ZEBRA MANUAL

A Reference Handbook for Bioterrorism Agents

Arizona Department of Health Services
Division of Public Health Services
Office of Public Health Emergency Preparedness and Response

602-364-3289

Visit Our Website at http://www.azdhs.gov/phs/edc/edrp/index.htm

Arizona Department of Health Services

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JANET NAPOLITANO, GOVERNOR
CATHERINE R. EDEN, DIRECTOR

Date: September 7, 2004

Dear Infection Control Personnel:
Dear Health Care Professionals:
Dear Public Health Professionals:

Re: ZEBRA MANUAL: A REFERENCE HANDBOOK FOR BIOTERRORISM AGENTS

Infection control personnel, healthcare providers and public health personnel need to know how to recognize symptoms of exposure to a bioterrorism agent. The Arizona Department of Health Services is distributing this updated version of the Zebra Manual to assist you in responding properly to a possible patient exposure to such an agent.

The medical school adage, "when you hear hoof beats, think horses, not zebras" has a new twist in this age of threats of bioterrorism. We can learn how to recognize a zebra among the horses by increasing our awareness of the clinical syndromes associated with each potential bioterrorism agent.

This enhanced Zebra Manual contains fact sheets, diagnostic guidelines, and infection control information for all Category "A" and "B" biological agents, as well as extensive smallpox information.

If you have questions about specific diseases or about disease reporting, please contact your County Health Department or visit our web site: www.azdhs.gov/phs/edc/edrp/index.htm

Sincerely,

David M. Engelthaler, M.S.
Office Chief
Office of Public Health
Emergency Preparedness and Response

Sincerely,

Karen Lewis, M.D.
Emergency Preparedness Medical Coordinator
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ZEBRA MANUAL

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Arizona Department of Health Services

BIOTERRORISM SYNDROMES

If an unusual illness is seen which leads you to suspect bioterrorism, IMMEDIATELY call your county health department to arrange for specialized lab testing, guidelines for treatment, and infection control guidance.
You may also call the Arizona Department of Health Services at 602-364-3289 or the Centers for Disease Control and Prevention's 24-hour bioterrorism response office at 770-488-7100

Syndrome	Biological Threat Disease Description	Differential Diagnosis	Initial Laboratory and Other Diagnostic Test Results	Immediate Public Health and Infection Control Actions
Acute Respiratory Distress with Fever	**Inhalational Anthrax** Abrupt onset of fever, chest pain; respiratory distress without radiographic findings of pneumonia; no history of trauma or chronic disease; progression to shock and death within 24-36 hours.	Bacterial mediastinitis, coccidioidomycosis, influenza, Legionnaires' disease, tularemia, Q fever, psittacosis, histoplasmosis, ruptured aneurysm, superior vena cava syndrome (SVC syndrome), SARS.	Chest x-ray with widened mediastinum; gram-positive bacilli in sputum or blood; definitive testing available through public health laboratory network	Call Local Health Department. Alert laboratory to possibility of anthrax. Standard precautions. Contact precautions for skin lesions.
	Pneumonic Plague Severe community-acquired pneumonia but with hemoptysis, cyanosis, gastrointestinal symptoms, shock.	Severe bacterial or viral pneumonia, inhalational anthrax, pulmonary infarct, pulmonary hemorrhage, hantavirus pulmonary syndrome, meningococcemia, rickettsiosis, influenza, mycoplasma pneumonia, SARS.	Gram-negative bacilli or coccobacilli in sputum, blood, or lymph node; safety-pin appearance with Wright or Giemsa stain; definitive testing available through public health laboratory network.	Standard and droplet precautions with a regular surgical mask. Call hospital infection control and Local Health Department. Family members/close contacts of patients may need chemoprophylaxis; get detailed address and phone number information. Alert laboratory of possibility of plague.
	Ricin (aerosolized) Acute onset of fever, chest pain, and cough, progressing to respiratory distress and hypoxemia; not improved with antibiotics; death in 36-72 hours.	Plague, tularemia, Q fever, Staphylococcal enterotoxin B, phosgene.	Chest x-ray with pulmonary edema. Consult with Local Health Department regarding specimen collection and diagnostic testing procedures.	Call Local Health Department. Standard precautions.
	Staphylococcal Enterotoxin B Acute onset of fever, chills, headache, nonproductive cough, and myalgia (influenza-like illness) with a NORMAL chest x- ray.	Influenza, adenovirus.	Primarily clinical diagnosis. Consult with Local Health Department regarding specimen collection and diagnostic testing procedures.	Call Local Health Department. Standard precautions.
Acute Rash with Fever	**Smallpox** Fever followed by papular rash that begins on the face and extremities and uniformly progresses to vesicles and pustules; headache, vomiting, back pain, and delirium common. Severely ill.	Atypical varicella, drug eruption, disseminated herpes zoster, Stevens-Johnson syndrome, atypical measles, secondary syphilis, erythema multiforme, meningococcemia, monkeypox, cowpox.	Clinical with laboratory confirmation; vaccinated, gowned and gloved person wearing N95 respirator obtains specimens (scabs or swabs of vesicular or pustular fluid). Call public health immediately and before obtaining specimen; definitive testing available through public health laboratory network.	Call hospital infection control and Local Health Department immediately. Standard, contact, and airborne precautions required. Family members/close contacts of patients may need prophylaxis; get detailed address and phone number information.
	Viral Hemorrhagic Fever (e. g., Ebola) Fever with mucous membrane bleeding, petechiae, thrombocytopenia, and hypotension in a patient without underlying malignancy.	Bacteremia (especially meningococcemia), malaria, typhus, leptospirosis, borreliosis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS).	Definitive testing available through public health laboratory network--call public health immediately.	Call hospital infection control and Local Health Department immediately. Standard, airborne, and scrupulous contact precautions. Family members/close contacts of patients may need follow-up; get detailed address and phone number information.
Neurologic Syndromes	**Botulism** Acute afebrile, symmetric descending flaccid paralysis beginning with cranial nerve palsies. Normal mental status.	Guillain-Barré syndrome, myasthenia gravis, midbrain stroke, polio, tick paralysis, chemical intoxication, organophosphate, carbon monoxide, paralytic shellfish, belladonna-like alkaloid poisoning, Eaton-Lambert myasthenia syndrome.	CSF protein normal; EMG with repetitive nerve stimulation shows augmentation of muscle action potential; toxin assays of serum, feces, or gastric aspirate available through public health laboratory network.	Request botulinum antitoxin from local/state health department; call Local Health Department. Standard precautions.
	Encephalitis (Venezuelan, Eastern, Western) Encephalopathy with fever and seizures and/or focal neurologic deficits.	Herpes simplex, Epstein Barr virus, mycoplasma, West Nile virus, post-infectious encephalitis, rabies, syphilis, TB, other arboviruses.	Serologic testing available through public health laboratory network.	Call Local Health Department. Droplet precautions pending evaluation.
Influenza-like Illness	**Brucellosis** Irregular fever, chills, malaise, headache, weight loss, profound weakness and fatigue. Arthralgias, sacroiliitis, paravertebral abscesses. Anorexia, nausea, vomiting, diarrhea, hepatosplenomegaly. May have cough and pleuritic chest pain.	Inhalational anthrax, influenza, mycoplasma pneumonia, Legionnaire's disease, Q fever, plague, psittacosis, hantavirus pulmonary syndrome, tularemia, SARS	Tiny, slow-growing, faintly-staining, gram-negative coccobacilli in blood or bone marrow culture. Leukocyte count normal or low. Anemia, thrombocytopenia possible. CXR nonspecific: normal, broncho-pneumonia, abscesses, single or miliary nodules, enlarged hilar nodes, effusions. Serologic testing and culture available through public health laboratory network.	Notify laboratory if brucellosis suspected – microbiological testing should be done in a biological safety cabinet to prevent lab-acquired infection. Call Local Health Department. Standard precautions.
	Tularemia (Typhoidal, Pneumonic) Fever, chills, rigors, headache, myalgias, coryza, sore throat initially; followed by weakness, anorexia, weight loss. Substernal discomfort, dry cough if pneumonic disease.	Inhalational anthrax, influenza, mycoplasma pneumonia, Legionnaire's disease, Q fever, plague, psittacosis, hantavirus pulmonary syndrome, brucellosis, SARS	Small, faintly-staining, slow-growing, gram-negative coccobacillus in smears or cultures of sputum, blood. CXR may show infiltrate, hilar adenopathy, effusion. Definitive testing available public health laboratory network.	Notify laboratory if tularemia suspected – microbiological testing should be done in a biological safety cabinet to prevent lab-acquired infection. Call Local Health Department. Standard precautions.

Adapted from California State and Local Health Department Bioterrorism Surveillance and Epidemiology Working Group, 2001
Courtesy of Los Angeles County Department of Health Services – Public Health

American Medical Association
Physicians dedicated to the health of America

Quick Reference Guide

Biological Weapons

September 2002

Characteristics of Selected Bioterrorism Agents[1, 4]

Disease/ Agent	Incubation Period	Clinical Syndrome	Lethality	Diagnostic Tests	Treatment[2]	Vaccine	Chemoprophylaxis
BACTERIAL AGENTS							
Anthrax *Bacillus anthracis*	1-5 days (possibly up to 60 days). Data from 22 patients infected in October and November 2001 indicate a median incubation period of 4 days (range of 4-7 days) incubation period for inhalational anthrax and 1-10 days (mean of 5 days) incubation period for cutaneous anthrax.	**Cutaneous:** Evolving skin lesion (face, neck, arms), progresses to vesicle, depressed ulcer, and black necrotic lesion	20% if untreated, otherwise rarely fatal	Gram stain and culture of blood, pleural and ascitic fluids, CSF, vesicular fluid or lesion exudate. Sputum rarely positive. Confirmatory serological and PCR tests available through public health laboratory network. Widened mediastinum on chest x-ray (CXR) for inhalational and occasionally, GI anthrax. CXR abnormalities also include paratracheal and hilar fullness and may be subtle. Consider chest computerized tomography (CT) if diagnosis is uncertain.	Ciprofloxacin; doxycycline. Combination therapy of ciprofloxacin or doxycycline **plus** one or two other antimicrobials should be considered with inhalational anthrax.[3] Penicillin should be considered if strain is susceptible and does not possess inducible beta-lactamases. If meningitis is suspected, doxycycline may be less optimal because of poor CNS penetration. Steroids may be considered for severe edema and for meningitis.	Inactivated vaccine (licensed but not readily available). 6 injections and annual booster	Ciprofloxacin or doxycycline, with or without vaccination; if strain is susceptible, penicillin or amoxicillin should be considered.
		Gastrointestinal (GI): Nausea, vomiting, abdominal pain, bloody diarrhea, sepsis	Approaches 100% if untreated but data are limited. Rapid, aggressive treatment may reduce mortality.				
		Inhalational: Abrupt onset of "flu-like" symptoms, fever with or without chills, sweats, fatigue or malaise, non- or minimally productive cough, nausea and vomiting, dyspnea, headache, chest pain, followed in 2 to 5 days by severe respiratory distress, mediastinitis, hemorrhagic meningitis, sepsis, shock. Limited data from the October 2001 infections indicate hemorrhagic pleural effusions to be strongly associated with inhalational anthrax and rhinorrea was present in only 1/10 patients.	Once respiratory distress develops, mortality rates may approach 90%. Begin treatment when inhalational anthrax is suspected, do not wait for confirmatory testing. Data from the 2001 infections indicate that early treatment significantly decreases the mortality rate.				
Brucellosis *B. mellitensis, B. suis, B. abortus, and B. canis*	5-60 days (usually 1-2 months)	Nonspecific "flu-like" symptoms, fever, headache, profound weakness and fatigue, gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea or constipation. Osteoarticular complications common.	Less than 5% even if untreated. Tends to incapacitate rather than kill.	Blood and bone marrow culture (may require 6 weeks to grow *Brucella*) Confirmatory culture and serological testing available through public health laboratory network.	Doxycycline **plus** streptomycin or rifampin. Alternative therapies: ofloxacin **plus** rifampin; doxycycline **plus** gentamicin; TMP/SMX **plus** gentamicin.	None. Only animal vaccine exists.	Doxycycline **plus** streptomycin or rifampin
Inhalational (pneumonic) tularemia *Francisella tularensis*	3-5 days (range of 1-21 days)	Sudden onset of acute febrile illness, weakness, chills, headache, generalized body aches, elevated WBCs. Pulmonary symptoms such as dry cough, chest pain or tightness with or without objective signs of pneumonia, are present. Progressive weakness, malaise, anorexia, and weight loss occurs, potentially leading to sepsis and organ failure.	About 30%-60% if untreated	Largely clinical diagnosis. Culture of blood, sputum, biopsies, pleural fluid, bronchial washings (culture is difficult and potentially dangerous). Confirmatory serological testing available through public health laboratory network.	Streptomycin; gentamicin. An alternative is ciprofloxacin.	Live attenuated vaccine (USAMRIID, investigational) given by scarification; currently under review by FDA, limited availability.	Tetracycline; doxycycline; ciprofloxacin
Pneumonic plague *Yersinia pestis*	1-10 days (typically 2-3 days)	Acute onset of "flu-like" prodrome: fever, myalgia, weakness, headache. Within 24 hours of prodrome, chest discomfort, cough, and dyspnea appear. By day 2-4 of illness, symptoms progress to cyanosis, respiratory distress and hemodynamic instability.	Almost 100% if untreated. 20%-60% if appropriately treated within 18-24 hours of symptoms. Begin treatment when diagnosis of plague is suspected, do not wait for confirmatory testing.	Gram stain and culture of blood, CSF, sputum, lymph node aspirates, bronchial washings. Confirmatory serological and bacteriological tests available through public health laboratory network.	Streptomycin; gentamicin. Other alternatives include doxycycline, tetracycline, ciprofloxacin, and chloramphenicol. Chloramphenicol is 1st choice for meningitis except in pregnant or lactating women.	Inactivated whole cell vaccine licensed but not readily available. Injection with boosters. Vaccine not protective against aerosol in animals.	Tetracycline; doxycycline; ciprofloxacin

Q-Fever *Coxiella burnetii*	2-14 days (may be up to 40 days)	Nonspecific febrile disease, chills, cough, weakness and fatigue, pleuritic chest pain, pneumonia may be present.	1%-3% Fatalities are uncommon even if untreated, but relapsing symptoms may occur.	Isolation of organism may be difficult. Confirmatory testing via serology or PCR available through public health laboratory network.	Tetracycline; doxycycline	Inactivated whole-cell vaccine (investigational). Skin test to determine prior exposure to *C. burnetii* recommended before vaccination.	Tetracycline; doxycycline
VIRAL AGENTS							
Smallpox *Variola major virus*	7-17 days	Prodrome of high fever, malaise, prostration, headache, vomiting, delirium followed in 2-3 days by maculopapular rash uniformly progressing to pustules and scabs, mostly on extremities and face. Requires astute clinical evaluation; may be confused with chickenpox, erythema multiforme with bullae, or allergic contact dermatitis.	30% in unvaccinated persons	Pharyngeal swab, vesicular fluid, biopsies, scab material for definitive testing through public health laboratory network. Notify CDC Poxvirus Section at 404 639-2184.	Supportive care. Cidofovir shown to be effective *in vitro*, and in experimental animals infected with surrogate orthopox virus.	Attenuated-strain vaccinia vaccinederived from calf lymph; given by scarification (licensed, limited supply). Vaccination may be effective within 3-4 days of exposure.	Vaccination given within 3-4 days following exposure can prevent, or decrease the severity of, disease.
Viral Encephalitis *Venezuelan (VEE)* *Eastern (EEE)* *Western (WEE)*	VEE: 2-6 days EEE, WEE: 7-14 days	Systemic febrile illness, with encephalitis developing in some populations. Generalized malaise, spiking fevers, headache, myalgia. Incidence of seizures and/or focal neurologic deficits may be higher after biological attack.	VEE: less than 10% EEE: 50-75% WEE: 10%	Clinical and epidemiological diagnosis. WBC count may show striking leukopenia and lymphopenia. Confirmatory serological tests and viral isolation available through public health laboratory network.	Supportive care; analgesics, anticonvulsants as needed	Several IND vaccines, poorly immunogenic, highly reactogenic.	None available
Viral Hemorrhagic Fevers (VHFs) *Arenaviruses (Lassa, Junin, and related viruses);* *Bunyaviruses (Hanta, Congo-Crimean, Rift Valley);* *Filoviruses (Ebola, Marburg);* *Flaviviruses (Yellow Fever, Dengue, various tick-borne disease viruses)*	4-21 days	Fever with mucous membrane bleeding, petechiae, thrombocytopenia and hypotension in patients w/o underlying malignancies. Malaise, myalgias, headache, vomiting, diarrhea may occur.	Variable depending on viral strain 15% to 25% with Lassa fever to as high as 90% with Ebola	Confirmatory serological testing and viral isolation available through public health laboratory network. Notify CDC Special Pathogens Office at 404 639-1115.	Supportive therapy. Ribavirin may be effective for Lassa fever, Argentine hemorrhagic fever, and Congo-Crimean hemorrhagic fever.	Yellow fever vaccine is the only licensed vaccine available. Vaccines for some of the other VHFs exist but are for investigational use only.	Ribavarin is suggested for Congo-Crimean hemorrhagic fever and Lassa fever.
Disease/ Agent	**Incubation Period**	**Clinical Syndrome**	**Lethality**	**Diagnostic Tests**	**Treatment[2]**	**Vaccine**	**Chemoprophylaxis**

Abbreviations:

CDC - Centers for Disease Control and Prevention
CSF - Cerebrospinal Fluid
IND - Investigational New Drug
PCR - Polymerase Chain Reaction
RBC - Red Blood Cell
SMX - Sulfamethoxazole
TMP - Trimethoprim
USAMRIID - United States Army Medical Research Institute of Infectious Diseases
WBC - White Blood Cell

(See reverse side for more information.)

