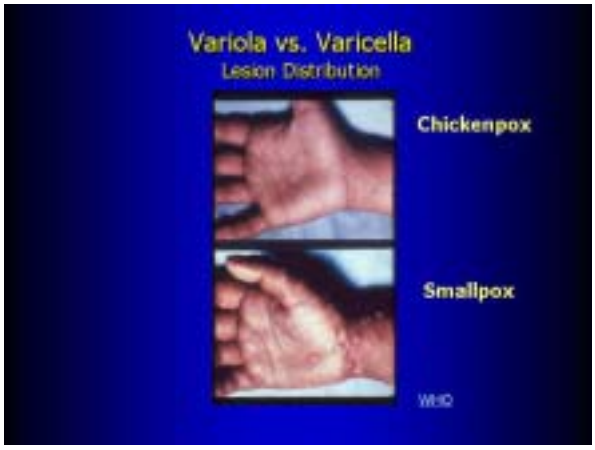
The most likely condition with which smallpox would be confused is chickenpox (varicella). Fortunately, smallpox and chickenpox have several useful features that help distinguish the two. These differences are noted in slides 37 and 38.

In smallpox, lesions appear first on the buccal and pharyngeal mucosa followed by the face, forearms, and hands, and then spread centrally. Lesions are most dense peripherally (centrifugal distribution). In chickenpox, lesions appear first, and are most concentrated, on the trunk.

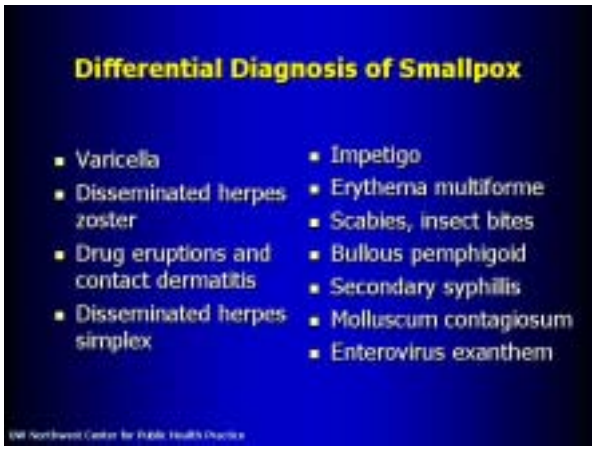
Smallpox lesions are firm, "shotty" (i.e., as if filled with bird shot) and more deeply embedded in the dermis. Chickenpox lesions are more superficial and "flimsy."

In chickenpox, fever and rash onset are coincident, in smallpox, fever precedes rash by several days

Slides 39 and 40 compare the appearance of smallpox to chickenpox. Note that lesions are present on the palms in smallpox, but not chickenpox, and the much heavier distribution of lesions on the face in smallpox versus chickenpox. In addition, Slide 40 illustrates lesions in varying stages of evolution in the chickenpox case (bottom) and in the same stage of evolution in the smallpox case (top).

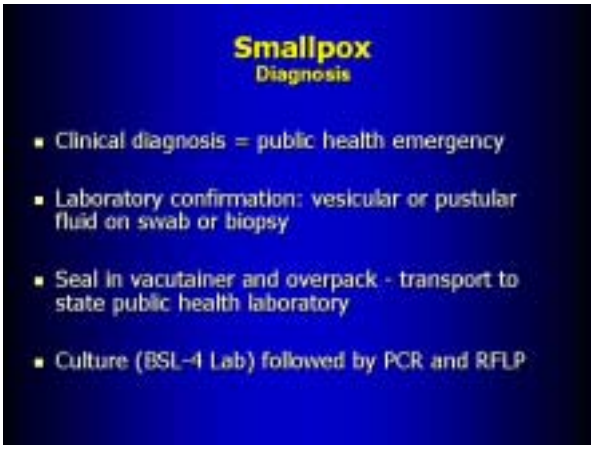


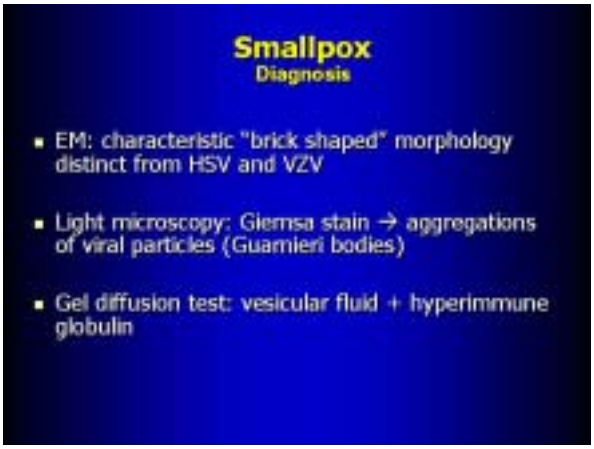
Other diseases included in the differential diagnosis of smallpox are listed in slide 41.



Herpes zoster can usually be distinguished from smallpox by its dermatomal distribution. Immunocompromised or elderly persons may develop disseminated zoster that can be confused with smallpox or varicella. In patients with a drug-induced rash, there is a history of exposure to medications. The rash of contact dermatitis is often pruritic and localized in a pattern suggesting external contact. The history may reveal contact with potential allergens. Disseminated herpes simplex occurs in immunocompromised hosts; the lesions are indistinguishable from varicella. Impetigo presents classically as honey-colored crusted plaques with bullae, but may begin with vesicles. Patients are usually not ill-appearing and the rash is regionally distributed. Erythema multiforme classically presents as target, "bull's eye" lesions; the major form involves mucous membranes and conjunctivae. The scabies or insect bite lesions are often pruritic; patients are afebrile. Bullous pemphigoid is a rare, relatively benign , pruritic, subepidermal blistering disease that occurs most commonly in individuals over the age of sixty. The rash is usually generalized, but the most common sites are the lower part of the abdomen, the groin, and the flexor surfaces of the arms and legs. In adults, the lesions of molluscum contagiosum are most often on the lower abdominal wall, pubis, genitalia or inner thighs; lesions in children are usually on the face, trunk and proximal extremities. The rash may disseminate in immunocompromised persons. Enteroviral exanthems occur in summer and fall, and are preceded by one to two days of fever and mild pharyngitis. Lesions are initially maculopapular, but evolve into whitish-grey tender, flat, often oval vesicles with a peripheral distribution.