Characteristics of Selected Bioterrorism Agents[1, 4]

Toxin/ Agent	Incubation Period	Clinical Syndrome	Lethality	Diagnostic Tests	Treatment[2]	Vaccine	Chemopro-phylaxis
BIOLOGICAL TOXINS							
Botulinum toxin *Clostridium botulinum*	1-5 days (typically 12-36 hours)	Blurred vision, diplopia, dry mouth, ptosis, fatigue. As disease progresses, acute bilateral descending flaccid paralysis, respiratory paralysis resulting in death.	60% without ventilatory support	Treatment and reporting is based on clinical diagnosis. Serum and stool should be assayed for toxin by mouse neutralization bioassay, which may require several days.	Supportive care - ventilation may be necessary. Trivalent equine antitoxin (serotypes A,B,E - licensed, available from the CDC) should be administered immediately following clinical diagnosis. Anaphylaxis and serum sickness are potential complica-tions from antitoxin. Aminoglycosides and clindamycin must not be used.	Pentavalent toxoid (A-E), yearly booster (investigation-al, CDC) Not available to the public	Antitoxin might be sufficient to prevent illness following exposure but is not recommended until patient is showing symptoms.
Enterotoxin B *Staphylo-coccus aureus*	3-12 hours	Acute onset of fever, chills headache, nonproductive cough. Normal chest x-ray.	Probably low (little data available for respiratory exposure).	Clinical diagnosis. Serology on acute and convalescent serum can confirm diagnosis.	Supportive care.	No vaccine available	None available
Ricin toxin *Ricinus communis*	18-24 hours (acute symptoms may appear as early as 4-8 hours following exposure)	Weakness, chest tightness, fever, cough, pulmonary edema, respiratory failure, circulatory collapse, hypox-emia resulting in death (usually within 36-72 hours).	Mortality data not available but potential for death is likely to be high with extensive exposure.	Clinical and epidemiological diagnosis. Confirmatory serological testing available through public health laboratory network.	Supportive care. Treatment for pulmonary edema. Gastric decontamination if toxin is ingested.	No vaccine available	None available
T-2 mycotoxins *Fusarium, Myrotecium, Trichoderma, Stachybotrys and other filamentous fungi*	Minutes to hours	Abrupt onset of mucocutaneous and airway irritation and pain may include skin, eyes, and gastrointestinal tract; systemic toxicity may follow.	Severe exposure can cause death in hours to days.	Consult with local health department regarding specimen collection and diagnostic testing procedures. Confirmation requires testing of blood, tissue and environmental samples.	Clinical support. Soap and water washing within 4-6 hours reduces dermal toxicity; washing within 1 hour may eliminate toxicity entirely. No effective medications or antidotes.	No vaccine available	None available
Toxin/ Agent	Incubation Period	Clinical Syndrome	Lethality	Diagnostic Tests	Treatment[2]	Vaccine	Chemopro-phylaxis

Abbreviations:

CDC - Centers for Disease Control and Prevention
CSF - Cerebrospinal Fluid
IND - Investigational New Drug
PCR - Polymerase Chain Reaction
RBC - Red Blood Cell
SMX - Sulfamethoxazole
TMP - Trimethoprim
USAMRIID - United States Army Medical Research Institute of Infectious Diseases
WBC - White Blood Cell

(See reverse side for more information.)

Important Note

1. Physicians should report noticeable increases in unusual illnesses, symptom complexes, or disease patterns (even without definitive diagnosis) to public health authorities. Prompt reporting of unusual patterns of illness can allow public health officials to initiate an epidemiologic investigation earlier than would be possible if the report awaited definitive etiologic diagnosis. **If you suspect an unusual disease or possible outbreak, please call your state or local health department.** These numbers are available at: ***http://www.statepublichealth.org/directory.php*** and ***http://www.naccho.org/general8.cfm***

   Information contained in this table was current as of September 2002, and is intended for educational purposes only. Medication information should be researched and verified before initiation of patient treatment.

2. **Different scenarios may require different treatment regimens. Please consult listed references and an infectious disease specialist for definitive dosage information.**

3. Other agents with *in vitro* activity suggested for use in conjunction with ciprofloxacin or doxycycline for treatment of inhalational anthrax include rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin, and clarithromycin.

4. **This table was compiled from the following references:**

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SZA:02-381:10.5M:9/02

Arizona Department of Health Services

CHARACTERISTICS of BIOTERORRISM AGENTS

	Disease	Incubation Period	Duration of Illness	Lethality (approx. case fatality rates)	Infection Control Measures
Bacteria	**Anthrax (inhalation)**	1-60 days (usually < 2 weeks)	3-5 days (usually fatal if untreated)	High	Standard
	Anthrax (cutaneous)	1-12 days (usually < 2 weeks)	1-2 weeks	20% untreated <1% treated	Standard (includes gloves if touching wound)
	Brucellosis	5-60 days (usually 3-4 weeks)	Weeks to months	<5% untreated	Standard
	Cholera	4 hours - 5 days (usually 2-3 days)	≥ 1 week	Low with treatment, high without	Contact (if incontinent)
	Glanders (pneumonic)	10-14 days	Death in 7-10 days in septicemic form	>50%	Standard
	Plague (pneumonic)	1-10 days (usually 2-3 days)	1-6 days (usually fatal)	High unless treated within 12-24 hours	Droplet
	Q Fever	10-40 days (usually 14-22 days)	2-14 days	Very low	Standard
	Tularemia (pneumonic)	1-21 days (usually 3-5 days)	≥ 2 weeks	Moderate if untreated	Standard
Viruses	**Smallpox**	7-17 days (average 12 days)	4 weeks	High to moderate	Contact and Aerosol
	Venezuelan Equine Encephalitis	2-6 days	Days to weeks	Low	Droplet
	Viral Hemorrhagic Fevers	4-21 days (depends on type of VHF virus)	Death between 7-16 days	Moderate to high	Contact and Aerosol
Toxins	**Botulism (food borne)**	12-48 hours (range: 6 hours-8 days)	Death in 24-72 hours; paralysis can last months if not fatal	High without respiratory support	Standard
	Ricin	4-8 hours	Inhalation – death within 3-5 days Ingestion – death within 10-12 days	High	Standard
	Staphylococcal Enterotoxin B	3-12 hours after inhalation	3-4 days	<1%	Standard
	Tricothecene Mycotoxins	2-4 hours	Skin, GI, resp: Hours-days Bone marrow suppression: 2-8 weeks later if survived	Moderate	Standard

References: USAMRIID. Medical Management of Biological Casualties Handbook, 4th Edition. 2001
American Academy of Pediatrics. Red Book: 2003 Report of the Committee on Infectious Diseases, 26th Edition. 2003
Roy MJ, ed. Physician's Guide to Terrorist Attack. Humana Press, Inc. 2004

THERAPEUTICS, PROPHYLAXES, and VACCINES for AGENTS of BIOTERRORISM

	DISEASE	CHEMOTHERAPY (Rx)	CHEMOPROPHYLAXIS (Px)	VACCINE	COMMENTS
BACTERIA	Anthrax	*Inhalational:* Ciprofloxacin or Doxycycline and at least 1 or 2 other effective antibiotics *Cutaneous*: Ciprofloxacin, Doxycycline, or Amoxicillin	Ciprofloxacin, Doxycycline, Amoxicillin (Amoxicillin for sensitive organisms only)	Licensed	Other effective antibiotics include vancomycin, clindamycin, imipenem, clarithromycin, ampicillin, or penicillin
	Brucellosis	Doxycycline plus Rifampin (most common regimen)	Doxycycline plus Rifampin	No Human Vaccine Available	In children < 8 years old, TMP-SMZ substituted for doxycycline
	Cholera	Oral rehydration therapy during period of high fluid loss Tetracycline, Doxycycline, or Ciprofloxacin	Household contacts: Tetracycline, doxycycline, or trimethoprim-sulfamethoxazole (TMP-SMZ)	Not Licensed in US	Vaccine not recommended for routine protection in endemic areas (50% efficacy, short term) Alternate Rx for cipro/doxy resistant strains: erythromycin, trimethoprim-sulfamethoxazole, and furazolidone
	Glanders	Severe disease: Ceftazidime followed by TMP-SMZ Local disease: TMP-SMZ and/or Amoxicillin-Clavulanate	Post-exposure prophylaxis may be tried with TMP-SMX	No Vaccine Available	Adjust antibiotics based on sensitivities
	Plague	Streptomycin, Gentamicin, Alternate: Doxycycline or Ciprofloxacin	Doxycycline Alternate: Ciprofloxacin	Licensed (no longer available)	Chloramphenicol for plague meningitis
	Q Fever	Tetracycline or Doxycycline	Tetracycline or Doxycycline	Investigational New Drug (IND)	Alternate treatment: Ciprofloxacin or Chloramphenicol
	Tularemia	Streptomycin or Gentamicin, Alternate: Doxycycline, Ciprofloxacin, or Chloramphenicol	Doxycycline Alternate: Ciprofloxacin	IND	
VIRUSES	Smallpox	Supportive Rx, Possibly Cidovofir (IND)	Vaccine within 7 days of exposure	Licensed	All caretakers should be vaccinated
	Viral Encephalitides (VEE, EEE, WEE)	Supportive Therapy: Analgesics and Anticonvulsants	Not Applicable	IND for VEE	
	Viral Hemorrhagic Fevers	Ribavirin for Crimean-Congo hemorrhagic fever or Lassa fever (IND)	Not Applicable	Some have IND vaccines	Aggressive supportive care and management of hypotension
TOXINS	Botulism	CDC trivalent equine antitoxin for serotypes A, B, E (Licensed) DoD heptavalent equine despeciated antitoxin for serotypes A-G (Investigational New Drug)	Not Applicable	IND	Skin test for hypersensitivity before equine antitoxin administration
	Ricin	Inhalation: supportive therapy GI: gastric lavage, superactivated charcoal, cathartics	Not Applicable	No vaccine available	Meticulous attention to fluid and electrolyte balance optimizes survival
	Staphylococcus Enterotoxin B	Ventilatory support for inhalation exposure	Not Applicable	No vaccine available	Respiratory distress stabilizes within hours
	Trichothecene Mycotoxins	Inhalational and dermal: Supportive GI: Superactivated charcoal	Decontamination of clothing and skin	No vaccine available	Flush eyes with normal saline

Refer to detailed information sources regarding dosing and individual patient considerations. Expert opinion recommendations may not necessarily be approved by the Food and Drug Administration.

References: USAMRIID. Medical Management of Biological Casualties Handbook, 4th Edition. 2001
American Academy of Pediatrics. Red Book: 2003 Report of the Committee on Infectious Diseases, 26th Edition. 2003
Henderson DA, Inglesby TV, O'Toole T. Bioterrorism: Guidelines for Medical and Public Health Management. American Medical Association. 2002
Roy MJ, ed. Physician's Guide to Terrorist Attack. Humana Press, Inc. 2004

Arizona Department of Health Services

MEDICAL SAMPLE COLLECTION for AGENTS of BIOTERRORISM

		Blood Serum (Red top or marble top tube) unless otherwise specified	Body Fluid or Tissue	Culture Standard techniques unless otherwise qualified
Bacteria and Rickettsia	**Anthrax** *Bacillus anthracis*	Acute and convalescent antibody	PCR on bronchial secretions or sputum NP swabs not useful for screening for exposure	Blood, vesicle or bulla fluid, lesion drainage, fluid from under eschar, tissue, ascites, stool, vomitus or gastric aspirate, sputum, CSF
	Brucellosis *Brucella abortus, suis, & melitensis*	Acute and convalescent antibody	PCR on bronchial secretions or sputum	Blood, bone marrow, tissue aspirate or biopsy, spleen or liver biopsy. Rarely CSF, urine, pleural or peritoneal fluid. May take weeks to grow. Notify lab of R/O brucellosis
	Cholera *Vibrio cholerae*	N/A	N/A	Feces or rectal swab
	Glanders *Burkholderia mallei*	Acute and convalescent antibody	PCR on bronchial secretions or sputum	Blood, skin lesion, lymph node
	Plague *Yersinia pestis*	Acute and convalescent antibody	PCR on bronchial secretions, sputum, or bacterial isolates Direct fluorescent antibody (DFA) on bacterial isolates	Blood, bubo aspirate or drainage, CSF, sputum, bronchial washings, throat culture
	Q-Fever *Coxiella burnetii*	Acute and convalescent antibody	PCR on bronchial secretions, sputum, or tissue Immunoassay on heart valves	Potentially dangerous to culture
	Tularemia *Francisella tularensis*	Acute and convalescent antibody	PCR on bronchial secretions or sputum	Blood, lymph node, skin lesion scraping, biopsy, sputum, bronchial washings, pleural fluid Notify lab of R/O tularemia; culture difficult and potentially dangerous
Viruses	**Equine Encephalomyelitis** VEE, EEE and WEE	Acute and convalescent arbovirus panel *Specify suspected organism*	CSF: Arbovirus panel *Specify suspected organism*	Exclude other viral processes with NP, rectal, and CSF viral culture as appropriate
	Pox (smallpox, monkey pox) *Orthopoxvirus*	Serum Buffy coat (purple top tube)	Scabs for PCR and EM Vesicle fluid touch prep Scrape base of pox for PCR and EM Biopsy of lesion (½ in formalin, ½ without viral transport medium)	Throat culture, vesicle fluid (no viral culture medium) Only lab workers vaccinated against smallpox should work with suspected orthopox samples **Culture only in BSL-4 laboratory**
	Viral Hemorrhagic Fever (e.g. Ebola)	Acute and convalescent antibody Antigen detection (antigen-capture ELISA) Reverse transcriptase PCR	All body fluids are highly contagious	Notify lab for if viral hemorrhagic fever is suspected **Culture only in BSL-4 laboratory**
Toxins	**Botulism** Botulinum toxin from *Clostridium botulinum*	Serum for toxin *Approval for botulism toxin must go through ADHS before submission to CDC*	Feces and suspected food for toxin *Environmental samples for toxin, if applicable*	Wound if suspected source of botulism Feces and/or suspected food NP swab (aerosol exposure)
	Ricin Intoxication Ricin toxin from Castor beans	Serum for toxin Acute and convalescent antibody	NP swab and urine for toxin *Environmental samples for toxin, if applicable*	N/A
	Staph enterotoxicosis *Staphylococcus Enterotoxin B (SEB)*	Acute and convalescent antibody Serum for toxin	NP swab for toxin *Environmental samples for toxin, if applicable*	If *S. aureus* is isolated in a patient with suspected SEB, test for toxin production
	T-2 toxicosis Trichothecene mycotoxin	Serum for toxin	NP swab and urine for toxin *Environmental samples for toxin, if applicable*	N/A

CSF=cerebrospinal fluid NP=nasopharyngeal PCR=polymerase chain reaction EM=electron microscopy
VEE=Venezuelan equine encephalitis EEE=Eastern equine encephalitis WEE=Western equine encephalitis

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Section 2:
Infection Control Information