Diagnosis (Slides 42-45)



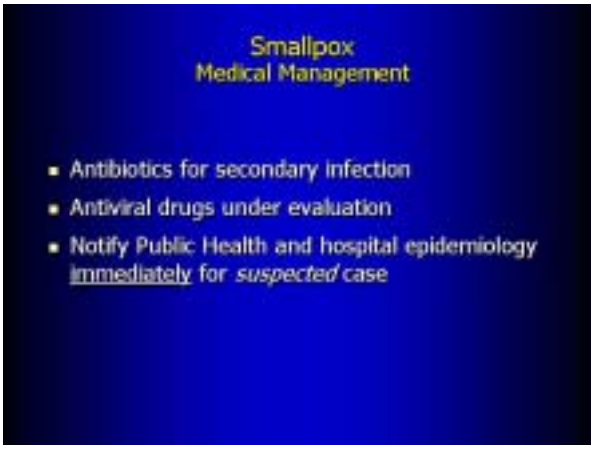


Laboratory diagnosis and specimen collection of smallpox are discussed in slides 42-45. Laboratory diagnosis must be performed in BSL-4 conditions (i.e., CDC). The local or state health department must be contacted if smallpox is suspected and will provide instructions on specimen collection and transportation. This information should be reviewed in advance and incorporated into smallpox response plans at clinical facilities (see www.bt.cdc.gov).

Diagnostic confirmation is via culture of vesicular fluid, electron microscopy, polymerase chain reaction (PCR), or restriction length fragment polymorphism (RLFP) analysis of viral genetic material. Light microscopy and gel diffusion are other useful diagnostic tests when electron microscopy and PCR are not available. Appropriate clinical and public health action should commence based on clinical suspicion and not await laboratory confirmation.

The recommendations for personnel involved in specimen collection from: Centers for Disease Control and Prevention. Smallpox Response Plan and Guidelines (Version 3.0). Sep 21, 2002. http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp

Medical Management and Infection Control (slides 46 -47)



Although there is no specific treatment for smallpox at this time, antiviral agents, including cidofovir, are being evaluated for potential utility. Medical management is supportive, with fluid and electrolyte replacement, nutritional support, and antimicrobial drug treatment for secondary infections of skin lesions or the eyes,and widespread skin involvement.

Smallpox is less transmissible than chickenpox, measles, and influenza. Secondary attack rates among unvaccinated contacts range from 37-87%. Most secondary cases involve household contacts and health care workers. Communicability is greatest from the onset of rash through days 7-10. Patients with severe disease or cough are at highest risk for transmission infection. In an outbreak in a hospital in Germany in 1970, for example, a single smallpox case with cough infected 19 persons on three floors.

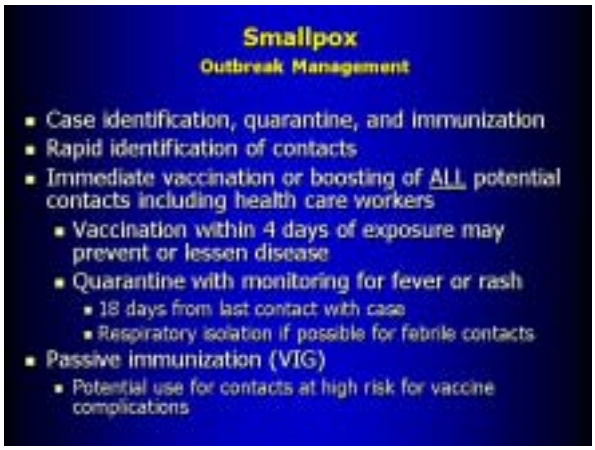
Patients should be in strict respiratory and contact isolation in a negative pressure room with HEPA-filtered exhaust, if possible, from the time they first enter the facility. All health care workers should use protective clothing including gowns, gloves, eye protection, and appropriate (N95) HEPA-filtered respirators regardless of immunization status. Persons entering the rooms of smallpox cases should be recently, successfully vaccinated or, if not possible, have no contraindications to vaccination. Current infection control recommendations from CDC should be reviewed to check for revisions and updates (http://www.bt.cdc.gov).

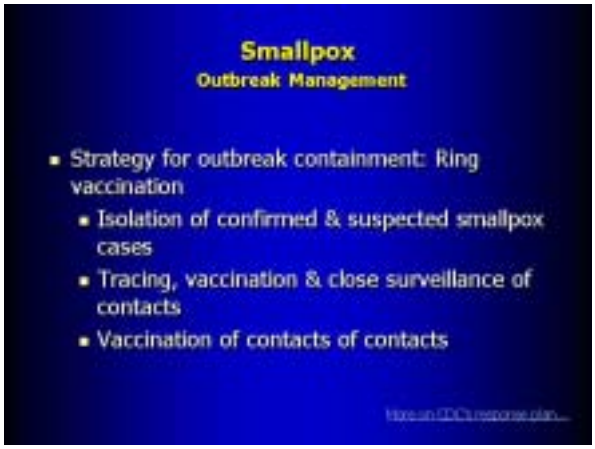
Key Points, Slides 48-62

1. The smallpox vaccine has potentially serious adverse effects; therefore vaccination in an outbreak should be targeted according to risk of exposure.
2. Control of a smallpox outbreak would involve the vaccination of potential contacts, and contacts of contacts with live vaccinia virus.
3. Vaccinia immune globulin is effective in lessening some of the adverse effects following vaccination, but is in limited supply.

Outbreak Management (Slides 48-53)

The successful global eradication of smallpox campaign was based on an "isolation and containment" strategy that included case isolation, vaccination of contacts (including health care workers and other persons likely to come in contact with smallpox cases), and vaccination of contacts of contacts (ring vaccination strategy). This strategy is the current basis for CDC's plan to control the spread of smallpox in the event of a BT attack. A broader vaccination campaign may be instituted by public health authorities if the initial number of smallpox cases or identified locations of smallpox outbreaks is considered too large to allow contact tracing with vaccination to be effective as the only vaccination strategy for outbreak containment, the incidence of new cases fails to show a decline after two or more generations from the initial case(s), or after 30% of vaccine supplies have been utilized.

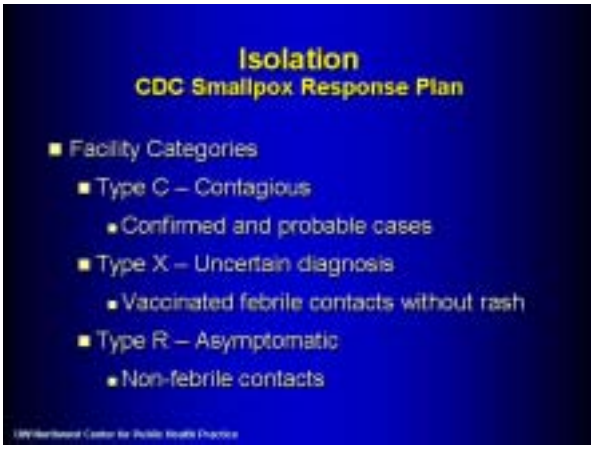




It may be necessary to use diluted preparations of vaccine for broader vaccination campaigns. A recent study (Frey et al. New Engl J Med 346(17), 2002) demonstrated that a 1:10 dilution of smallpox vaccine is capable of producing a successful vaccination.