Arizona Department of Health Services

INFECTION CONTROL PRECAUTIONS for BIOTERRORISM AGENTS

Agent		Precautions			
		Standard	Droplet	Contact	Airborne
Anthrax		X			
Botulinum Toxin		X			
Brucella		X			
Cholera		X		X**	
Equine Encephalitis	Venezuelan	X	X		
	Eastern, Western	X			
Glanders	Cutaneous	X			
	Pneumonic	X	X		
Mycotoxin		X			
Plague	Bubonic	X			
	Pneumonic	X	X		
Q Fever		X			
Ricin		X			
Salmonella		X		X**	
Smallpox		X		X	X***
Staphylococcal Enterotoxin B		X			
Tularemia	Ulceroglandular	X			
	Pneumonic	X	X		
	Other	X			
Viral Hemorrhagic Fevers		X		X****	X

* See reverse side for definitions of the above precautions
** If diapered or incontinent patient
*** Irrespective of vaccination history
**** Extreme contact precautions (see reverse side)

For more information see American Journal of Infection Control 1996; 24: 24-52

Arizona Department of Health Services
Division of Public Health Services
Office of Public Health Emergency Preparedness and Response

INFECTION CONTROL PRECAUTIONS for BIOTERRORISM AGENTS

SUMMARY OF INFECTION CONTROL PRECAUTIONS

Standard	Droplet	Contact	Extreme Contact	Airborne
All body fluids are considered to be infectious • Gloves for touching body fluids or wounds • Gown if clothes could be soiled by body fluids • Mask and eye protection if splattering is possible • Good handwashing frequently, including before and after glove use	• Mask and eye cover within 3 feet of the patient	• Gloves for touching patient and environment • Gown if clothes will touch patient or environment	*For severe hemorrhaging as with suspected viral hemorrhagic fever* • Double gloving • Impermeable gowns • Leg protection • Shoe protection • Eye protection • N95 respirator	• Negative pressure room • N95 respirator

MEASURES TO DECREASE PATIENT INFECTIVITY FOR TRANSPORT

If Patient is on Droplet or Airborne Precautions	If Patient is on Contact or Standard Precautions
• Surgical mask on patient	• Cover skin lesions or draining wounds

For more information contact your facility's infection control practitioner, your local health department, or the Arizona Department of Health Services Office of Public Health Emergency Preparedness and Response at 602-364-3289

Arizona Department of Health Services

EMPIRIC INFECTION CONTROL PRECAUTIONS

Syndrome	Infection Control Measures			
	Standard	Droplet	Contact	Airborne
Skin Lesion	X			
Pneumonia or Severe Respiratory Distress	X	X		
Severe Gastro-Intestinal Illness	X		X	
Afebrile Neurologic Illness	X			
Febrile Neurologic Illness	X	X		
Generalized Vesicular Rash	X		X	X*
Severe Hemorrhaging	X	X	X**	

* N95 respirator for everyone if smallpox or monkey pox is a possibility; for chickenpox, only a surgical mask is required for those not immune to VZV
** See Extreme Contact below

SUMMARY OF INFECTION CONTROL PRECAUTIONS

Standard	Droplet	Contact	Extreme Contact	Airborne
All body fluids are considered to be infectious • Gloves for touching body fluids or wounds • Gown if clothes could be soiled by body fluids • Mask and eye protection if splattering is possible • Good handwashing frequently, including before and after glove use	• Mask and eye cover within 3 feet of the patient	• Gloves for touching patient and environment • Gown if clothes will touch patient or environment	*For severe hemorrhaging as with suspected viral hemorrhagic fever* • Double gloving • Impermeable gowns • Leg protection • Shoe protection • Eye protection • Mask appropriate to suspected agent • N95 respirator if suspected viral hemorrhagic fever	• Negative pressure room • Mask appropriate to suspected agent • N95 mask for smallpox or monkey pox • Surgical mask for chickenpox if not immune

MEASURES TO DECREASE PATIENT INFECTIVITY FOR TRANSPORT

If Patient is on Droplet or Airborne Precautions	If Patient is on Contact or Standard Precautions
• Surgical mask on patient	• Cover skin lesions or draining wounds

Arizona Department of Health Services
Division of Public Health Services
Office of Public Health Emergency Preparedness and Response

Bioterrorism Infection Control Precautions

Standard Precautions

- Wash hands before and after patient contact.
- Wear gloves when touching blood, body fluids, secretions, excretions, and contaminated items.
- Wear protective gown, mask, and eye protection (or 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 place used disposable sharps in a sharps container.
- Use a mouthpiece or other ventilation device when giving mouth-to-mouth resuscitation, when practical.
- Standard precautions are required for the care of ALL patients.

Bioterrorism-related Diseases for which standard precautions are adequate:
Inhalational anthrax, botulism, tularemia, bubonic plague.

Droplet Precautions

Use all standard precautions plus:

- Place patient in a private room or cohort them with someone with the same infection, if possible. If not feasible, then maintain distance of at least 3 feet between patients.
- Wear a mask when working within 3 feet of patient.
- Limit movement and transport of patient. Place a mask on patient if they need to be moved.

Conventional Diseases requiring Droplet Precautions:
Invasive *Haemophilus influenzae* and meningococcal disease, diphtheria, pertussis, mycoplasma, influenza, mumps, rubella, and parvovirus.

Bioterrorism-Related Diseases Requiring Droplet Precautions: Pneumonic plague.

Contact Precautions

Use all standard precautions plus:

- Place patient in a private room or cohort them with someone with the same infection, if possible.
- Wear gloves and protective gown when entering room, and change gloves and/or gown after contact with infectious material.
- Limit the movement or transport of patient from the room.
- Ensure that patient care items, bedside equipment, and frequently touched surfaces receive daily cleaning.
- Dedicate use of non-critical patient-care equipment (e.g., stethoscope) to a single patient, or cohort of patients with the same pathogen. If not feasible, adequate disinfection of equipment between patients is necessary.

Conventional Diseases Requiring Contact Precautions:
VRE, *Clostridium difficile*, RSV, parainfluenza, and enterovirus.

Bioterrorism-Related Diseases Requiring Contact Precautions:
Viral Hemorrhagic Fevers, smallpox, and cutaneous anthrax.
Viral Hemorrhagic Fevers and smallpox also require *airborne* precautions.

Airborne Precautions

Use all standard precautions plus:

- Place the patient in a private room that has monitored negative air pressure (i.e., a minimum of six air changes/hour) with appropriate filtration of air before discharge from room.
- Wear respiratory protection when entering the room. For measles and varicella, this means that the healthcare worker should wear a surgical mask unless they are known to be immune. For all other diseases requiring airborne precautions (such as infectious pulmonary tuberculosis), surgical masks do not give healthcare workers adequate protection. Instead, respiratory protective devices such as appropriately fit-tested N95 respirators are required.
- Limit movement and transport of the patient. Place a surgical mask on the patient if they need to be moved.

Conventional Diseases Requiring Airborne Precautions:
Measles, varicella, pulmonary Tuberculosis.

Bioterrorism-Related Diseases Requiring Airborne Precautions:
Smallpox (variola) and Viral Hemorrhagic Fevers
Smallpox and Viral Hemorrhagic Fevers also require *strict contact* precautions.

For more information call (602) 364-3289

Section 3:
Categories of Bioterrorism Agents

Definitions of Bioterrorism Categories

Category A Diseases/Agents

The U.S. public health system and primary healthcare providers must be prepared to address various biological agents, including pathogens that are rarely seen in the United States. High-priority agents include organisms that pose a risk to national security because they:

- can be easily disseminated or transmitted from person to person;
- result in high mortality rates and have the potential for major public health impact;
- might cause public panic and social disruption; and
- require special action for public health preparedness.

Category B Diseases/Agents

Second highest priority agents include those that:

- are moderately easy to disseminate;
- result in moderate morbidity rates and low mortality rates; and
- require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.

Category C Diseases/Agents

Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of:

- availability;
- ease of production and dissemination; and
- potential for high morbidity and mortality rates and major health impact.

For more information call (602) 364-3289

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Report Summary

Public Health Assessment of Potential Biological Terrorism Agents

As part of a Congressional initiative begun in 1999 to upgrade national public health capabilities for response to acts of biological terrorism, the Centers for Disease Control and Prevention (CDC) was designated the lead agency for overall public health planning. A Bioterrorism Preparedness and Response Office has been formed to help target several areas for initial preparedness activities, including planning, improved surveillance and epidemiologic capabilities, rapid laboratory diagnostics, enhanced communications, and medical therapeutics stockpiling (1). To focus these preparedness efforts, however, the biological agents towards which the efforts should be targeted had to first be formally identified and placed in priority order. Many biological agents can cause illness in humans, but not all are capable of affecting public health and medical infrastructures on a large scale.

The military has formally assessed multiple agents for their strategic usefulness on the battlefield (2). In addition, the Working Group on Civilian Biodefense, using an expert panel consensus-based process, has identified several biological agents as potential high-impact agents against civilian populations (3-7). To guide national public health bioterrorism preparedness and response efforts, a method was sought for assessing potential biological threat agents that would provide a reviewable, reproducible means for standardized evaluations of these threats.

In June 1999, a meeting of national experts was convened to 1) review potential general criteria for selecting the biological agents that pose the greatest threats to civilians and 2) review lists of previously identified biological threat agents and apply these criteria to identify which should be evaluated further and prioritized for public health preparedness efforts. This report outlines the overall selection and prioritization process used to determine the biological agents for public health preparedness activities. Identifying these priority agents will help facilitate coordinated planning efforts among federal agencies, state and local emergency response and public health agencies, and the medical community.

Overview of Agent Selection and Prioritization Process

On June 3-4, 1999, academic infectious disease experts, national public health experts, Department of Health and Human Services agency representatives, civilian and military intelligence experts, and law enforcement officials[1] met to review and comment on the threat potential of various agents to civilian populations. The following general areas were used as criteria: 1) public health impact based on illness and death; 2) delivery potential to large populations based on stability of the agent, ability to mass produce and distribute a virulent agent, and potential for person-to-person transmission of the agent; 3) public perception as related to public fear and potential civil disruption; and 4) special public health preparedness needs based on stockpile requirements, enhanced surveillance, or diagnostic needs. Participants reviewed lists of biological warfare or potential biological threat agents and selected those they felt posed the greatest threat to civilian populations.

The following unclassified documents containing potential biological threat agents were reviewed: 1) the Select Agent Rule list, 2) the Australian Group List for Biological Agents for Export Control, 3) the unclassified military list of biological warfare agents, 4) the Biological Weapons Convention list, and 5) the World Health Organization Biological Weapons list (8-12). Participants with appropriate clearance levels reviewed intelligence information regarding classified suspected biological agent threats to civilian populations. Genetically engineered or recombinant biological agents were considered but not included for final prioritization because of the inability to predict the nature of these agents and thus identify specific preparedness activities for public health and medical response to them. In addition, no information was available about the likelihood for use of one biological agent over another. This aspect, therefore, could not be considered in the final evaluation of the potential biological threat agents.

Participants discussed and identified agents they felt had the potential

[1]Participants are listed in Acknowledgments.

for high impact based on subjective assessments in the four general categories. After the meeting, CDC personnel then attempted to identify objective indicators in each category that could be used to further define and prioritize the identified high-impact agents and provide a framework for an objective risk-matrix analysis process for any potential agent. The agents were evaluated in each of the general areas according to the objective parameters and were characterized by the rating schemes outlined in the Appendix. Final category assignments (A, B, or C) of agents for public health preparedness efforts were then based on an overall evaluation of the ratings the agents received in each of the four areas.

Results

Based on the overall criteria and weighting, agents were placed in one of three priority categories for initial public health preparedness efforts: A, B, or C (Table 1). Agents in Category A have the greatest potential for adverse public health impact with mass casualties, and most require broad-based public health preparedness efforts (e.g., improved surveillance and laboratory diagnosis and stockpiling of specific medications). Category A agents also have a moderate to high potential for large-scale dissemination or a heightened general public awareness that could cause mass public fear and civil disruption.

Most Category B agents also have some potential for large-scale dissemination with resultant illness, but generally cause less illness and death and therefore would be expected to have lower medical and public health impact. These agents also have lower general public awareness than Category A agents and require fewer special public health preparedness efforts. Agents in this category require some improvement in public health and medical awareness, surveillance, or laboratory diagnostic capabilities, but presented limited additional requirements for stockpiled therapeutics beyond those identified for Category A agents. Biological agents that have undergone some development for widespread dissemination but do not otherwise meet the criteria for Category A, as well as several biological agents of concern for food and water safety, are included in this category.

Table 1. Critical biological agent categories for public health preparedness

Biological agent(s)	Disease
Category A	
Variola major	Smallpox
Bacillus anthracis	Anthrax
Yersinia pestis	Plague
Clostridium botulinum (botulinum toxins)	Botulism
Francisella tularensis	Tularemia
Filoviruses and Arenaviruses (e.g., *Ebola virus, Lassa virus*)	Viral hemorrhagic fevers
Category B	
Coxiella burnetii	Q fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Alphaviruses (VEE, EEE, WEE[a])	Encephalitis
Rickettsia prowazekii	Typhus fever
Toxins (e.g., Ricin, Staphylococcal enterotoxin B)	Toxic syndromes
Chlamydia psittaci	Psittacosis
Food safety threats (e.g., *Salmonella spp*., *Escherichia coli* O157:H7)	
Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)	
Category C	
Emerging threat agents (e.g., *Nipah virus*, hantavirus)	

[a]Venezuelan equine (VEE), eastern equine (EEE), and western equine encephalomyelitis (WEE) viruses

Biological agents that are currently not believed to present a high bioterrorism risk to public health but which could emerge as future threats (as scientific understanding of these agents improves) were placed in Category C. These agents will be addressed nonspecifically through overall bioterrorism preparedness efforts to improve the detection of unexplained illnesses and ongoing public health infrastructure development for detecting and addressing emerging infectious diseases (13).

Agents were categorized based on the overall evaluation of the different areas considered. Table 2 shows the evaluation schemes as applied to agents in Categories A and B. For example, smallpox would rank higher than brucellosis in the public health impact criterion because of its higher untreated mortality (approximately 30% for smallpox and $\leq$2% for brucellosis); smallpox has a higher dissemination potential because of its capability for person-to-person transmission. Smallpox also ranks higher for special public health preparedness needs, as additional vaccine must be manufactured and enhanced surveillance, educational, and diagnostic efforts must be undertaken. Inhalational anthrax and plague also have higher public health impact ratings than brucellosis because of their higher morbidity and mortality. Although mass production of *Vibrio cholera* (the biological cause of cholera) and *Shigella* spp. (the cause of

Table 2. Criteria and weighting[a] used to evaluate potential biological threat agents

Disease	Public health impact		Dissemination potential		Public perception	Special preparation	Category
	Disease	Death	P-D[b]	P - P[c]			
Smallpox	+	++	+	+++	+++	+++	A
Anthrax	++	+++	+++	0	+++	+++	A
Plague[d]	++	+++	++	++	++	+++	A
Botulism	++	+++	++	0	++	+++	A
Tularemia	++	++	++	0	+	+++	A
VHF[e]	++	+++	+	+	+++	++	A
VE[f]	++	+	+	0	++	++	B
Q Fever	+	+	++	0	+	++	B
Brucellosis	+	+	++	0	+	++	B
Glanders	++	+++	++	0	0	++	B
Melioidosis	+	+	++	0	0	++	B
Psittacosis	+	+	++	0	0	+	B
Ricin toxin	++	++	++	0	0	++	B
Typhus	+	+	++	0	0	+	B
Cholera[g]	+	+	++	+/-	+++	+	B
Shigellosis[g]	+	+	++	+	+	+	B

[a]Agents were ranked from highest threat (+++) to lowest (0).
[b]Potential for production and dissemination in quantities that would affect a large population, based on availability, BSL requirements, most effective route of infection, and environmental stability.
[c]Person-to-person transmissibility.
[d]Pneumonic plague.
[e]Viral hemorrhagic fevers due to Filoviruses (*Ebola, Marburg*) or Arenaviruses (e.g., *Lassa, Machupo*).
[f]Viral encephalitis.
[g]Examples of food- and waterborne diseases.

shigellosis) would be easier than the mass production of anthrax spores, the public health impact of widespread dissemination would be less because of the lower morbidity and mortality associated with these agents. Although the infectious doses of these bacteria are generally low, the total amount of bacteria that would be required and current water purification and food-processing methods would limit the effectiveness of intentional large-scale water or food contamination with these agents.

Discussion

Although use of conventional weapons such as explosives or firearms is still considered the most likely means by which terrorists could harm civilians (14), multiple recent reports cite an increasing risk and probability for the use of biological or chemical weapons (15-18). Indeed, the use of biological and chemical agents as small- and large-scale weapons has been actively explored by many nations and terrorist groups (19-20). Although small-scale bioterrorism events may actually be more likely in light of the lesser degrees of complexity to be overcome, public health agencies must prepare for the still-possible large-scale incident that would undoubtedly lead to catastrophic public health consequences. The selection and prioritization of the potential biological terrorism agents described in this report were not based on the likelihood of their use, but on the probability that their use would result in an overwhelming adverse impact on public health.

Most evaluations of potential risk agents for biological warfare or terrorism have historically been based on military concerns and criteria for troop protection. However, several characteristics of civilian populations differ from those of military populations, including a wider range of age groups and health conditions, so that lists of military biological threats cannot simply be adopted for civilian use. These differences and others may greatly increase the consequences of a biological attack on a civilian population. Civilians may also be more vulnerable to food- or waterborne terrorism, as was seen in the intentional *Salmonella* contamination of salad bars in The Dalles, Oregon, in 1984 (21). Although food and water systems in the United States are among the safest in the world, the occurrence of nationwide outbreaks due to unintentional food or water contamination demonstrates the ongoing need for vigilance in protecting food and water supplies (22-23). Overall, many other factors must be considered in defining and focusing multiagency efforts to protect civilian populations against bioterrorism.

Category A agents are being given the highest priority for preparedness. For Category B, public health preparedness efforts will focus on identified deficiencies, such as improving awareness and enhancing surveillance or laboratory diagnostic capabilities. Category C agents will be further assessed for their potential to threaten large populations as additional information becomes available on the epidemiology and pathogenicity of these agents. In addition, special epidemiologic and laboratory surge capacity will be maintained to assist in the investigation of naturally occurring outbreaks due to Category C "emerging" agents. Linkages established with established programs for food safety, emerging infections diseases, and unexplained illnesses will augment the overall bioterrorism preparedness efforts for many Category B and C agents.

The above categories of agents should not be considered definitive. The prioritization of biological agents for preparedness efforts should continue. Agents in each category may

change as new information is obtained or new assessment methods are established. Disease elimination and eradication efforts may result in new agents being added to the list as populations lose their natural or vaccine-induced immunity to these agents. Conversely, the priority status of certain agents may be reduced as the identified public health and medical deficiencies related to these agents are addressed (e.g., once adequate stores of smallpox vaccine and improved diagnostic capabilities are established, its rating within the special preparedness needs category would be reduced, as would its overall rating within the risk-matrix evaluation process). To meet the ever-changing response and preparedness challenges presented by bioterrorism, a standardized and reproducible evaluation process similar to the one outlined above will continue to be used to evaluate and prioritize currently identified biological critical agents, as well as new agents that may emerge as threats to civilian populations or national security.

Appendix

Risk-Matrix Analysis Process Used to Evaluate Potential Biological Threat Agents

In the area of public health impact, disease threat presented by an agent was assessed by evaluating whether the illness resulting from exposure could be treated without hospitalization. In addition, mortality rates for exposed, untreated persons were considered (24-26). Biological agents were given a higher rating for morbidity (++) if illness would most likely require hospitalization and a lower rating (+) if outpatient treatment might be possible for a large part of the affected population. Agents were also rated highest (+++) for expected untreated mortality $\geq$50%, medium (++) for mortality of 21% to 49%, and lowest (+) for an expected mortality $\leq$20%.

Agents were rated according to their overall potential for initial dissemination to a large population (+ to +++) and their potential for continued propagation by person-to-person transmission (0 to ++). Overall dissemination potential of an agent was based on an assessment of 1) the capability for mass production of the agent (assessment based on availability of agent and Biosafety Level (BSL) requirements for quantity production of an agent), and 2) their potential for rapid, large-scale dissemination (assessment based on the most effective route of infection and the general environmental stability of the agent). Agents were rated (++) if they were readily obtainable from soil, animal/insect, or plant sources (most available; e.g., *B. anthracis*), (+) if mainly available only from clinical specimens, clinical laboratories, or regulated commercial culture suppliers (e.g., *Shigella* spp.), and (0) if available only from nonenvironmental, noncommercial, or nonclinical sources such as high-level security research laboratories (least readily available; e.g., *Variola* or *Ebola* viruses).

BSL requirements for an agent were based on recommended levels for working with large quantities of an agent (27). BSL ratings were used to estimate the level of technical expertise and containment facilities that would be required to work with and mass produce an agent safely. Agents that required higher BSL levels were given lower ratings, as they would require greater technical capabilities and containment facilities to be produced in large quantities. Agents were given (+) for BSL 4 production safety requirements, (++) for BSL 3 requirements, and (+++) for BSL 2 or lower requirements.

Agents were also assessed with regard to their main routes of infection, with the assumption that those causing infection via the respiratory route could be more readily disseminated to affect large populations. Agents were assigned (++) if most effective at causing illness via an aerosol exposure route (air release potential) and (+) if most effective when given by the oral route (food/water release potential). Dissemination potential should also take into account the stability of an agent following its release. Information regarding the expected general environmental stability of agents was obtained from multiple sources (24,28-31). Agents that may remain viable in the environment for $\geq$1 year were given (+++), while agents considered less environmentally stable were given (++) (potentially viable for days to months) or (+) (generally viable for minutes to hours). The ratings system for environmental stability was assigned to reflect the wide range of stability of the agents, while maintaining a simple overall scheme that contained only a few categories (minutes to hours, days to months, >1 year). The ratings for all the subcategories evaluated for production and dissemination potential were then totaled and agents were assigned a final rating for production and dissemination capability. If the total rating in the subcategories was $\geq$9, the agent was given (+++); for a total of 7-8, the agent was given a (++); and for a total of $\leq$6, the agent was given a final rating of (+) for the overall production and dissemination capability.

As potential outbreak propagation through continued person-to-person transmission would also increase the overall dissemination capabilities of an agent, they were evaluated separately for this characteristic. Agents were rated highest if they had potential for both person-to-person respiratory and contact spread (+++) and lower for mainly respiratory (++) or contact spread potential alone (+). Agents were rated (0) if they presented low or no transmission risk.

Agents were also assessed (0 to +++) according to preexisting heightened public awareness and interest, which may contribute to mass public fear or panic in biological terrorism events. The number of times an agent or disease appeared in a selected form of media was used as a surrogate to determine the current level of public awareness and interest for the agent or disease. Titles of newspaper articles and radio and television transcripts from June 1, 1998, to June 1, 1999, in an Internet database (32) were retrospectively searched by agent name and disease. This database contained articles and transcripts from approximately 233 newspapers and 70 radio or television sources. If a disease was caused by multiple agents (e.g., viral hemorrhagic fever), the database was searched for each of the agents in addition to the name of the disease. Articles or transcripts were only counted if the name of the agent, disease, or other general terms such as bioterrorism, biological terrorism, terrorism, and weapons of mass destruction appeared in the title. Multiple hits for the same title were counted only once unless they appeared in different newspapers or transcripts. Agents were rated based on the number of times they appeared in these forms of media within the 1-year period. Agents were given (0)

rating for <5 titles, (+) for 5-20 titles, (++) for 21-45 titles, and (+++) for >45 titles identified within the search period.

Requirements for special public health preparedness were also considered. Higher ratings were given to agents with different requirements for special preparedness. An agent was given a (+) for each special preparedness activity that would be required to enhance the public health response to that agent. These distinct preparedness requirements included 1) stockpiling of therapeutics to assure treatment of large numbers of people (+), 2) need for enhanced public health surveillance and education (+), and 3) augmentation of rapid laboratory diagnostic capabilities (+). Therefore, if all three special preparedness efforts would be required to provide a strong public health response for that agent, it was given (+++) for this category. Agents that did not require all special preparedness efforts were given lower ratings (++ or +).

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Section 4:
Category A Agents

Arizona Department of Health Services

ANTHRAX

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: *Bacillus anthracis* is a spore-forming, rod-shaped gram-positive bacillus.

Routes of Transmission: Inhalation; dermal inoculation; or ingestion through consumption of insufficiently cooked contaminated meat. Person-to-person transmission of anthrax does not occur.

Incubation Period: The incubation period following an inhalation exposure to anthrax is 1-60 days, with most cases occurring 1-6 days after exposure. The incubation period for cutaneous anthrax is 1-5 days after inoculation. Although rare, esophageal and gastrointestinal anthrax occurs after an incubation period of 2-5 days.

Clinical Effects: Anthrax can present in three clinical forms: inhalation, cutaneous, or gastrointestinal. Patients with inhalation anthrax will initially experience a non-specific prodrome of flu-like symptoms including fever, myalgia, headache, non-productive cough, and mild chest discomfort. Upper respiratory symptoms such as nasal congestion or rhinorrhea are not consistent with an anthrax infection. Following the prodromal period, patients may experience a brief interim improvement. Two to four days after initial symptoms, patients will experience abrupt onset of respiratory distress, high fever and hemodynamic collapse. Symptoms of respiratory stridor and dyspnea are caused by massive mediastinal lymphadenopathy, thoracic edema, and pleural effusions rather than bronchopneumonia. In its final stage, widened mediastinum is a distinguishing though inconsistent feature of anthrax infection. Approximately 50% of all cases of inhalation anthrax are accompanied by fatal hemorrhagic meningitis.

Cutaneous anthrax begins with a localized pruritic papule or macule. The lesion develops into a vesicle filled with serosanguinous fluid and localized satellite vesicles may also appear. The vesicle ruptures leaving a painless, necrotic ulcer. A black eschar forms in the base of the ulcer and remains for 2-3 weeks before separating. The ulcer is usually accompanied by fever, malaise and headache. Severe local edema and lymphadenitis may be present.

Lethality: Without treatment, the mortality rate for inhalation anthrax is almost 100%. Rapid treatment increase the chance of survival. In the anthrax outbreak of 2001 in the United States, six out of eleven patients with inhalational anthrax survived. Up to 20% of untreated cutaneous anthrax cases may die from septicemia; however, when appropriately treated with antibiotics, less than 1% die.

Transmissibility: Person-to-person transmission of inhalational anthrax does not occur. Vegetative bacteria can be grown from the bullae and under the eschar of cutaneous anthrax lesions, so care must be taken with draining lesions to prevent person-to-person spread.

Primary Contamination & Methods of Dissemination: *B. anthracis* (anthrax bacteria) may be delivered through aerosolization, direct dermal inoculation with spores, or contamination of food products. It is now documented that in some conditions, spores can be disseminated from an ordinarily sealed paper envelope during mechanical mail sorting activities and by simply removing the contents from a contaminated envelope.

Secondary Contamination & Persistence of Organism: Spores can persist in the environment indefinitely. However, secondary aerosolization of spores from clothing or skin is uncommon.

Decontamination & Isolation:
Patients – Exposed areas of skin should be washed with soap and water after potential contact with contaminated materials. Patients with anthrax infection should be managed using standard precautions.
Equipment, clothing & other objects – A 0.5% hypochlorite solution is effective in cleaning the environment (1 part household bleach + 9 parts water = 0.5% solution). Contact with hypochlorite solution should be maintained for 10 minutes, to effectively kill any spores present. Sporicidal disinfectants may be effective. Contaminated clothing should be washed in soap and water, with or without bleach.

Outbreak Control: Only those people who were exposed directly to anthrax should receive prophylaxis. There is no need to immunize or give prophylaxis to people who have later contact with anthrax-exposed individuals.

Laboratory testing: The most useful microbiologic test is the standard blood and or wound culture, which should show growth within 24 hours. If the laboratory has been alerted to the possibility of *B. anthracis* (anthrax), biochemical testing and review of colonial morphology should provide a preliminary diagnosis within 12 to 24 hours. A direct fluorescent antibody test (DFA) is currently available for preliminary diagnosis at the Arizona State Health Laboratory. Laboratory confirmation for diagnosis requires an additional 1 to 2 days of testing. Sputum or nasal cultures are <u>not</u> useful for screening exposures.

For cutaneous lesions, collect vesicular fluid on sterile swabs. If it is in the eschar stage, use sterile swab to collect lesion material under eschar. For evaluation of inhalational anthrax, collect a routine blood culture and sputum culture.

For suspected gastrointestinal anthrax collect cultures of blood, stool, and vomitus. In addition a chest radiograph and/or chest CT scan is needed to evaluate for a widened mediastinum and pleural effusions. If symptoms of meningitis are present, cerebrospinal fluid should be cultured.

Therapeutic Treatment: For inhalation anthrax, ciprofloxacin or doxycycline should be used for initial intravenous therapy until antimicrobial susceptibility results are known. In addition, there should be added at least one or two other antibiotics predicted to be effective, these include: vancomycin, rifampin, imipenem, chloramphenicol, clarithromycin, penicillin, or ampicillin. Although many strains of *B. anthracis* are sensitive to penicillin, treatment of systemic anthrax infection using penicillin alone (i.e., penicillin G or ampicillin) is not recommended until sensitivities are known.

For cutaneous anthrax infections, ciprofloxacin or doxycycline are first line therapeutic drugs. As for inhalation infection, intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax if there is extensive edema, systemic involvement, or for lesions on the head and neck.

Prophylactic Treatment: The recommended post-exposure prophylaxis for asymptomatic patients with confirmed or highly likely exposure to *B. anthracis* is ciprofloxacin or doxycycline. High dose penicillin (e.g., amoxicillin or penicillin VK) may be an option for antimicrobial prophylaxis when ciprofloxacin or doxycycline are contraindicated. Amoxicillin is the preferred prophylaxis for children or pregnant women if it is known that the anthrax strain is sensitive to penicillin.

Differential Diagnosis: Anthrax should be considered in any previously healthy patient that presents with acute mediastinitis. Differential diagnoses may include bacterial pneumonias, (including pneumonic plague and tularemia pneumonia), gram negative sepsis, influenza, and other influenza-like illnesses.

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For more information call (602) 364-3289

Frequently Asked Questions About Anthrax

What is anthrax?
Anthrax is a serious disease caused by *Bacillus anthracis*, a bacterium that forms spores. A bacterium is a very small organism made up of one cell. Many bacteria can cause disease. A spore is a cell that is dormant (asleep) but may come to life with the right conditions.

There are three types of anthrax:
- Skin (cutaneous)
- Lungs (inhalation)
- Digestive (gastrointestinal)

How do you get it?
Anthrax is not known to spread from one person to another.

- *Anthrax from animals* – Humans can become infected with anthrax by handling products from infected animals or by breathing in anthrax spores from infected animal products (like wool, for example). People also can become infected with gastrointestinal anthrax by eating undercooked meat from infected animals.
- *Anthrax as a weapon* – Anthrax also can be used as a weapon. This happened in the United States in 2001. Anthrax was deliberately spread through the postal system by sending letters with powder containing anthrax. This caused 22 cases of anthrax infection.

How dangerous is anthrax?
The Centers for Disease Control and Prevention classify agents with recognized bioterrorism potential into three priority areas (A, B and C). Anthrax is classified a Category A agent. Category A agents are those that:
- Pose the greatest possible threat for a bad effect on public health
- May spread across a large area or need public awareness
- Need a great deal of planning to protect the public's health

In most cases, early treatment with antibiotics can cure cutaneous anthrax. Even if untreated, 80 percent of people who become infected with cutaneous anthrax do not die. Gastrointestinal anthrax is more serious because between one-fourth and more than half of cases lead to death. Inhalation anthrax is much more severe. In 2001, about half of the cases of inhalation anthrax ended in death.

What are the symptoms?
The symptoms (warning signs) of anthrax are different depending on the type of the disease:

- *Cutaneous* – The first symptom is a small sore that develops into a blister. The blister then develops into a skin ulcer with a black area in the center. The sore, blister and ulcer do not hurt.
- *Gastrointestinal* – The first symptoms are nausea, loss of appetite, bloody diarrhea, and fever, followed by bad stomach pain.
- *Inhalation* – The first symptoms of inhalation anthrax are similar to influenza with fever, fatigue, a dry cough, and muscle aches. Later symptoms include worsening cough, chest discomfort, and shortness of breath. (Caution: Most people with cold or influenza symptoms do not have inhalation anthrax.)

How soon do infected people get sick?
Symptoms usually appear within 7 days of coming in contact with the bacterium for all three types of anthrax. However, for inhalation anthrax, symptoms can sometimes take up to 42 days to appear.

How is anthrax treated?
Antibiotics are used to treat all three types of anthrax. Early identification and treatment are important.

- *Prevention after exposure* – Antibiotics such as ciprofloxacin, doxycycline, or penicillin will be given to people who are known to be exposed to anthrax, but are not yet sick. In addition, anthrax vaccine may be used.
- *Treatment after infection* – Treatment involves a 60-day course of effective antibiotics. Response to therapy depends on how ill the patient is, where the infection is located, and how quickly effective antibiotics are begun.