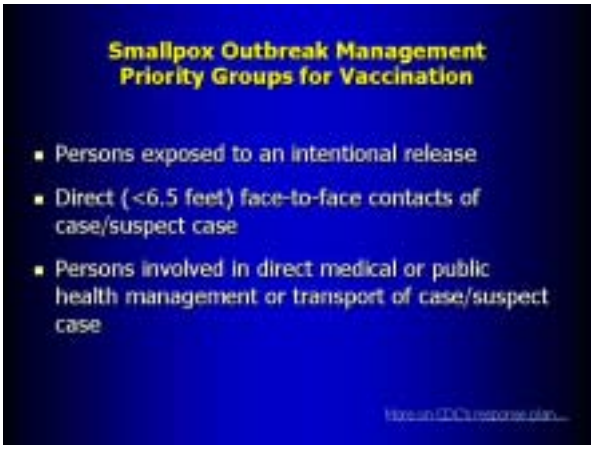
Local and state health departments, in collaboration with health care providers and institutions, should develop plans for management of smallpox cases, including isolation and quarantine. Asymptomatic contacts of cases can remain at home provided they monitor their temperature twice daily for 14 days beyond successful vaccination, or 18 days from last contact with a confirmed case, and stay within 20 miles of their city of residence. They should notify the local or state health department if they have an oral temperature of ≥ 101°F on two successive readings. (These contacts would now be considered febrile, and thus should be transported to a designated isolation facility.) Ideally, once a large outbreak of smallpox is confirmed, all confirmed and suspected cases of smallpox will be isolated in facilities designated for that purpose. However, prior to the confirmation of a smallpox outbreak or activation of the designated facility, admission of confirmed or suspected smallpox patients into a hospital facility that is not designated for the sole purpose of isolating smallpox patients may be unavoidable. Contact and respiratory precautions should be maintained, as outlined in slide 46. Patient should be covered with a linen sheet and wear at least a surgical mask when being transported through the hospital to the isolation room (See the CDC Smallpox Response Plan for more details). Smallpox isolation facilities are described in slide 50.

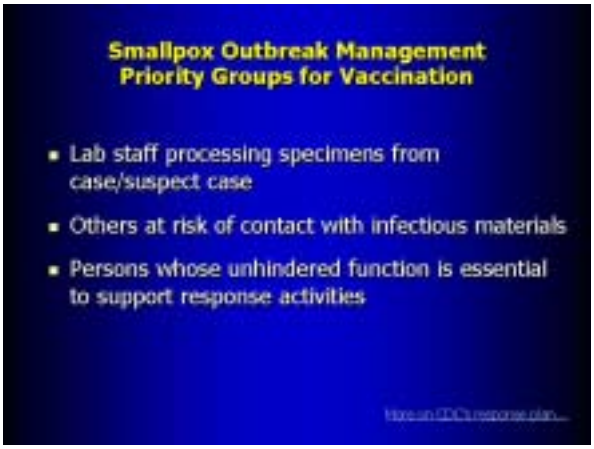
Slide 50 describes the proposed plans for isolation facilities/locations in a smallpox outbreak, as outlined in CDC's Smallpox Response Plan. The establishment of three types of facilities, based on case status (i.e., confirmed, probable/suspected, afebrile contact, asymptomatic contact), will help to minimize transmission of smallpox from infected individuals to those exposed but not necessarily infected (I.e., individuals being monitored for the development of smallpox). Examples of isolation facilities include dedicated hospitals, motels and college dormitories. Non-febrile contacts will be monitored for fever, and transferred to a Type X facility, should fever develop. All individuals entering a Type X or Type C facility (including staff) will be vaccinated for smallpox at the time of entry. Ambulance personnel should be vaccinated prior to or within 24 hours after transporting patients to a Type C or X facility. A Type R facility may be a person's home or other non-medical facility. Appropriate infection control precautions should be followed, and the ambulance should be decontaminated before being used to transport non-smallpox patients.

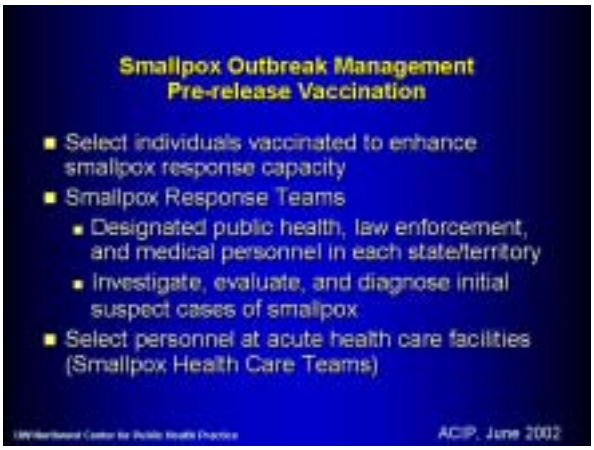


Please refer to the CDC Smallpox Response Plan and Guidelines (http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp) for more details on preparation of, and transportation of confirmed or suspected smallpox cases to, isolation and quarantine facilities

Vaccination within four days of exposure may prevent or lessen disease severity. Smallpox cases and contacts should be vaccinated as soon as possible. During outbreaks in which smallpox cases are cohorted in an institution, suspected cases should also be vaccinated upon admission to the facility in case they do not actually have smallpox. Vaccinia Immune Globulin (VIG) may be useful in preventing adverse reactions in those with a contraindication to vaccine administration, when given within the first week following exposure, and concurrently with vaccine.







The following groups would be prioritized for smallpox vaccination after exposure to smallpox virus or during an outbreak:

Persons exposed to an intentional release of smallpox virus

Persons with direct (defined as closer than 6.5 feet) face-to-face, household, or other contact with an infectious smallpox case or suspected case

Persons involved in the direct medical or public health evaluation, management, or transportation of confirmed, probable, or suspected smallpox cases

Other persons at increased risk of contacting infectious material from a smallpox case (hospital laundry, medical waste handlers)

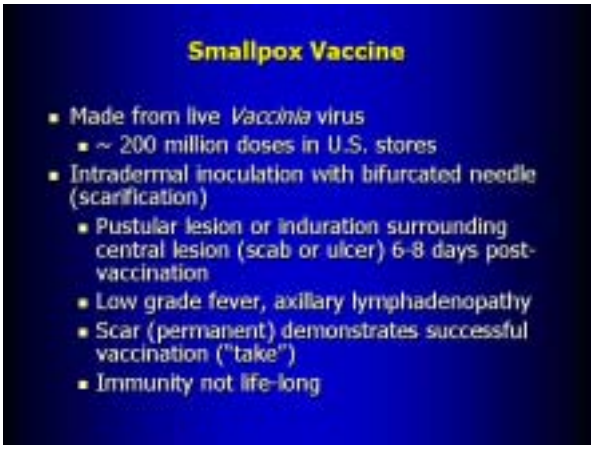
Other groups whose unhindered function is essential to the support of response activities

Vaccination of the general population is not recommended in the absence of confirmed smallpox and when the risk of attack is considered low. The Advisory Committee on Immunization Practices (ACIP) does however recommend the pre-release vaccination of select individuals to enhance the nation‘s ability to respond in the event of a smallpox release (ACIP, 2002).

ACIP recommended that each state develop a plan to immunize a limited number of teams and hospital staff who would be "first responders" pre-designated to investigate, care for, or evaluate the initial cases of smallpox in the event of an attack or outbreak. . On December 13, 2002, the federal government announced a National Smallpox Vaccination Plan for the U.S. in order to provide a measure of protection in case smallpox were to be used in a biological attack. In stage one of the plan, teams of acute care hospital and public health workers with specific skills are to be voluntarily vaccinated in order to form smallpox response teams to provide hospital care for the initial suspected or confirmed smallpox cases and to conduct public health disease control activities. The rationale for this is that having teams of health care and public health workers vaccinated and designated to perform specific roles in response to the first smallpox cases will allow a more effective response to a smallpox outbreak while minimizing exposure of large numbers of people to the vaccine. Also in stage one, the US military will begin using smallpox vaccine. The timing for stage one has not been announced, but may begin as early as January 2003. Health care workers interested in volunteering for hospital-based smallpox health care teams should contact their hospital administration or infection control team.

In stage two, smallpox vaccine will be available to additional health care workers and other first responders such as police, fire, and other public safety responders. The timing for stage two has not been announced, but would be expected to follow completion of stage one. The vaccine to be used in stages one and two is the same licensed, undiluted smallpox vaccine as was previously used in the U.S. when smallpox vaccination was routine, over 30 years ago. The vaccine has been preserved by the federal government. Stage three of the plan will make smallpox vaccine available to the general public on a voluntary basis after a new version of the vaccine is produced and licensed (expected in 2004), or before that time under study protocols. If a smallpox outbreak does occur before that time, sufficient amounts of vaccine are available to immunize the public. Because the risk of smallpox occurring is low and because the smallpox vaccine has serious side effects, including death, smallpox vaccine is not recommended or available for the general public at this time.

Smallpox Vaccine **and** Vaccinia Immune Globulin (Slides 54-62)



Successful smallpox vaccination confers immunity in more than 95% of recipients. The duration of protection after smallpox immunization is not precisely known but may be 5 years for primary vaccination and 10 years or longer after revaccination. Considering that routine vaccination of the general public ended in 1971, and of the military, in 1990, most individuals are now considered susceptible to smallpox.

Smallpox vaccine consists of live vaccinia virus (not variola virus), and the neutralizing antibodies produced by vaccination are cross-protective for other Orthopoxviruses.

Smallpox vaccine is administered by repeatedly puncturing the skin of the recipient with a bifurcated needle, a technique called scarification.

Slide 55 illustrates the vaccination process

The vaccine is administered by a sterile bifurcated needle dipped into reconstituted vaccine. Fifteen jabs are given intradermally into a 0.5 cm diameter area of the upper deltoid; a small amount of blood should appear at the site within 20-25 seconds. Alcohol will inactivate the vaccine virus, and should not be used to prepare the skin prior to administration (no skin prep is required). The vaccination site should be covered with a sterile gauze loosely held down by tape. The needle should be disposed of in a puncture-resistant sharps container after use. In the context of limited supplies in a smallpox outbreak, re-use of needles may be necessary. In this case, needles should be cleaned between cases using moist or dry heat sterilization (See CDC's Smallpox Response Plan for details).

Persons who may be administering smallpox vaccine should undergo training on vaccine administration and follow-up of vaccinated persons.

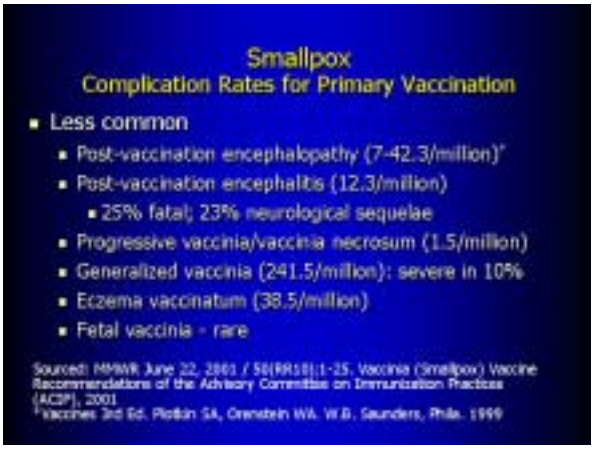
At this time, routine vaccination is currently recommended only for laboratory workers with occupational exposure to vaccinia cultures, or animals contaminated or infected with non-highly attenuated vaccinia virus, recombinant vaccinia viruses derived from non-highly attenuated vaccinia strains, or other Orthopoxviruses that infect humans.

A successful reaction to primary vaccination can be defined as "a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer" (ACIP, 2001). Revaccination is considered successful if "a pustular lesion is present or an area of definite induration or congestion surrounding a central lesion (i.e., scab or ulcer) is visible" 6-8 days following vaccination (ACIP, 2001). Equivocal reactions require revaccination.

Vaccine Complications (Slides 57-60)

Complications following smallpox vaccination are most common in infants and primary vaccinees. Rates of serious adverse events are significantly lower with revaccination. Serious complications are associated with immune system compromise. Slides 57 and 58 list potential complications by incidence rate; these are also listed below by severity and are described in more detail. Incidence rates are from: Vaccinia (Smallpox) Vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recommendations and Reports 2001 June 22;50(RR-10):1-25; and Plotkin SA & Orenstein WA, eds. Vaccines (3rd ed), 1999: Philadelphia.