Can anthrax be prevented?
There is a vaccine to prevent anthrax, but it is not yet available for the general public. Anyone who may be exposed to anthrax, including certain members of the U.S. armed forces, laboratory workers, and workers who may enter or re-enter contaminated areas, may get the vaccine. Also, in the event of an attack using anthrax as a weapon, people exposed could get the vaccine.

What should I do if I think I have anthrax?
If you are showing symptoms of anthrax infection, call your health-care provider.

What should I do if I think I have been exposed to anthrax?
Contact local law enforcement immediately if you think that you may have been exposed to anthrax. This includes being exposed to a suspicious package or envelope that contains powder.

For more information, call (602) 364-3289

BOTULISM

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: A group of seven related toxins produced by the bacillus, *Clostridium botulinum*. The seven distinct toxins (A through G) are produced by different strains of the bacillus.

Routes of Exposure: Inhalation, oral (infant botulism and wound botulism are not included in the discussion below)

Toxic Dose: 1 ng/kg (for type A toxin)

Incubation Period: Neurologic symptoms of foodborne botulism generally begin 12-36 hours after ingestion. Neurologic symptoms of inhalational botulism generally begin 24-72 hours after aerosol exposure. However, the incubation period for both can range from 6 hours to 10 days.

Clinical Effects: Acute, afebrile, symmetric descending paralysis. Botulinum toxins are neurotoxins that act to prevent the release of acetylcholine presynaptically and thus block neurotransmission. Multiple cranial nerve palsies are often the first symptoms seen. Bulbar palsies are prominent early, with eye symptoms such as blurred vision due to mydriasis, diplopia, ptosis and photophobia, in addition to other bulbar signs such as dysarthria, dysphonia, and dysphagia. Skeletal muscle paralysis follows with a symmetrical descending and progressive weakness, which may culminate abruptly in respiratory failure. Deep tendon reflexes may be present or absent.

Lethality: The mortality rate from botulism is 60% if the patient goes untreated and less than 5% if the patient receives appropriate treatment. All the botulinum toxins are slightly less toxic when exposure is by the pulmonary route.

Transmissibility: Botulinum toxin cannot be transmitted person-to-person.

Primary Contaminations & Methods of Dissemination: The use of botulinum toxin as a biological weapon would likely be by aerosolization, or by intentional contamination of food or water supplies.

Secondary Contamination & Persistence of Organism: The toxin does not penetrate intact skin. *C. botulinum* spores can persist in the environment, and wound botulism can result when an open wound is contaminated.

Decontamination & Isolation:

Patients – Patients can be managed using standard precautions. No decontamination is necessary following foodborne exposure. Following aerosol exposure to botulinum toxin, skin should be rinsed with soap and water.

Equipment, clothing & other objects – A 0.5% hypochlorite solution (1 part household bleach + 9 parts water = 0.5% solution) applied for 10 to 15 minutes and/or soap and water should be used for environmental decontamination. Clothing should be washed with soap and water.

Laboratory Testing: For detection of inhaled aerosolized botulinum toxin, gastric aspirate and possibly stool may contain the toxin. In suspected food borne disease the appropriate specimens for toxin assay are serum, stool, gastric aspirate, vomitus, and the implicated food (if available). The confirmatory test is based on a mouse bioassay demonstrating the toxin. Diagnostic services are available only through the CDC via the state health department.

Therapeutic Treatment: Treatment is the same for inhalation (aerosolized) exposure as for ingestion (foodborne). Care is supportive. Long term mechanical ventilation may be needed for several weeks to months. A trivalent equine antitoxin for food-borne botulism is available from the CDC through the Arizona Department of Health Services. Use of the antitoxin requires skin testing for horse serum sensitivity prior to administration. Providers should refer to the information sheet that comes with the antitoxin.

Prophylactic Treatment: Currently, there is no commercially available vaccine.

Differential Diagnosis: Single cases may be confused with various neuromuscular disorders such as atypical Guillain-Barré syndrome, myasthenia gravis, or tick paralysis. Botulism could also be confused with enteroviral infections, but in these patients, fever is present, paralysis is often asymmetrical, and the CSF is abnormal. It may be necessary to distinguish nerve agent and atropine poisoning from botulinum intoxication. In organophosphate nerve agent poisoning pupils are miotic and copious secretions are present. In atropine poisoning, the pupils are dilated and mucous membranes are dry, but central nervous system excitation with hallucinations and delirium is present.

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Frequently Asked Questions About Botulism

What is botulism?
Botulism is a rare but serious paralytic illness caused by a nerve toxin that is produced by the bacterium *Clostridium botulinum*. There are three main kinds of botulism. Foodborne botulism is caused by eating foods that contain the botulism toxin. Wound botulism is caused by toxin produced from a wound infected with *Clostridium botulinum*. Infant botulism is caused by consuming the spores of the botulinum bacteria, which then grow in the intestines and release toxin. All forms of botulism can be fatal and are considered medical emergencies.

What kind of germ is *Clostridium botulinum*?
Clostridium botulinum is the name of a group of bacteria commonly found in soil. These rod-shaped organisms grow best in low oxygen conditions. The bacteria form spores that allow them to survive in a dormant state until exposed to conditions that can support their growth. There are seven types of botulism toxin designated by the letters A through G.

How common is botulism?
In the United States an average of 110 cases of botulism are reported each year. Of these, approximately 25% are foodborne, 72% are infant botulism, and the rest are wound botulism. Outbreaks of foodborne botulism involving two or more persons occur most years and usually caused by eating contaminated home-canned foods. The number of cases of foodborne and infant botulism has changed little in recent years, but wound botulism has increased because of the use of black-tar heroin, especially in California.

What are the symptoms of botulism?
The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. Infants with botulism appear lethargic, feed poorly, are constipated, and have a weak cry and poor muscle tone. These are all symptoms of the muscle paralysis caused by the bacterial toxin. If untreated, these symptoms may progress to cause paralysis of the arms, legs, trunk and respiratory muscles. In foodborne botulism, symptoms generally begin 18 to 36 hours after eating a contaminated food, but they can occur as early as 6 hours or as late as 10 days.

How is botulism diagnosed?
Physicians may consider the diagnosis if the patient's history and physical examination suggest botulism. However, these clues are usually not enough to allow a diagnosis of botulism. Other diseases such as Guillain-Barré syndrome, stroke, and myasthenia gravis can appear similar to botulism, and special tests may be needed to exclude these other conditions. These tests may include a brain scan, spinal fluid examination, nerve conduction test (electromyography, or EMG), and a tensilon test for myasthenia gravis. The most direct way to confirm the diagnosis is to demonstrate the botulinum toxin in the patient's serum or stool by injecting serum or stool into mice and looking for signs of botulism. The bacteria can also be isolated from the stool of persons with foodborne and infant botulism. These tests can be performed at the Centers for Disease Control and Prevention.

How can botulism be treated?
The respiratory failure and paralysis that occur with severe botulism may require a patient to be on a breathing machine (ventilator) for weeks, plus intensive medical and nursing care. After several weeks, the paralysis slowly improves. If diagnosed early, foodborne and wound botulism can be treated with an antitoxin that blocks the action of toxin circulating in the blood. This can prevent patients from worsening, but recovery still takes many weeks. Physicians may try to remove contaminated food still in the gut by inducing vomiting or by using enemas. Wounds should be treated, usually surgically, to remove the source of the toxin-producing bacteria. Good supportive care in a hospital is the mainstay of therapy for all forms of botulism.

Are there complications from botulism?
Botulism can result in death due to respiratory failure. However, in the past 50 years the proportion of patients with botulism who die has fallen from about 50% to 8%. A patient with severe botulism may require a breathing machine as well as intensive medical and nursing care for several months. Patients who survive an episode of botulism poisoning may have fatigue and shortness of breath for years and long-term therapy may be needed to aid recovery.

How can botulism be prevented?
Botulism can be prevented. Foodborne botulism has often been from home-canned foods with low acid content, such as asparagus, green beans, beets and corn. However, outbreaks of botulism have occurred from more unusual sources such as chopped garlic in oil, chili peppers, tomatoes, improperly handled baked potatoes wrapped in aluminum foil, and home-canned or fermented fish. Persons who do home canning should follow strict hygienic procedures to reduce contamination of foods. Oils infused with garlic or herbs should be refrigerated. Potatoes that have been baked while wrapped in aluminum foil should be kept hot until served or refrigerated. Because botulism toxin is destroyed by high temperatures, persons who eat home-canned foods should consider boiling the food for 10 minutes before eating it to ensure safety. Instructions on safe home canning can be obtained from county extension services or from the US Department of Agriculture. Because honey can contain spores of *Clostridium botulinum* and this has been a source of infection for infants, children less than 12 months old should not be fed honey. Honey is safe for persons 1 year of age and older. Wound botulism can be prevented by promptly seeking medical care for infected wounds and by not using injectable street drugs.

What are public health agencies doing to prevent or control botulism?
Public education about botulism prevention is an ongoing activity. Information about safe canning is widely available for consumers. State health departments and CDC have persons knowledgeable about botulism available to consult with physicians 24 hours a day. If antitoxin is needed to treat a patient, it can be quickly delivered to a physician anywhere in the country. Suspected outbreaks of botulism are quickly investigated, and if they involve a commercial product, the appropriate control measures are coordinated among public health and regulatory agencies. Physicians should report suspected cases of botulism to county or state health departments.

For information and guidelines on canning foods at home visit the USDA Home Canning Guide at http://foodsafety.cas.psu.edu/canningguide.html

For more information call (602) 364-3289

Arizona Department of Health Services

PLAGUE

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Gram-negative bacillus *Yersinia pestis*.

Routes of Exposure: Inhalation, fleabite, and direct contact with infected blood and tissues.

Infective Dose & Infectivity: 10-500 organisms

Incubation Period: The incubation period for pulmonary exposure ranges from 1 to 6 days with an average of 2-4 days.

Clinical Effects: Onset of pneumonic plague is acute and often fulminant. The presentation includes high fever, cough, chest pain, malaise, hemoptysis, and muco-purulent or watery sputum with gram-negative rods on gram stain. Patients commonly show evidence of bronchopneumonia. The pneumonia progresses rapidly, resulting in dyspnea, stridor and cyanosis. Gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal pain might also be present. Buboes (regional lymphadenopathy) are rarely seen. Other advanced signs of pneumonic plague include respiratory failure, circulatory collapse, and bleeding diathesis.

Lethality: The mortality rate of untreated pneumonic plague usually is 90-100%. However, with prompt appropriate treatment, the mortality rate drops to 5% or less.

Transmissibility (person to person): Person-to-person transmission occurs via respiratory droplets.

Primary Contamination & Methods of Dissemination: Dissemination of plague as a biological weapon would most likely be through aerosolization.

Secondary Contamination & Persistence of organism: *Y. pestis* is very sensitive to sunlight and heat and does not survive long outside of the host. Therefore**,** secondary contamination is not a concern.

Decontamination & Isolation:

Patients – Patients with suspected pneumonic plague should be managed with droplet precautions. Plague patients without pneumonia require only standard precautions. Drainage from buboes should be considered infectious and treated with appropriate personal protective equipment (e.g. gloves when touching drainage, gowns if clothes could be contaminated).

Equipment & other objects – Environmental decontamination can be done using a 0.5% hypochlorite solution (1 part household bleach + 9 parts water = 0.5% solution), prior to normal cleaning or washing.

Outbreak control – All patients with pneumonic plague should be in droplet isolation for the first 48 hours after the initiation of treatment. This means that a healthcare worker should use a surgical mask within 3 feet of the patient. Those who have been in household or face-to-face contact with patients with pneumonic plague should be given antibiotic prophylaxis and placed under fever surveillance for 7 days.

Laboratory Testing: A presumptive diagnosis can be made microscopically by identification of the gram-negative coccobacillus with safety-pin bipolar staining in Gram or Wayson's stained smears from peripheral blood, sputum, or cerebrospinal fluids sample. When available, immunofluorescent staining is very useful.

1. Cultures of blood, sputum, buboes, and CSF, should be processed on blood agar, MacConkey agar or infusion broth. The organism grows slowly at normal incubation temperatures, and may be misidentified by automated systems because of delayed biochemical reactions. Confirmation of organism is done by DFA, phage typing, and/or PCR.
2. Antibody response test- A four-fold rise in antibody titer by ELISA or passive hemagglutination in patient serum is also diagnostic.

Therapeutic Treatment: Historically, the treatment of choice for bubonic, septicemic, and pneumonic plague has been streptomycin. However, since streptomycin is no longer readily available, gentamicin appears just as effective. Doxycycline or ciprofloxacin* are alternative antibiotics. Once the patient is stable, an effectice oral antibiotic can be used to complete the course of therapy. IV chloramphenicol is the drug of choice for plague meningitis.

Prophylactic Treatment: Because of oral administration and relative lack of toxicity, the antibiotic for prophylaxis or for use in face-to-face contacts of patients with pneumonic plague is doxycycline.

Differential diagnosis: For pneumonic plague the differential diagnoses should include any acute pneumonia, tularemia, hantavirus pulmonary syndrome, and anthrax.

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For more information call (602) 364-3289

* Ciprofloxicin does not have an FDA approved indication for treatment of plague

Frequently Asked Questions About Plague

What is plague?
Plague is a disease caused by *Yersinia pestis* (*Y. pestis*), a bacterium found in rodents and their fleas in many areas around the world.

Why are we concerned about pneumonic plague as a biological weapon?
Yersinia pestis used in an aerosol attack could cause cases of the pneumonic form of plague. One to six days after becoming infected with the bacteria, people would develop pneumonic plague. Once people have plague pneumonia, the bacteria can spread to others who have close contact with them. Because of the delay between being exposed to the bacteria and becoming sick, people could travel a long distance before then becoming contagious and possibly infecting others. Controlling the disease would then be more difficult. A biological weapon that spreads *Y. pestis* is possible because the bacterium occurs in nature and could be isolated and grown in quantity in a laboratory. Even so, manufacturing an effective weapon using *Y. pestis* would require advanced knowledge and technology.

Is pneumonic plague different from bubonic plague?
Yes. Both are caused by *Yersinia pestis*, but they are transmitted differently and their symptoms differ. Pneumonic plague can be transmitted directly from person-to-person by coughing. Bubonic plague is hardly ever spread person to person. Pneumonic plague affects the lungs and is transmitted when a person breathes in *Y. pestis* particles in the air. Bubonic plague is transmitted through the bite of an infected flea or exposure to infected material through a break in the skin. Symptoms include swollen, tender lymph glands called buboes. If bubonic plague is not treated, however, the bacteria can spread through the bloodstream and infect the lungs, causing a secondary case of pneumonic plague.

What are the signs and symptoms of pneumonic plague?
Patients usually have fever, weakness, and rapidly developing pneumonia with shortness of breath, chest pain, cough, and sometimes bloody or watery sputum. Nausea, vomiting, and abdominal pain may also occur. Without early treatment, pneumonic plague usually leads to respiratory failure, shock, and rapid death.

How do people become infected with pneumonic plague?
Pneumonic plague occurs when *Yersinia pestis* infects the lungs. Transmission can take place if someone breathes in *Y. pestis* particles, which could happen in an aerosol release during a bioterrorism attack. Pneumonic plague is also transmitted by breathing in *Y. pestis* suspended in respiratory droplets from a person (or animal) with pneumonic plague. Respiratory droplets are spread most readily by coughing or sneezing. Becoming infected in this way usually requires direct and close (within 6 feet) contact with the ill person or animal. Pneumonic plague may also occur if a person with bubonic or septicemic plague is untreated and the bacteria spread to the lungs.

Does plague occur naturally in the United States and in Arizona?
Yes. Today, plague remains a naturally occurring infection of rats, ground squirrels, prairie dogs, and other rodents on every populated continent except Australia. In the U.S. plague is most common in the southwestern states, particularly New Mexico and Arizona. An average of 1 to 2 cases of human plague occur naturally each year in Arizona. Most cases are seen in the northwest portion of the state, although cases can likely occur anywhere in the state above 4000 feet of elevation.

Can a person exposed to pneumonic plague avoid becoming sick?
Yes. People who have had close contact with an infected person can greatly reduce the chance of becoming sick if they begin treatment within 7 days of their exposure. Treatment consists of taking antibiotics for at least 7 days.

How quickly would someone get sick if exposed to plague bacteria through the air?
Someone exposed to *Yersinia pestis* through the air—either from an intentional aerosol release or from close and direct exposure to someone with plague pneumonia—would become ill within 1 to 6 days.