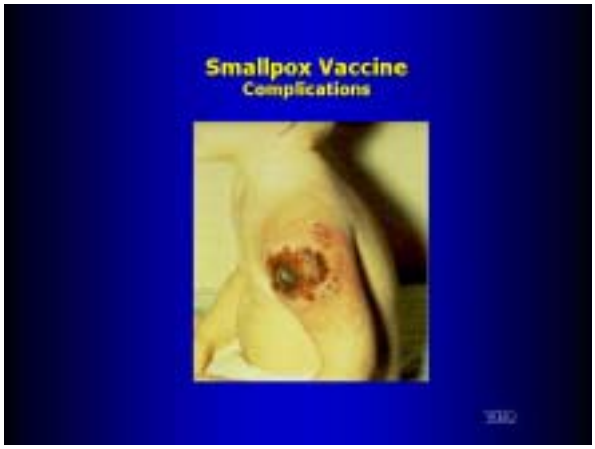
Less Severe Reactions



Inadvertent inoculation (from the site of vaccination to other sites) accounts for half of all post-vaccination complications. Autoinoculation usually occurs on the face, eyelid, nose, mouth, genitalia, or rectum. Slide 58 illustrates a case of inadvertent inoculation. Infection of the cornea is especially problematic. A variable amount of fever, malaise, and regional lymphadenitis lasting one to two days commonly develop at the end of the first week after vaccination, especially in children. Erythematous and urticarial rashes may also occur approximately 10 days following vaccination and usually resolve within two to four days.

Generalized vaccinia results from bloodborne dissemination of vaccinia virus and causes a vesicular or pustular rash that may be limited or diffuse. The overall rate is 241.5/million primary vaccinations. It is usually self-limited in persons with uncompromised immune systems, but can be severe in 10% of cases.

Severe Reactions



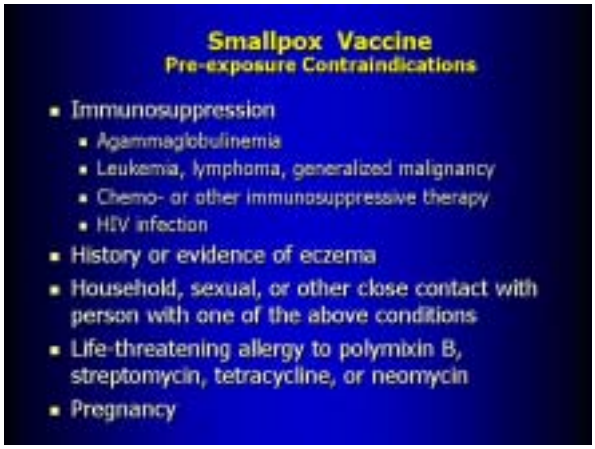
Post-vaccination encephalitisis occurs at an overall rate of 12.3/million primary vaccinations between 8-15 days following vaccination. The rate is highest among children <1 year of age. Approximately 15-25% of cases were fatal, and an additional 25% had permanent neurological impairment.

Progressive vaccinia, or vaccinia necrosusm or gangrenosa, is a severe and potentially fatal complication occurring in approximately 1.5/million primary vaccinations, and almost exclusively in individuals with cellular immunodeficiency. Progressive necrosis develops in the area of vaccination (illustrated in slide 59). Secondary progressive necrotizing lesions can occur in other body sites, including internal organs.

Eczema vaccinatum occurs in 38.5/million primary vaccinations (illustrated in slide 58) and results from dissemination of vaccinia virus in individuals with a history of eczema or other chronic or exfoliative skin condition. It is usually self-limited but can be severe and occasionally fatal. Severity is independent of the extent of underlying disease. Cases have also occurred in unvaccinated individuals with a history of eczema who have had contact with recently vaccinated individuals.

There have been fewer than 50 cases of *fetal vaccinia*, and these have mostly occurred following primary vaccination of the mother. Fetal vaccinia usually results in stillbirth or death of the infant shortly after delivery.

Vaccine Pre-exposure Contraindications



Contradindications for pre-exposure smallpox vaccine administration (i.e., prophylaxis) are listed in slide 61.

At this time, persons with certain medical conditions, primarily related to immune system compromise, are considered to have contraindications to smallpox vaccine:

Persons with diseases or conditions that cause immunodeficiency

Persons with serious, life-threatening allergies to the antibiotics polymyxin B, streptomycin, tetracycline, or neomycin

Persons who have ever been diagnosed with eczema, even if the condition is mild or not presently active.

Women who are pregnant

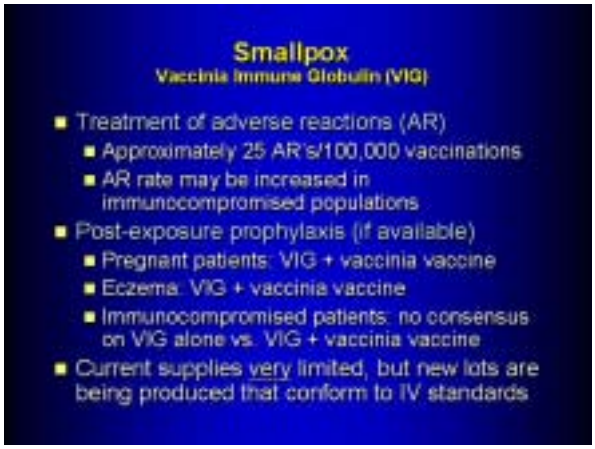
Persons with other acute or chronic skin conditions, such as atopic dermatitis, burns, impetigo, or varicella zoster, (until the condition resolves).

In the event of a known exposure to smallpox, no absolute contraindications to vaccination currently exist.

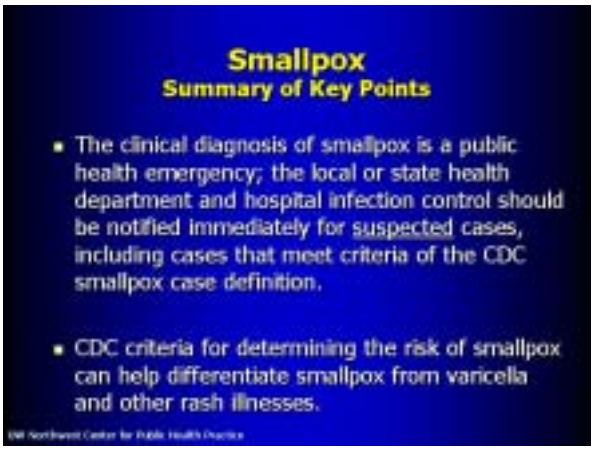
When deciding to administer smallpox vaccine to persons in the absence of a smallpox outbreak, health officials and providers must weigh the risks and benefits of vaccination against the likelihood of infection. For most persons at this time, the risks associated with vaccination clearly outweigh the likelihood of smallpox infection. In addition, the frequencies of adverse reactions described in the literature are from a time when there were fewer immunocompromised persons in society. A higher frequency of adverse reactions may result today from inadvertent vaccination of immunocompromised persons or transmission of vaccinia virus to immunocompromised contacts of vaccinees. As information on the risk of smallpox changes, or with the development of safer smallpox vaccines, the risk-benefit equation will need to be re-assessed.

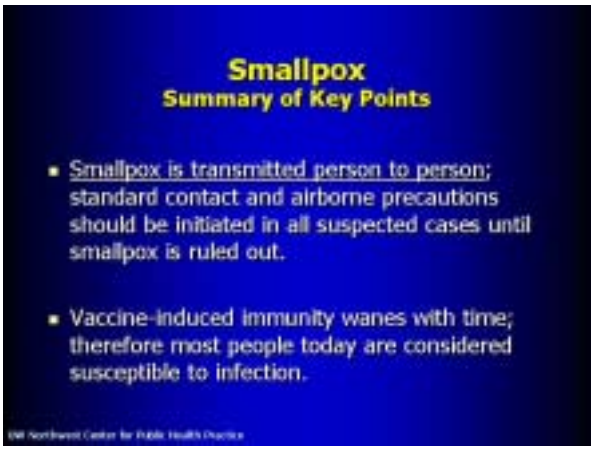
Vaccine Immune Globulin (VIG)

VIG can be used to treat eczema vaccinatum, generalized vaccinia in an extremely ill patient or one with serious underlying disease, inadvertent inoculation (except in the case of vaccinial keratitis, where increased scarring can occur), and possibly progressive vaccinia (depending on the immune status of the patient). VIG can only be obtained from CDC. A recombinant form of VIG may be developed in the future. Current supplies of VIG are limited (i.e., there is enough to treat about 600 serious adverse events), however recently, a contract for the production of VIG has been made with Cangene, and additional stores of the material are being supplied. There is sufficient intramuscular vaccinia immune globulin (IM-VIG) stored at the CDC to serve approximately 600-800 adverse events if appropriate recommendations are followed. New lots of intravenous (IV-VIG) are being produced that conform to intravenous standards. If available in sufficient quantities, VIG may also be an acceptable alternative to vaccination for post-exposure prophylaxis in persons at high-risk of vaccine complications and who are exposed to smallpox.