Can pneumonic plague be treated?
Yes. Several types of antibiotics are effective for curing the disease, and also for preventing it. Available oral medications are a tetracycline (such as doxycycline) or a fluoroquinolone (such as ciprofloxacin). For injection or intravenous use, streptomycin or gentamicin antibiotics are used.

Would enough medication be available in the event of a bioterrorism attack involving pneumonic plague?
National and state public health officials have large supplies of drugs needed in the event of a bioterrorism attack. These supplies can be sent anywhere in the United States within 12 hours.

What should someone do if they suspect they or others have been exposed to plague?
Get immediate medical attention. A person who has been exposed to pneumonic plague should rapidly receive antibiotics to prevent illness. Local or state health departments should be notified of the possibility of a patient with plague. They will then immediately investigate to determine whether the illness were due to naturally occurring disease.

How can someone reduce the risk of getting pneumonic plague from another person or giving it to someone else?
People having direct and close contact with someone with pneumonic plague should wear disposable surgical masks. Patients with the disease should be isolated and medically supervised for at least the first 48 hours of antibiotic treatment. People who have been exposed to a contagious person can be protected from developing plague by receiving prompt antibiotic treatment.

How is plague diagnosed?
The first step is receiving an evaluation by a health worker. If the health worker suspects pneumonic plague, samples of the patient's blood, sputum, or lymph node aspirate are sent to a laboratory for testing. Some preliminary laboratory results can be available in just a few hours, though more definite results usually take several days.

How long can plague bacteria exist in the environment?
Yersinia pestis is easily destroyed by sunlight and drying. Even so, when released into air, the bacterium will survive for up to one hour, depending on conditions.

Is a vaccine available to prevent pneumonic plague?
Currently, no plague vaccine is available in the United States. Research is in progress, but we are not likely to have vaccines for several years or more.

For more information call (602) 364-3289

SMALLPOX

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Smallpox is an acute viral illness caused by variola, one of the orthopox viruses. There are two different strains of the virus, variola major and variola minor. Variola major causes a more severe illness. No cases of smallpox have been observed in the world since 1978. The World Heath Organization declared the world free smallpox free in 1980.

Routes of Exposure: Inhalation or contact with skin lesions or secretions

Infective Dose: The infectious dose is unknown, but it is believed to be 10-100 virions.

Incubation Period: The incubation period of ranges from 7-17 days, with an average of 12 days.

Clinical Effects: The illness begins with a prodrome lasting 2-3 days, with generalized severe malaise, fever, rigors, headache, and backache. Abdominal pain and delirium are sometimes present. These symptoms are followed by a rash that progresses over 7 to 10 days. Lesions develop at the same stage, starting first as macules, and then changing to papules, then to vesicles, then to pustules and finally to scabs. The lesions are most concentrated on the face and extremities, and they are least dense on the trunk. The lesions are firm and deep-seated.

Approximately 10% of cases will have an atypical type of rash described as either flat smallpox or hemorrhagic smallpox. These patients also have a prostrating febrile prodrome. In the flat form, the skin lesions never fully organize; instead they remain soft, flattened and velvety to the touch. In the hemorrhagic form there is bleeding under the skin and overwhelming DIC without the development of characteristic pox lesions.

Lethality: The mortality rate of smallpox is 20-50% in unvaccinated individuals. Hemorrhagic and malignant cases are 95-100% fatal.

Transmissibility: Smallpox is not contagious during the incubation period. Persons with smallpox become infectious at the onset of the rash, and remain infectious until all of the scabs have fallen off. Person-to-person transmission occurs by droplet exposure to oropharyngeal secretions, and by contact with skin lesions. Close, face-to-face contact is usually required for transmission, although airborne transmission in a hospital may have occurred in one outbreak.

Primary contamination & Methods of Dissemination: Any case of smallpox would be considered an act of terrorism. Smallpox virus could be delivered via aerosol, or by means of an intentionally infected individual.

Secondary Transmission & Persistence of organism: Humans are the only for host for smallpox. People have been infected by contact with smallpox patients' linen, presumably by fomite transmission. However, smallpox has only been found to spread when there is an identifiable patient with active infection.

Decontamination & Isolation:
Patients – Airborne and contact precautions should be observed in addition to standard precautions.
Equipment, clothing & other objects – Contaminated clothing and bed linens can spread the virus. Laundry should be bagged with minimal agitation to prevent contamination of air, surfaces, or people. Only immunized workers using proper PPE should handle contaminated laundry. Laundering should be done using hot water to which bleach has been added. Disinfectants that are used for standard hospital control, such as hypochlorite or quaternary ammonia, are effective for cleaning surfaces possibly contaminated with virus. Waste should be placed in biohazard bags and discarded according to medical waste regulations.

Outbreak control: Control of smallpox is based upon vaccination with the vaccinia virus and isolation of cases. A suspect case of smallpox should be considered a public health emergency. Local, tribal and state health departments should be notified immediately. As soon as the diagnosis of smallpox is made, all suspected smallpox cases should be isolated. Additionally, all household and face-to-face contacts should be vaccinated as soon as possible. The smallpox vaccine does not confer lifelong immunity.

Laboratory testing: Smallpox virus can be found in vesicular or pustular fluid by PCR or by culture. Electron microscopy can identify an orthopox virus, but cannot differentiate between variola, vaccinia, or monkeypox. Smallpox virus testing is currently only available through the CDC.

Local and state health departments should be contacted immediately if smallpox is a consideration.

People who collect samples to test for smallpox should wear proper personal protective equipment and have received a recent smallpox vaccine. Smallpox evaluation is done by sampling skin lesions, drawing blood, and doing throat swabs for testing by culture, EM, PCR, and serology.

Therapeutic Treatment: There is no proven effective anti-viral treatment for smallpox. Cidofovir has *in vitro* activity against smallpox and could be available by an investigational new drug protocol.

Prophylactic Treatment: A highly effective smallpox vaccine exists using vaccinia virus, another orthopox virus. It is being used by the military and for public health preparedness. It is not being offered to the general public since as of July 2004 there is no one in the world with smallpox infection. There is enough vaccine available to vaccinate everyone in the United States, if there were a smallpox outbreak. Vaccination within 3 days of exposure will prevent or significantly modify smallpox in the vast majority of persons. Vaccination 4 to 7 days protects against death, but will not prevent infection.

Differential Diagnosis: The differential diagnosis of a generalized vesicular rash should include varicella (chickenpox) and monkey pox. The lesions of varicella arise in crops, are superficial, and are almost never found on the palms or soles. In contrast, the rash associated with smallpox does not appear in crops: all lesions on one part of the body will be at the same stage of development. Smallpox lesions are deep and firm, and are most concentrated on the face and extremities, including palms and soles. Monkey pox, a naturally occurring relative of smallpox, occurs in Africa. The lesions are clinically indistinguishable from smallpox, they are fewer in number and the patients are less toxic. Smallpox cases that present in the hemorrhagic form can be misdiagnosed as meningococcemia or severe acute leukemia. The CDC website has an algorithm to assess the risk of a rash for smallpox: http://www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm/index.asp

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For more information call (602) 364-3289

Frequently Asked Questions About Smallpox

What should I know about smallpox?
Smallpox is an acute, contagious, and sometimes fatal disease caused by the variola virus (an orthopoxvirus), and marked by fever and a distinctive progressive skin rash. In 1980, the disease was declared eradicated following worldwide vaccination programs. However, in the aftermath of the events of September and October, 2001, plans are in place to deal with a bioterrorist attack using smallpox as a weapon.

If I am concerned about a smallpox attack, can I go to my doctor and get the smallpox vaccine?
At the moment, the smallpox vaccine is not available for members of the general public. In the event of a smallpox outbreak, however, there is enough smallpox vaccine to vaccinate everyone who would need it.

What are the symptoms of smallpox?
The symptoms of smallpox begin with high fever, head and body aches, and sometimes vomiting. A rash follows that spreads and progresses to raised bumps and pus-filled blisters that crust, scab, and fall off after about three weeks, leaving pitted scars.

If someone comes in contact with smallpox, how long does it take to show symptoms?
After exposure, it takes between 7 and 17 days for symptoms of smallpox to appear (average incubation time is 12 to 14 days). During this time, the infected person feels fine and is not contagious.

Is smallpox fatal?
The majority of patients with smallpox recover, but death may occur in up to 30% of cases. Many smallpox survivors have permanent scars over large areas of their body, especially their face. Some are left blind.

How is smallpox spread?
Smallpox normally spreads from contact with infected persons. Generally, direct and fairly prolonged face-to-face contact is required to spread smallpox from one person to another. Smallpox also can be spread through direct contact with infected bodily fluids or contaminated objects such as bedding or clothing. Indirect spread is less common. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains. Smallpox is not spread by insects or animals.

If smallpox is released in aerosol form, how long does the virus survive?
The smallpox virus is fragile. In laboratory experiments, 90% of aerosolized smallpox virus dies within 24 hours. In the presence of ultraviolet (UV) light, this percentage is even greater. Therefore, if an aerosol release of smallpox were to occur, most of the smallpox virus matter would be inactivated or dissipated within 24 hours.

How many people would have to get smallpox before it is considered an outbreak?
One confirmed case of smallpox is considered a public health emergency.

Is smallpox contagious before the smallpox symptoms show?
A person with smallpox will have a fever and be quite ill for several days before the rash appears. A person is not contagious until the rash begins. The infected person is contagious until the last smallpox scab falls off.

Is there any treatment for smallpox?
Smallpox can be prevented through use of the smallpox vaccine. There is no proven treatment for smallpox, but research to evaluate new antiviral agents is ongoing. Early results from laboratory studies suggest that the drug cidofovir may fight against the smallpox virus; currently, studies with animals are being done to better understand the drug's ability to treat smallpox disease. Patients with smallpox can benefit from supportive therapy (e.g., intravenous fluids, medicine to control fever or pain) and antibiotics for any secondary bacterial infections that may occur.

What is the smallpox vaccine?
The smallpox vaccine is the only way to prevent smallpox. The vaccine is made from a virus called *vaccinia*, which is another "pox"-type virus related to smallpox. The vaccine cannot cause smallpox. The vaccine helps the body develop immunity to smallpox. It was successfully used to eradicate smallpox from the human population.

Should I get vaccinated against smallpox?
The smallpox vaccine is not available to the public at this time.

Many vaccinations are required. Why don't people have to get the smallpox vaccine?
The last case of smallpox in the United States was in 1949. The last naturally occurring case in the world was in Somalia in 1977. 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.

If someone is exposed to smallpox, is it too late to get a vaccination?
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 likely offers some protection from disease or may modify the severity of disease.

How long does a smallpox vaccination last?
Past experience indicates that the first dose of the vaccine offers protection from smallpox for 3 to 5 years, with decreasing immunity thereafter. If a person is vaccinated again later, immunity lasts longer.

For more information call (602) 364-3289

TULAREMIA

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Tularemia is a zoonotic disease caused by the gram-negative coccobacillus *Francisella tularensis*.

Routes of Exposure: Tularemia can be acquired by humans by inoculation of the skin or mucous membranes with blood or tissue from infected animals, or bites of infected deerflies, mosquitoes, or ticks. Less commonly, inhalation of contaminated dust or ingestion of contaminated foods or water can also cause human disease. The animal reservoirs of disease include rabbits, muskrats, and squirrels.

Infective Dose & Infectivity: 10-50 organisms

Incubation Period: The incubation period ranges from 1 to 14 days with an average of 3 to 5 days.

Clinical Effects: Different clinical forms of disease are seen depending on the route of exposure. Disease resulting from intentional aerosol release of *F. tularensis* would primarily cause typhoidal tularemia. Gastrointestinal symptoms such as diarrhea and pain may also be present. Typhoidal tularemia manifests with fever, prostration, weight loss, but with no adenopathy. Pneumonia is most common with the typhoidal form. Tularemia pneumonia is generally a severe atypical pneumonia that may be fulminating and can result from either inhalation of infectious aerosols or from aspiration of organisms from the pharynx. Tularemia pneumonia can also be secondary to a tularemia bacteremia. Tularemia pneumonia generally manifests with fever, headache, substernal discomfort, and non-productive cough. Radiographic evidence of pneumonia or mediastinal lymphadenopathy may or may not be present. Oculoglandular tularemia can result from inoculation of the conjunctivae with hand or fingers contaminated by tissue and/or fluids from an infected animal. The gastrointestinal form of tularemia manifests as abdominal pain, nausea, vomiting and diarrhea.

Lethality: The mortality rate without treatment is 33%. However, with appropriate treatment, the mortality rate is less than 2%.

Transmissibility: There is no known person-to-person transmission.

Primary contaminations & Methods of Dissemination: Tularemia would most likely be delivered via aerosolization, or sabotage of food and/or water.

Secondary Contamination & Persistence of organism: Secondary transmission is not an issue. However, *F. tularensis* can persist in cold, moist environments for extended periods.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Contact precautions should be used with skin lesions and secretions. Patients with direct exposure to aerosols, as well as their clothing, should be washed with soap and water.

Equipment, clothing & other objects – Heat, 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) will kill the organisms and can be used for environmental decontamination.

Outbreak control: Following an intentional release, the risk of acquiring infection from local animals is minimal. The risk can be further minimized by educating the public in avoidance of sick animals as well as personal protective measures against bites from mosquitoes, deerflies, or ticks. Standard levels of chlorine in municipal water sources should protect against waterborne infection. In warm, arid environments, organisms in the soil are unlikely to survive for significant periods of time and are unlikely to present a hazard.

Laboratory testing: Serology is the most common diagnostic test; acute and convalescent serology is the most helpful. Identification of organisms by gram staining ulcer fluids or sputum is generally not helpful. Rapid testing of secretions, exudates and biopsies can be done by direct fluorescent antibody or PCR. Routine culture is difficult due to unusual growth requirements and/or overgrowth of commensal bacteria. Culturing is difficult and potentially dangerous. If tularemia is suspected, and cultures are obtained, the laboratory should be notified because of the high risk to laboratory workers due to transmissibility of the bacteria. *F. tularensis* can be grown from wounds, tissues, blood, and respiratory secretions.

Therapeutic Treatment: The recommended treatment for tularemia in a contained casualty setting is streptomycin or gentamicin*. Alternate choices include doxycycline, ciprofloxacin*, or chloramphenicol*. In a mass casualty setting where patients cannot be managed individually, the recommended treatments are doxycycline or ciprofloxacin*.

Prophylactic Treatment: Exposed individuals can be treated prophylactically with doxycycline or ciprofloxacin*.

Differential Diagnosis: The differential diagnoses should include typhoidal syndromes such as *Salmonella*, rickettsia, malaria, and any atypical pneumonic process.

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For more information call (602) 364-3289

* Gentamicin, Ciprofloxacin, and Chloramphenicol do not have an FDA approved indication for tularemia

Frequently Asked Questions About Tularemia

What is tularemia?
Tularemia is an infectious disease caused by a hardy bacterium, *Francisella tularensis*, found in animals (especially rodents, rabbits, and hares).

How do people become infected with the tularemia bacteria?
Typically, persons become infected through the bites of arthropods (most commonly, ticks and deerflies) that have fed on an infected animal, by handling infected animal carcasses, by eating or drinking contaminated food or water, or by inhaling infected aerosols.

Does tularemia occur naturally in the United States and in Arizona?
Yes. It is a widespread disease of animals. Approximately 200 cases of tularemia in humans are reported annually in the United States, mostly in persons living in the south-central and western states. Tularemia in humans is relatively rare in Arizona. There were five cases reported in Arizona over the last ten years and 28 cases over the last twenty-five years. Nearly all cases occur in rural areas and are associated with the bites of infective ticks and biting flies or with the handling of infected rodents, rabbits, or hares. Occasional cases result from inhaling infectious aerosols and from laboratory accidents.

Why are we concerned about tularemia as a biological weapon?
Francisella tularensis is highly infectious: a small number of bacteria (10-50 organisms) can cause disease. If *F. tularensis* were used as a biological weapon, it would likely be spread through the air as an aerosol. Persons who inhale an infectious aerosol would generally experience severe respiratory illness, including life-threatening pneumonia and systemic disease, if they were not treated. The bacteria that cause tularemia occur widely in nature and could be isolated and grown in quantity in a laboratory, although manufacturing an effective aerosol weapon would require considerable sophistication.

Can someone become infected with the tularemia bacteria from another person?
No. Infected individuals have not been known to transmit the infection, so infected persons do not need to be isolated.

How quickly would someone become sick if they were exposed to the tularemia bacteria?
The incubation period for tularemia is typically 3 to 5 days, with a range of 1 to 14 days.

What are the signs and symptoms of tularemia?
Depending on the route of exposure, the tularemia bacteria may cause skin ulcers, swollen and painful lymph glands, inflamed eyes, sore throat, oral ulcers, or pneumonia. If the bacteria were inhaled, symptoms would include the abrupt onset of fever, chills, headache, muscle aches, joint pain, dry cough, and progressive weakness. Persons with pneumonia can develop chest pain, difficulty breathing, bloody sputum, and respiratory failure. Forty percent or more of persons with the lung and systemic forms of the disease may die if they are not treated with appropriate antibiotics.

What should someone do if they suspect they or others have been exposed to the tularemia bacteria?
Seek prompt medical attention. If a person has been exposed to *Francisella tularensis*, treatment with tetracycline antibiotics is often recommended.

Local and state health departments should be immediately notified so an investigation and control activities can begin quickly. If the exposure is thought to be due to criminal activity (bioterrorism), local and state health departments will notify CDC, the FBI, and other appropriate authorities.

How is tularemia diagnosed?
When tularemia is clinically suspected, the healthcare worker will collect specimens, such as blood or sputum, from the patient for testing in a diagnostic or reference laboratory. Laboratory test results for tularemia may be presumptive or confirmatory.

Sometimes presumptive (preliminary) identification may take only a few hours, but confirmatory testing will usually take longer.

Can tularemia be effectively treated with antibiotics?
Yes. After potential exposure or diagnosis, early treatment is recommended with an antibiotic from the tetracycline (such as doxycycline) or fluoroquinolone (such as ciprofloxacin) class. Other antibiotics such as streptomycin or gentamicin, are also effective, but can only be given intramuscularly or intravenously. Sensitivity testing of the tularemia bacterium can be done to determine which antibiotics would be most effective.

How long can *Francisella tularensis* exist in the environment?
Francisella tularensis can remain alive for weeks in water and soil.

Is there a vaccine available for tularemia?
A vaccine for tularemia is available for use in laboratory workers, but it is not licensed for general use.

For more information call (602) 364-3289

VIRAL HEMORRHAGIC FEVERS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent:
Arenaviridae – Junin virus (Argentine hemorrhagic fever), Machupo virus (Bolivian hemorrhagic fever), Guanarito virus (Venezuelan hemorrhagic fever), Sabia virus (Brazillian hemorrhagic fever), Lassa virus (Lassa fever)
Bunyaviridae – Rift Valley fever virus, Crimean-Congo hemorrhagic fever virus, Hantaan and related viruses of the hantavirus genus (hemorrhagic fever with renal syndrome)
Filoviviridae – Ebola virus, Marburg virus
Flaviviridae – Dengue virus, Yellow fever virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus

Routes of Transmission: Dependent on the specific virus. Routes transmission include the bite of an infected tick or mosquito, inhalation of aerosol generated from infected rodent excreta, contact with infected animal carcasses, or person-to-person transmission by close contact with infectious body fluids.

In the laboratory all the viral hemorrhagic fever agents, except dengue virus, are infectious by aerosol.

Incubation Period: The overall incubation period ranges from 2 to 21 days.

Clinical Effects: There is great diversity in the symptoms of these illnesses and infection by these viruses does not necessarily lead to viral hemorrhagic fever disease. Common presenting symptoms and complaints include high fever, headache, malaise, arthralgias, myalgias, nausea, abdominal pain, and nonbloody diarrhea. Clinical examination may reveal fever, hypotension, relative bradycardia, tachypnea, conjunctivitis, and pharyngitis. Rash and cutaneous flushing are typical manifestations, though the specific characteristics of the rash differ by disease. Full blown viral hemorrhagic fevers can evolve to progressive hemorrhagic diathesis, such as petechiae, mucous membrane and conjunctival hemorrhage; hematuria; hematemesis; and melena, disseminated intravascular coagulation, and circulatory shock.

Arenaviruses progress to illness gradually, while filoviruses are characterized by an abrupt onset of disease.

Lethality: The mortality rate varies greatly among these diseases, from 0.5% for Omsk hemorrhagic fever to 90% for Ebola (subtype Zaire).

Transmissibility: Some viral hemorrhagic fevers can be spread person to person. These are: Argentine hemorrhagic fever, Bolivian hemorrhagic fever, Venezuelan hemorrhagic fever, Brazillian hemorrhagic fever, Lassa fever, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndrome, Ebola hemorrhagic fever, and Marburg hemorrhagic fever.

Primary Contamination & Methods of Dissemination: A likely method of dissemination as a biological weapon would be through aerosolization.

Secondary Contamination & Persistence of Organism: Some of the viral hemorrhagic fever viruses can remain present in bodily fluids for long periods after clinical recovery. Because of this continued risk of contagion patients convalescing from an arenaviral or a filoviral infection should abstain from sexual activity for three months following clinical recovery.

Decontamination & Isolation:
Patients – Strict hand hygiene plus use of double gloves, impermeable gowns, face shields, eye protection, leg and shoe coverings, and N95 respirators are recommended. The majority of person-to-person transmission of filoviruses and arenaviruses has been due to direct contact with infected blood and bodily fluids.
Equipment, clothing & other objects – Environmental surfaces in patients' rooms and contaminated medical equipment should be disinfected with 0.5% hypochlorite solution (1 part household bleach + 9 parts water = 0.5% solution). Contaminated linens and clothes can be placed in double bags and washed without sorting in a normal hot water cycle with bleach. Alternatively, they may be autoclaved or incinerated.

Outbreak Control: All individuals who have been potentially exposed to a hemorrhagic fever virus should be placed under medical surveillance for 21 days and instructed to record their temperatures twice daily and report any symptoms they are experiencing, including any temperature 101º F or higher.

Laboratory testing: Laboratory detection consists of antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody detection by antibody-capture ELISA, RT-PCR, and viral isolation. The most useful of these for the clinical setting are antigen detection (by ELISA) and RT-PCR. If viral hemorrhagic fever is suspected, the laboratory should be notified so that they can avoid procedures that could aerosolize the virus.

Therapeutic Treatment: Treatment is mainly supportive and should include maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. Early vasopressor support with hemodynamic monitoring should be considered since some viral hemorrhagic fevers have a propensity for pulmonary capillary leaks and vigorous fluid resuscitation of hypotensive patients can contribute to pulmonary endema without reversing hypotension. Mechanical ventilation, renal dialysis, and antiseizure therapy may be required. Intramuscular injections, aspirin, nonsteroidal anti-inflammatory drugs, and other anticoagulant therapies that would aggravate a bleeding disorder should be avoided.

There are no antiviral drugs approved by the US Food and Drug Administration for treatment of viral hemorrhagic fevers. Ribavirin, a nucleoside analog, has some in vitro and in vivo activity against Arenaviridae and Bunyaviridae but no utility against Filoviridae or Flaviviridae. Ribavirin is available via compassionate use protocols.

Prophylactic Treatment: The prophylactic use of oral ribavirin has been suggested for high-risk contacts (those who have had direct exposure to body fluids) of patients with either Congo-Crimean hemorrhagic fever or Lassa fever.

Yellow fever is the only licensed vaccine for any of the viral hemorrhagic fevers, but it is not efficacious for post exposure disease prevention. Under an investigational new drug application vaccines are available for Argentine hemorrhagic fever and Rift Valley fever. A vaccine for Kyasanur Forest disease is also in existence.

Differential Diagnosis: Differential diagnoses should include illnesses that cause severe sepsis and hemorrhage, including influenza, viral hepatitis, staphylococcal or gram negative sepsis, toxic shock syndrome, meningococcemia, salmonellosis and shigellosis, rickettsial diseases (such as Rocky Mountain spotted fever), leptospirosis, borreliosis, psittacosis, dengue, hantavirus pulmonary syndrome, malaria, trypanosomiasis, septicemic plague, rubella, measles, hemorrhagic smallpox, idiopathic or thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acute leukemia, and collagen-vascular diseases.

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For more information call (602) 364-3289

Frequently Asked Questions About Viral Hemorrhagic Fevers

What are viral hemorrhagic fevers?
Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by several distinct families of viruses. In general, the term "viral hemorrhagic fever" is used to describe a severe multisystem syndrome (multisystem in that multiple organ systems in the body are affected). Characteristically, the overall vascular system is damaged, and the body's ability to regulate itself is impaired. These symptoms are often accompanied by hemorrhage (bleeding); however, the bleeding is itself rarely life-threatening. While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease.

How are hemorrhagic fever viruses grouped?
VHFs are caused by viruses of four distinct families: arenaviruses, filoviruses, bunyaviruses, and flaviviruses. Each of these families share a number of features:

- They are all RNA viruses, and all are covered, or enveloped, in a fatty (lipid) coating.
- Their survival is dependent on an animal or insect host, called the natural reservoir.
- The viruses are geographically restricted to the areas where their host species live.
- Humans are not the natural reservoir for any of these viruses. Humans are infected when they come into contact with infected hosts. However, with some viruses, after the accidental transmission from the host, humans can transmit the virus to one another.
- Human cases or outbreaks of hemorrhagic fevers caused by these viruses occur sporadically and irregularly. The occurrence of outbreaks cannot be easily predicted.
- With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs.

In rare cases, other viral and bacterial infections can cause a hemorrhagic fever; scrub typhus is a good example.

What carries viruses that cause viral hemorrhagic fevers?
Viruses associated with most VHFs are zoonotic. This means that these viruses naturally reside in an animal reservoir host or arthropod vector. They are totally dependent on their hosts for replication and overall survival. For the most part, rodents and arthropods are the main reservoirs for viruses causing VHFs. The multimammate rat, cotton rat, deer mouse, house mouse, and other field rodents are examples of reservoir hosts. Arthropod ticks and mosquitoes serve as vectors for some of the illnesses. However, the hosts of some viruses remain unknown -- Ebola and Marburg viruses are well-known examples.

Where are cases of viral hemorrhagic fever found?
Taken together, the viruses that cause VHFs are distributed over much of the globe. However, because each virus is associated with one or more particular host species, the virus and the disease it causes are usually seen only where the host species live(s). Some hosts, such as the rodent species carrying several of the New World arenaviruses, live in geographically restricted areas. Therefore, the risk of getting VHFs caused by these viruses is restricted to those areas. Other hosts range over continents, such as the rodents that carry viruses which cause various

forms of hantavirus pulmonary syndrome (HPS) in North and South America, or the different set of rodents that carry viruses which cause hemorrhagic fever with renal syndrome (HFRS) in Europe and Asia. A few hosts are distributed nearly worldwide, such as the common rat. It can carry Seoul virus, a cause of HFRS; therefore, humans can get HFRS anywhere where the common rat is found.

People usually become infected with hemorrhagic fevers only in areas where the specific host lives. However, people can be infected by an animal or insect exported from its native habitat. For example, Marburg virus outbreaks occurred in Yugoslavia, and in Marburg and Frankfurt, Germany when laboratory workers handled infected imported monkeys. Also, human travel can spread hemorrhagic fever beyond its natural habitat. In 1996, a health care worker in Gabon unknowingly became infected with Ebola hemorrhagic fever (Ebola HF). He later traveled to South Africa, required hospitalization, and fatally infected a nurse. As world-wide travel increases, so does the risk of spread of unusual infections such as hemorrhagic fevers.

How are hemorrhagic fever viruses transmitted?
Viruses causing hemorrhagic fever are initially transmitted to humans when the activities of infected reservoir hosts or vectors and humans overlap. The viruses carried in rodent reservoirs are transmitted when humans have contact with urine, fecal matter, saliva, or other body excretions from infected rodents. The viruses associated with arthropod vectors are spread most often when the vector mosquito or tick bites a human, or when a human crushes a tick. However, some of these vectors may spread virus to animals, livestock, for example. Humans then become infected when they care for or slaughter the animals.

Some viruses that cause hemorrhagic fever can spread from one person to another, once an initial person has become infected. Ebola, Marburg, Lassa and Crimean-Congo hemorrhagic fever viruses are examples. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids. For example, contaminated syringes and needles have played an important role in spreading infection in outbreaks of Ebola hemorrhagic fever and Lassa fever.

What are the symptoms of viral hemorrhagic fever illnesses?
Specific signs and symptoms vary by the type of VHF, but initial signs and symptoms often include marked fever, fatigue, dizziness, muscle aches, loss of strength, and exhaustion. Patients with severe cases of VHF often show signs of bleeding under the skin, in internal organs, or from body orifices like the mouth, eyes, or ears. However, although they may bleed from many sites around the body, patients rarely die because of blood loss. Severely ill patient cases may also show shock, nervous system malfunction, coma, delirium, and seizures. Some types of VHF are associated with renal (kidney) failure.

How are patients with viral hemorrhagic fever treated?
Patients receive supportive therapy, but generally speaking, there is no other treatment or established cure for VHFs. Ribavirin, an anti-viral drug, has been effective in treating some individuals with Lassa fever or HFRS. Treatment with convalescent-phase plasma has been used with success in some patients with Argentine hemorrhagic fever.

How can cases of viral hemorrhagic fever be prevented and controlled?
With the exception of yellow fever and Argentine hemorrhagic fever, for which vaccines have been developed, no vaccines exist that can protect against these diseases. Therefore, prevention efforts must concentrate on avoiding contact with the animals or insects that carry the infection.

If a case of human VHF does occur, efforts should focus on preventing further transmission. Because many of the hosts that carry hemorrhagic fever viruses are rodents, disease prevention efforts include:

- controlling rodent populations;
- discouraging rodents from entering or living in homes or workplaces;
- encouraging safe cleanup of rodent nests and droppings.

For hemorrhagic fever viruses spread by insects, prevention efforts often focus on community-wide insect control such as spraying and eliminating breeding places. In addition, people are encouraged to use personal protective measures, such as insect repellant, proper clothing, bednets, window screens, and other insect barriers to avoid being bitten.

For hemorrhagic fever viruses that can be transmitted from one person to another, the most important infection control measure is to avoid close physical contact with infected people and their body fluids. Proper infection control techniques include isolating infected individuals and wearing protective clothing. Other infection control recommendations include the proper use, disinfection, and disposal of instruments and equipment used in treating or caring for patients with VHF, such as needles and thermometers.

The World Health Organization and CDC have developed practical, hospital-based guidelines, titled Infection Control for Viral Haemorrhagic Fevers In the African Health Care Setting. This manual can help health-care facilities with few financial resources to recognize cases and prevent further hospital-based disease transmission using locally available materials.

What needs to be done to address the threat of viral hemorrhagic fevers?
Scientists and researchers are challenged with developing containment, treatment, and vaccine strategies for these diseases. Another goal is to develop immunologic and molecular tools for more rapid disease diagnosis, and to study how the viruses are transmitted and exactly how the disease affects the body (pathogenesis). A third goal is to understand the ecology of these viruses and their hosts in order to offer preventive public health advice for avoiding infection.

For more information call (602) 364-3289

Section 5:
Category B Agents

Arizona Department of Health Services

BRUCELLOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Brucellosis is a systemic zoonotic disease caused by one of four *Brucella* species: *B. melitensis,B. abortus, B. suis*, and *B. canis*. The organism is a small, gram-negative aerobic coccobacillus that grows within monocytes and macrophages.

Routes of Exposure: Transmission to humans occurs through (a) direct contact of infected tissue or body fluids with broken skin or conjunctivae, (b) inhalation of infected aerosols, or (c) ingestion of raw infected meat or unpasteurized dairy products. The primary reservoirs are goats, cattle, sheep, pigs and camels although animals such as elk, caribou, bison, deer and wild and domestic canine animals may be infected. Specifically, cattle and goats can carry *B. melitensis*, cattle can carry *B. abortus*, pigs can serve as reservoirs for *B. suis*, and dogs can serve as a reservoir for *B. canis.*

Infective Dose & Infectivity: 10-100 organisms

Incubation Period: Often 1-2 months, range 5 days to several months.

Clinical Effects: Brucellosis is a systemic infection characterized by an undulant fever pattern. It typically presents as an acute non-specific febrile illness with chills, sweats, headache, fatigue, myalgias, arthralgias, and anorexia. Approximately 15-25% of infected individuals will have cough. A normal chest radiograph is often present. Lymphadenopathy is present in 10-20% of patients, and 20-30% experience splenomegaly. Complications of brucellosis infection include: sacroiliitis, arthritis, vertebral osteomyelitis, epididymo-orchitis, and rarely, endocarditis. Routine labs are usually non-specific. In animals, abortion is the most obvious manifestation of the disease in females and epididymitis in males. The organism is shed in the milk, fetal membranes, and uterine discharges. Thus brucellosis can be both an occupational (veterinarians, farmers) or a foodborne disease.

Lethality: Brucellosis has a very low mortality rate, less than 5% of untreated cases, with most deaths caused by endocarditis or meningitis.