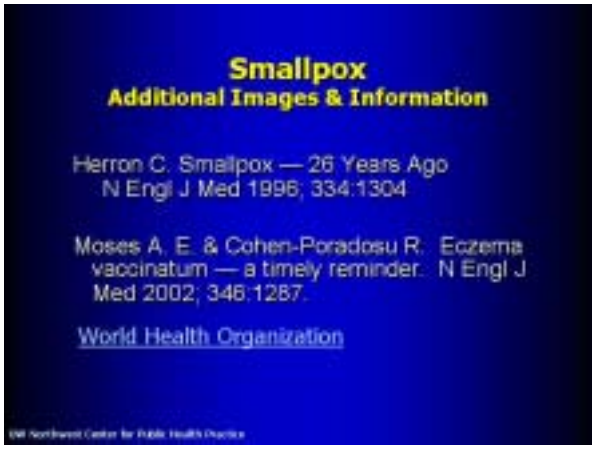


Summary of Key Points

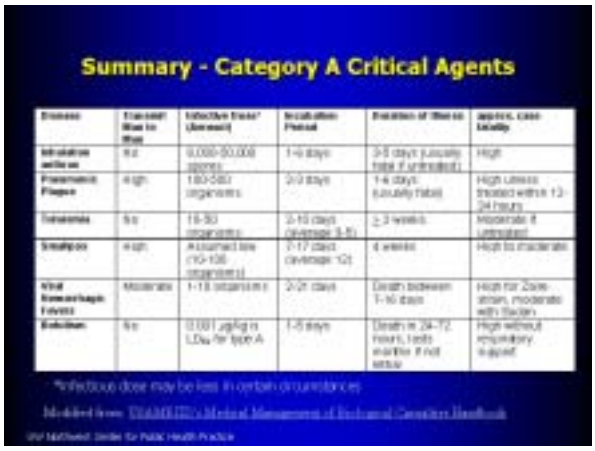


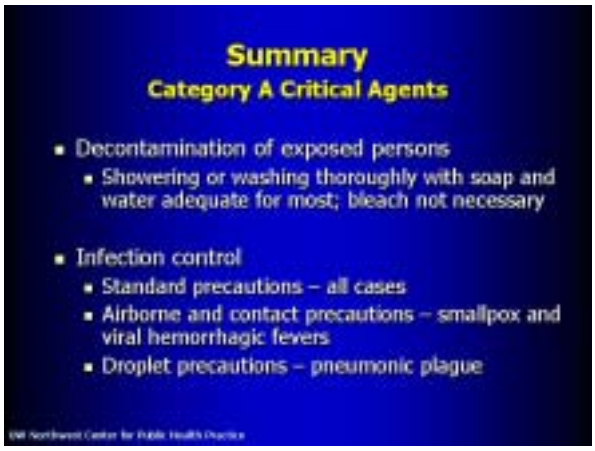


Additional Images & Information

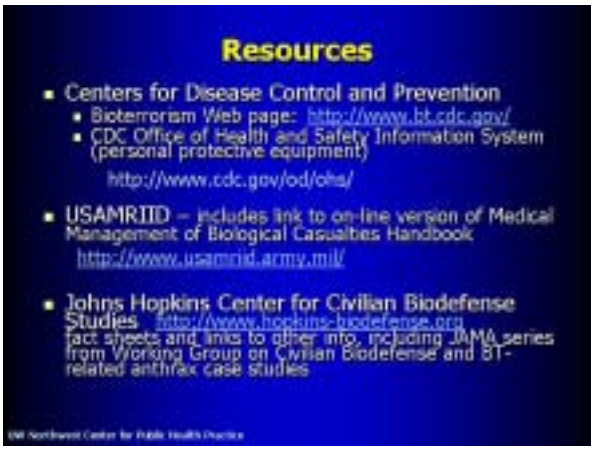


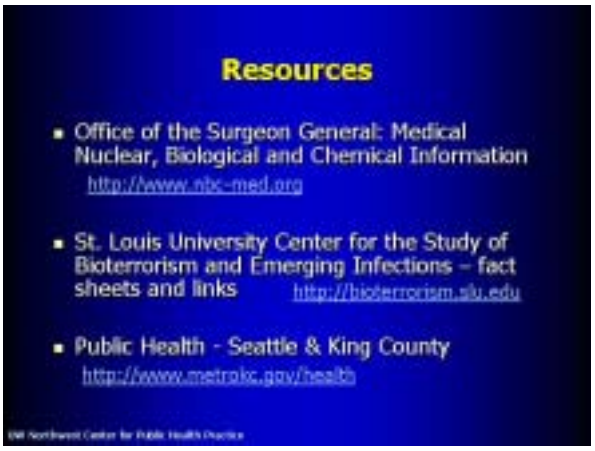
Summary: Category A Critical Agents

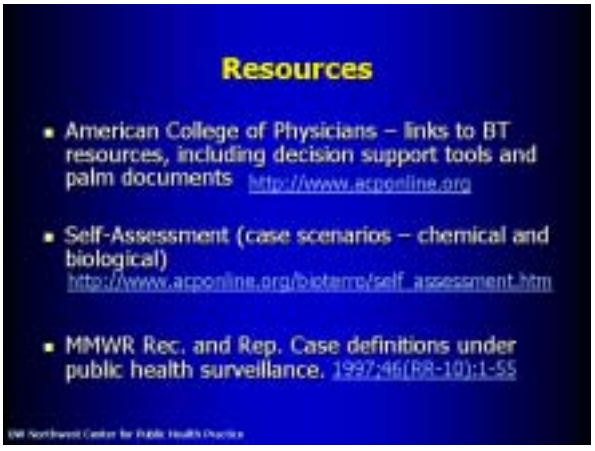




Resources

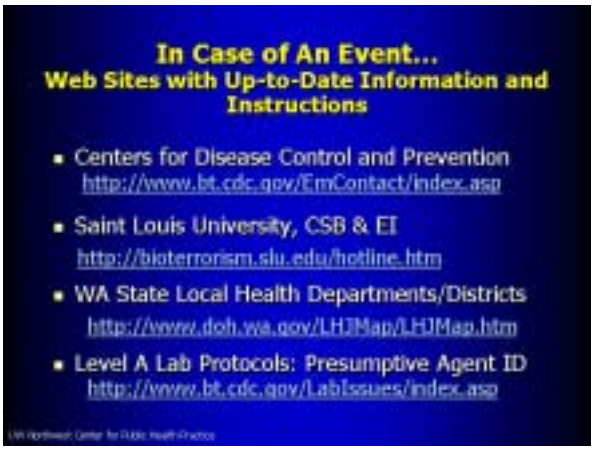

Resources
Centers for Disease Control and Prevention
Bioterrorism Web page: http://www.bt.cdc.gov/
CDC Office of Health and Safety Information System (personal protective equipment)
http://www.cdc.gov/od/ohs/
USAMRIID – includes link to on-line version of Medical Management of Biological Casualties Handbook
http://www.usamriid.army.mil/
Johns Hopkins Center for Civilian Biodefense Studies http://www.hopkins-biodefense.org
fact sheets and links to other info, including JAMA series from Working Group on Civilian Biodefense and BT-related anthrax case studies

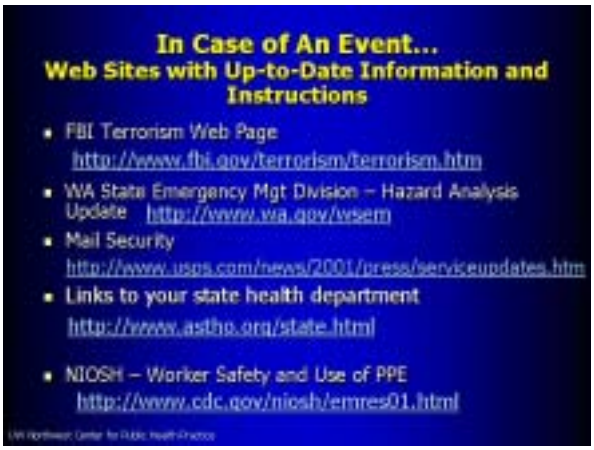

Resources
Office of the Surgeon General: Medical Nuclear, Biological and Chemical Information
http://www.nbc-med.org
St. Louis University Center for the Study of Bioterrorism and Emerging Infections – fact sheets and links http://bioterrorism.slu.edu
Public Health - Seattle & King County
http://www.metrokc.gov/health


Resources
American College of Physicians – links to BT resources, including decision support tools and palm documents http://www.acponline.org
Self-Assessment (case scenarios – chemical and biological)
http://www.acponline.org/bioterro/self_assessment.htm
MMWR Rec. and Rep. Case definitions under public health surveillance. 1997;46(RR-10):1-55

In Case of An Event…

The next two slides highlight Web-based resources valuable to clinicians during a BT event. Most of the links have been presented previously in the resources following the different sections of this curriculum. They are included here again because they contain answers to questions clinicians may have during the course of an event – updates on disease investigations and threats, current testing, treatment and prophylaxis recommendations, and contact numbers for additional information and reporting.





References

General Bioterrorism Information and Web sites

American College of Occupational and Environmental Medicine. Emergency Preparedness/Disaster Response. January 2002. http://www.acoem.org/member/trauma.htm

Centers for Disease Control and Prevention. Public Health Emergency Preparedness and Response. January 2002. http://www.bt.cdc.gov

Center for the Study of Bioterrorism and Emerging Infections at Saint Louis University School of Public Health. Home Page. January 2002. http://www.bioterrorism.slu.edu

Historical perspective of bioterrorism. Wyoming Epidemiology Bulletin;5(5):1-2, Sept-Oct 2000.

Journal of the American Medical Association. Bioterrorism articles. April 2002. http://pubs.ama-assn.org/bioterr.html

Johns Hopkins Center for Civilian Biodefense Studies. Home Page. January 2002. http://www.hopkins-biodefense.org/

Pavlin JA. Epidemiology of bioterrorism. Emerging Infect Dis [serial online] 1999 Jul-Aug; 5(4). http://www.cdc.gov/ncidod/EID/eid.htm

Tucker JB. Historical trends related to bioterrorism: an empirical analysis. Emerging Infect Dis [serial online] 1999 Jul-Aug; 5(4). http://www.cdc.gov/ncidod/EID/eid.htm

Washington State Department of Health. Home Page. January 2002. http://www.doh.wa.gov

Bioterrorism Preparedness and Response

Centers for Disease Control and Prevention. Biological and chemical terrorism: strategic plan for preparedness and response. MMWR 49(RR-4): 1-14.

Federal Bureau of Investigation. Home Page. January 2002. http://www.fbi.gov/

Federal Emergency Management Agency & United States Fire Administration-National Fire Academy. Emergency Response to Terrorism: Self-Study (ERT:SS) (Q534), June 1999. http://training.fema.gov/EMIWeb/crslist.htm

Geberding JL, Hughes JM, Koplan JP. Bioterrorism preparedness and response: clinicians and public health agencies as essential partners. JAMA 2002;287(7):898-900.

Koehler J, Communicable Disease Control, Epidemiology & Immunization Section, Public Health – Seattle & King County. Surveillance and Preparedness for Agents of Biological Terrorism (presentation). 2001.

O'Carroll PW, Halverson P, Jones DL, Baker EL. The health alert network in action. Northwest Public Health 2002;19(1):14-15.

Diseases of Bioterrorist Potential

Advisory Committee on Immunization Practices (ACIP). Use of smallpox (vaccinia vaccine), June 2002: supplemental recommendation of the ACIP.

Bolyard EA, Tablan OC, Williams WW, Pearson ML, Shapiro CN, Deithman SD. HICPAC. Guideline for infection control in health care personnel, 1998. Am J Infect Control 1998;26:289-354.
http://www.bt.cdc.gov/ncidod/hip/GUIDE/infectcont98.htm

Breman JG & Henderson DA. Diagnosis and management of smallpox. N Engl J Med 2002;346(17):1300-1308.

Centers for Disease Control and Prevention. Smallpox Response Plan and Guidelines (Version 3.0). Sep 21, 2002.

Centers for Disease Control and Prevention. CDC Responds: Smallpox: What Every Clinician Should Know, Dec. 13th, 2001.
Webcast: http://www.sph.unc.edu/about/webcasts/

Centers for Disease Control and Prevention. CDC Responds: Update on Options for Preventive Treatment for Persons at Risk for Inhalational Anthrax, Dec 21, 2001. Webcast: http://www.sph.unc.edu/about/webcasts/

Centers for Disease Control and Prevention, American Society for Microbiology & American Public Health Laboratories. Basic Diagnostic Testing Protocols for Level A Laboratories.
http://www.asmusa.org/pcsrc/biodetection.htm#Level%20A%20Laboratory%20Protocols

CDC. Considerations for distinguishing influenza-like illness from inhalational anthrax. MMWR 2001;50(44):984-986.

CDC. Notice to readers update: management of patients with suspected viral hemorrhagic fever – United States. MMWR. 1995;44(25):475-79.

CDC. The use of anthrax vaccine in the United States. MMWR 2000;49(RR-15):1-20.

CDC. Update: investigation of bioterrorism-related anthrax --- Connecticut, 2001. MMWR 2001;50(48):1077-9.

CDC. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2001;50(RR-10):1-25.

Chin J, ed. Control of Communicable Diseases Manual (17th ed), 2000: Washington DC.

Duchin JS, Communicable Disease Control, Epidemiology & Immunization Section Public Health – Seattle & King County. Bioterrorism: Recognition and Clinical Management of Anthrax and Smallpox (presentation). 2001.

Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its Eradication, 1988:Geneva.

Franz DR, Jarhling PB, Friedlander AM, McClain DJ, Hoover DL, Bryne R et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278:399-411.

Frey SE, Newman FK, Cruz J, Shelton WB, Tennant JM, Polach T et al. Dose-related effects of smallpox vaccine. N Engl J Med 2002;346(17):1265-74.

Fulco CE, Liverman CT, Sox HC, eds. Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines, 2000: Washington DC. URL: http://www.nap.edu.

Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy (3rd ed), 1996: St. Louis.

Jernigan JA, Stephens DS, Ashford DA, Omenaca C, Topiel MS, Galbraith M et al. Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States. Emerging Infect Dis [serial online] 2001 Jul-Aug; 7(6): 933-44. http://www.cdc.gov/ncidod/EID/eid.htm

Mandel GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases (5th ed), 2000: Philadelphia.

Michigan Department of Community Health Bureau of Epidemiology. Clinical Aspects of Critical Biologic Agents: web-based course, May 2001. http://www.mappp.org/epi/info/

New England Journal of Medicine. Smallpox Issue. April 25, 2002; 346(17).

Plotkin SA & Orenstein WA, eds. Vaccines (3rd ed), 1999: Philadelphia.

Rosen P, Barkin R, Danzl DF, et al, eds. Emergency Medicine: Concepts and Clinical Practice (4th ed), 1998: St. Louis, MO.

Rotz LD, Khan AS, Lillebridge SR. Public health assessment of potential biological terrorism agents. Emerging Infect Dis [serial online] 2002;8(2):225-230. http://www.cdc.gov/ncidod/EID/eid.htm.

US Army Medical Research Institute of Infectious Diseases. USAMRIID's Medical Management of Biological Casualties Handbook (4th ed). Fort Detrick, MD: 2001.

Zajtchuk R, Bellamy RF, eds. Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare. Office of The Surgeon General Department of the Army, United States of America. http://ccc.apgea.army.mil/reference_materials/textbook/HTML_Restricted/index.htm

Working Group on Civilian Biodefense Consensus Recommendations:

Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, et al. Botulinum toxin as a biological weapon: medical and public health management. JAMA 2001;285:1059-1070.

Borio L, Inglesby T, Peters CJ, Schmalijohn AL, Hughes JM, Jarhling PB et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. JAMA. 2002;287:2391-2405.

Dennis DT, Inglesby TV, Henderson DA, MD, Bartlett JG, Ascher MS, Eitzen E, et al. Tularemia as a biological weapon: medical and public health management. JAMA 2001;285:2763-73.

Henderson DA, Inglesby TV, Bartlett JG, Ascher MS, Eitzen E, Jahrling PB, et al. Smallpox as a biological weapon: medical and public health management. JAMA 1999;281(22): 2127-2137.

Inglesby TV, Dennis DT, Henderson DA, MD, Bartlett JG, Ascher MS, Eitzen E, et al. Plague as a biological weapon: medical and public health management. JAMA 2000;283:2281-90.

Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, et al. Anthrax as a biological weapon: medical and public health management. JAMA 1999;281:1735-45.

Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E et al. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287:2236-2252.

Psychological Aftermath of Crisis

Agency for Toxic Substances and Disease Registry: A Primer on Health Risk Communication Principles and Practices.
http://www.atsdr.cdc.gov/HEC/primer.html

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

American Psychiatric Association. Home Page. January 2002.
http://www.psych.org

Department of Health and Human Services, Substance Abuse and Mental Health Services Administration Center for Mental Health Services. Disaster manual for mental health and human services workers in major disasters.
http://www.mentalhealth.org/cmhs/EmergencyServices/fpubs.asp

Holloway HC, Norwood AE, Fullerton CS, Engel CC, Ursano RJ. The threat of biological weapons: prophylaxis and mitigation of psychological and social consequences. JAMA 1997;278:425-7.

Norwood AE, Ursano RJ, Fullerton CS. Disaster psychiatry: principles and practice. Psychiatr Q 2000 Fall;71(3):207-26.

Walker E, University of Washington Department of Psychiatry and Behavioral Sciences. Bioterrorism and Mental Health Issues (presentation). December 8, 2001.