Transmissibility: Person-to-person transmission of brucellosis is extremely rare.

Primary Contaminations & Methods of Dissemination: Likely methods of dissemination would either be through aerosolization or sabotage of food.

Decontamination & Isolation: Patients can be managed using standard precautions. Contact precautions are suggested if draining lesions are present. No airborne isolation is required.

Laboratory testing: If brucellosis is suspected, the diagnosis is usually made through acute and convalescent serology. *Brucella* can be cultured from blood, bone marrow, or other tissues, but it grows slowly. Additionally, if culture is to be done, the laboratory should be notified that brucellosis is suspected because of the high risk to laboratory workers due to transmissibility of the bacteria.

Therapeutic Treatment: The recommended treatment in adults for brucellosis is doxycycline or doxycycline plus rifampin for 6 weeks. In children under 8 years of age, trimethoprim-sulfamethoxazole is substituted for doxycycline.

Prophylactic Treatment: For cases of accidental inoculation or exposure, doxycycline and rifampin have been used as post-exposure prophylaxis. No approved human *Brucella* vaccine is available.

Differential Diagnosis: Because the initial symptoms are non-specific, the differential diagnosis is broad and includes bacterial, viral and mycoplasmal infections. Brucellosis may be indistinguishable from typhoid fever, or the typhoidal form of tularemia.

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For more information call (602) 364-3289

Frequently Asked Questions About Brucellosis

What is brucellosis?
Brucellosis is an infectious disease caused by the bacteria of the genus *Brucella*. These bacteria are primarily passed among animals, and they cause disease in many different vertebrates. Various *Brucella* species affect sheep, goats, cattle, deer, elk, pigs, dogs, and several other animals. Humans become infected by coming in contact with animals or animal products that are contaminated with these bacteria. In humans brucellosis can cause a range of symptoms that are similar to the flu and may include fever, sweats, headaches, back pains, and physical weakness. Sever infections of the central nervous systems or lining of the heart may occur. Brucellosis can also cause long-lasting or chronic symptoms that include recurrent fevers, joint pain, and fatigue.

How common is brucellosis?
Brucellosis is not very common in the United States, where only 100 to 200 cases occur each year. But brucellosis can be very common in countries where animal disease control programs have not reduced the amount of disease among animals.

Where is brucellosis usually found?
Although brucellosis can be found worldwide, it is more common in countries that do not have standardized and effective public health and domestic animal health programs. Areas currently listed as high risk are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Unpasteurized cheeses, sometimes called "village cheeses," from these areas may represent a particular risk for tourists.

How is brucellosis transmitted to humans, and who is likely to become infected?
Humans are generally infected in one of three ways: eating or drinking something that is contaminated with *Brucella*, breathing in the organism (inhalation), or having the bacteria enter the body through skin wounds. The most common way to be infected is by eating or drinking contaminated milk products. When sheep, goats, cows, or camels are infected, their milk is contaminated with the bacteria. If the milk is not pasteurized, these bacteria can be transmitted to persons who drink the milk or eat cheeses made it. Inhalation of *Brucella* organisms is not a common route of infection, but it can be a significant hazard for people in certain occupations, such as those working in laboratories where the organism is cultured. Inhalation is often responsible for a significant percentage of cases in abattoir employees. Contamination of skin wounds may be a problem for persons working in slaughterhouses or meat packing plants or for veterinarians. Hunters may be infected through skin wounds or by accidentally ingesting the bacteria after cleaning deer, elk, moose, or wild pigs that they have killed.

Can brucellosis be spread from person to person?
Direct person-to-person spread of brucellosis is extremely rare. Mothers who are breast-feeding may transmit the infection to their infants. Sexual transmission has also been reported. Although uncommon, transmission may also occur via contaminated tissue transplantation.

Is there a way to prevent infection?
Yes. Do not consume unpasteurized milk, cheese, or ice cream while traveling. If you are not sure that the dairy product is pasteurized, don't eat it. Hunters and animal herdsman should use rubber gloves when handling eviscerating animals. There is no vaccine available for humans.

My dog has been diagnosed with brucellosis. Is that a risk for me?
B. canis is the species of *Brucella* species that can infect dogs. This species has occasionally been transmitted to humans, but the vast majority of dog infections do not result in human illness. Although veterinarians exposed to blood of infected animals are at risk, pet owners are not considered to be at risk for infection. This is partly because it is unlikely that they will come in contact with blood, semen, or placenta of the dog. The bacteria may be cleared from the animal within a few days of treatment; however re-infection is common and some animal body fluids may be infectious for weeks. Immunocompromised persons (cancer patients, HIV-infected individuals, or transplantation patients) should not handle dogs known to be infected with *B. canis*.

How is brucellosis diagnosed?
Brucellosis is diagnosed in a laboratory by finding *Brucella* organisms in samples of blood or bone marrow. Also, blood tests can be done to detect antibodies against the bacteria. If this method is used, two blood samples should be collected 2 weeks apart.

Is there a treatment for brucellosis?
Yes, but treatment can be difficult. Doctors can prescribe effective antibiotics. Usually, doxycycline and rifampin are used in combination for 6 weeks to prevent reoccurring infection. Depending on the timing of treatment and severity of illness, recovery may take a few weeks to several months. The death rate from brucellosis is very low.

For more information call (602) 364-3289

CHOLERA

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: *Vibrio cholerae* is a motile, gram negative, non-sporulating rod. Two serogroups have been identified as causing symptoms in humans: O1 and O139. These organisms grow best at a pH of 7.0 but are able to tolerate an alkaline environment. Rather than invading the intestinal mucosa, they adhere to it. The clinical syndrome is caused by the action of the cholera toxin.

Route of Exposure: Ingestion of water or food contaminated with cholera organisms.

Infective Dose & Infectivity: 10 to 500 organisms

Incubation Period: The incubation period for cholera ranges from four hours to five days with an average of 2-3 days.

Clinical Effects: Sudden onset of vomiting, abdominal distension, headache and pain with little or no fever. These symptoms are followed rapidly by profuse watery diarrhea with a “rice water” appearance (colorless with small flecks of mucous). Fluid loss may exceed five to ten liters a day, and death can result from dehydration, hypovolemia and shock. In children, coma, seizures and hypoglycemia can occur.

Lethality: If appropriately treated the mortality rate is less than 1%. However, if untreated the mortality rate may exceed 50%.

Transmissibility: Cholera is not easily spread from person to person; infected food handlers can contaminate foods and drinks; in order to be an effective biological weapon, major drinking water supplies would need to be heavily contaminated.

Primary Contamination & Methods of Dissemination: Natural dissemination is through fecal contamination of food or water supply.

Secondary Contamination & Persistence of organism: Diarrheal fluids are highly infective, however, the organism is easily killed by desiccation. It is not viable in pure water but will survive up to 24 hours in sewage and as long as six weeks in water containing organic matter. *Vibrio cholerae* can also withstand freezing for 3 to 4 days.

Decontamination & Isolation:

Patients – Patients with cholera and uncontrolled diarrhea should be managed using contact precautions that means using gloves and gowns for any contact with the patient or his environment. Good hand washing before and after glove use is essential to prevent spread of pathogens. Diapered or incontinent patients should remain on contact isolation for the duration of diarrhea symptoms. No airborne isolation of patients is necessary.

Equipment, clothing & other objects – Vibrio cholerae is readily killed by dry heat at 117^{o} C, steam, boiling or by short exposure to ordinary disinfectants and chlorination of water. Clothing should be washed in soap and hot water.

Outbreak control: Quarantine is unnecessary. Any person who shared food or drink with a cholera patient should be under surveillance for five days, and objects contaminated with feces or vomitus should be disinfected prior to reuse. Feces and vomitus do not need to be disinfected if discharged into a normal sewage disposal system.

Laboratory Testing: *Vibrio cholerae* can be cultured from stool specimens.

Therapeutic Treatment: Treatment of cholera infection is through rehydration with oral or parenteral fluids. Antibiotics can be used to shorten the duration of the diarrhea and the shedding of the organism. Oral tetracycline or doxycycline should be used. If patients are infected with a tetracycline-resistant strain, ciprofloxacin or erythromycin can be used. Although tetracyclines are usually avoided in children under eight due to the concern of teeth staining, the short course of therapy is unlikely to cause problems.

Prophylactic Treatment: Although a vaccine exists, it is not recommended because of its partial efficacy. Household contacts with a high likelihood of secondary transmission may receive oral tetracycline or doxycycline prophylaxis. Mass antibiotic prophylaxis of whole communities is never indicated and can lead to antibiotic resistance.

Differential Diagnosis: The differential diagnosis for *V. cholerae* includes organisms causing secretory diarrhea such as enterotoxigenic *E. coli*, and *Vibrio parahemolyticus.*

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Available at http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html

For more information call (602) 364-3289

Frequently Asked Questions About Cholera

What is cholera?
Cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium *Vibrio cholerae*. The infection is often mild or without symptoms, but sometimes it can be severe. Approximately 1 in 20 infected persons has severe disease characterized by profuse watery diarrhea, vomiting, and leg cramps. In these persons, rapid loss of body fluids leads to dehydration and shock. Without treatment, death can occur within hours.

How does a person get cholera?
A person may get cholera by drinking water or eating food contaminated with the cholera bacterium. In an epidemic, the source of the contamination is usually the feces of an infected person. The disease can spread rapidly in areas with inadequate treatment of sewage and drinking water.

The cholera bacterium may also live in the environment in brackish rivers and coastal waters. Shellfish eaten raw have been a source of cholera, and a few persons in the United States have contracted cholera after eating raw or undercooked shellfish from the Gulf of Mexico. The disease is not likely to spread directly from one person to another; therefore, casual contact with an infected person is not a risk factor for becoming ill.

What is the risk for cholera in the United States?
In the United States, cholera was prevalent in the 1800s but has been virtually eliminated by modern sewage and water treatment systems. However, as a result of improved transportation, more persons from the United States travel to parts of Latin America, Africa, or Asia where they are infected by cholera. In addition, domestic foodborne outbreaks in the United States have been caused by cholera-contaminated seafood brought back by travelers.

What should travelers do to avoid getting cholera?
The risk for cholera is very low for U.S. travelers visiting areas with epidemic cholera. When simple precautions are observed, contracting the disease is unlikely.

All travelers to areas where cholera has occurred should observe the following recommendations:

- Drink only water that you have boiled or treated with chlorine or iodine. Other safe beverages include tea and coffee made with boiled water and carbonated, bottled beverages with no ice.
- Eat only foods that have been thoroughly cooked and are still hot, or fruit that you have peeled yourself.
- Avoid undercooked or raw fish or shellfish, including ceviche.
- Make sure all vegetables are cooked; avoid salads.
- Avoid foods and beverages from street vendors.
- Do not bring perishable seafood back to the United States.

A simple rule of thumb is "Boil it, cook it, peel it, or forget it. "

Is a vaccine available to prevent cholera?
No cholera vaccines are available in the United States. Two oral vaccines are available outside of the United States however, they are not generally recommended for travelers because of the brief and incomplete immunity they offer.

Can cholera be treated?
Cholera can be simply and successfully treated by immediate replacement of the fluid and salts lost through diarrhea. Patients can be treated with oral rehydration solution, a prepackaged mixture of sugar and salts to be mixed with water and drunk in large amounts. This solution is used throughout the world to treat diarrhea. Severe cases also require intravenous fluid replacement. With prompt rehydration, fewer than 1% of cholera patients die.

Antibiotics shorten the course and diminish the severity of the illness, but they are not as important as rehydration. Persons who develop severe diarrhea and vomiting in countries where cholera occurs should seek medical attention promptly.

What is the U.S. government doing to combat cholera?
U.S. and international public health authorities are working to enhance surveillance for cholera, investigate cholera outbreaks, and design and implement preventive measures. The Centers for Disease Control is investigating epidemic cholera wherever it occurs and is training laboratory workers in proper techniques for identification of *V. cholerae*. In addition, the Centers for Disease Control is providing information on diagnosis, treatment, and prevention of cholera to public health officials and is educating the public about effective preventive measures.

The U.S. Agency for International Development is sponsoring some of the international government activities and is providing medical supplies to affected countries.

The Environmental Protection Agency is working with water and sewage treatment operators in the United States to prevent contamination of water with the cholera bacterium.

The Food and Drug Administration is testing imported and domestic shellfish for *V. cholerae* and monitoring the safety of U.S. shellfish beds through the shellfish sanitation program.

With cooperation at the state and local, national, and international levels, assistance will be provided to countries where cholera is present, and the risk to U.S. residents will remain small.

Where can a traveler get information about cholera?
The global picture of cholera changes periodically, so travelers should seek updated information on countries of interest. The Centers for Disease Control maintains a travelers' information telephone line on which callers can receive recent information on cholera and other diseases of concern to travelers. Data for this service are obtained from the World Health Organization. The number is 877-FYI-TRIP (394-8747) or check out http://www.cdc.gov/travel.

For more information call (602) 364-3289

CRYPTOSPORIDIOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Cryptosporidiosis is a parasitic infection caused by *Cryptosporidium parvum*.

Route of Exposure: Fecal-oral, which includes person to person, animal to person, waterborne, and foodborne transmission.

Infective Dose & Infectivity: Less than 10 organisms, and presumably one organism, can initiate an infection. All people are believed to be susceptible, though people with intact immune systems may be asymptomatic. Individuals with impaired immunity and children ages 1 to 5 years old are most likely to become infected.

Incubation Period: The incubation period is not precisely known; 1-12 days is the likely range, with an average of about 7 days.

Clinical Effects: Asymptomatic infections are common and constitute a source of infection for others. The major symptom in humans is diarrhea, which may be profuse and watery, preceded by anorexia and vomiting in children. The diarrhea is associated with cramping abdominal pain. General malaise, fever, anorexia, nausea and vomiting occur less often. Symptoms often wax and wane but remit in fewer than 30 days in most immunologically healthy people. In patients who are immunocompromised, cryptosporidiosis usually causes chronic diarrhea; however, rarely, lung and biliary tract disease also occurs.

Lethality: Cryptosporidiosis is rarely lethal in healthy people. In persons with severely weakened immune systems, chronic gastrointestinal illness or more disseminated disease can lead to complications and death.

Transmissibility: It is transmitted by ingestion of fecally contaminated food or water, including water swallowed while swimming; by exposure to fecally contaminated environmental surfaces; and by the fecal-oral route from person to person (e.g. while changing diapers caring for an infected person, or engaging in certain sexual behaviors).

Primary Contamination & Methods of Dissemination: In a terrorist attack, *C. parvum* would most likely be disseminated through the intentional contamination of food or water supplies.

Secondary Contamination & Persistence of organism: Secondary transmission can result from exposure to the stool of infected individuals, both patients with acute infection and asymptomatic carriers. Oocysts, the infectious stage, appear in the stool at the onset of symptoms and are infectious immediately upon excretion. Oocysts continue to be excreted in the stool for several weeks after symptoms resolve; outside the body, they may remain infective for 2-6 months in a moist environment. Oocysts are highly resistant to chemical disinfectants used to purify drinking water.

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Decontamination & Isolation:

Patients – No decontamination necessary. Patients should be treated with standard precautions, with contact precautions for diapered or incontinent patients. Hand washing is of particular importance. For hospitalized patients, enteric precautions in the handling of feces, vomitus, and contaminated clothing and bed linen; exclusion of symptomatic individuals from food handling and from direct care of hospitalized and institutionalized patients; release to return to work in sensitive occupations when asymptomatic.

Equipment, clothing & other objects – Infection control is difficult because of oocyte resistance to common disinfectants. Heating to 113º F (45º C) for 5-20 minutes, 140º F (60º C) for 2 minutes, or chemical disinfection with 10% formalin or 5% ammonia solution is effective.

Laboratory Testing: Diagnosis is made by identification of oocysts in stool samples. However, routine laboratory testing for ova and parasites will not detect *C. parvum*. A specific request for *C. parvum* testing must be made. Commercially available tests include ELISA assays for stool, and a fluorescein-tagged monoclonal antibody is useful for detecting oocysts in both stool and environmental samples.

Therapeutic Treatment: Supportive therapy with rehydration as needed is important. Nitaxozanide suspension (Alina™, Romark Laboratories) was recently approved by the FDA for treatment of cryptosporidiosis. If the patient is taking immunosuppressive drugs, these should be stopped or reduced if possible.

Prophylactic Treatment: No vaccine is available.

Differential Diagnosis: The differential diagnosis for *Cryptosporidium parvum* includes *Giardia*, *Isospora*, microsporidia, *Cyclospora*, *Clostridium dificile, Salmonella, Shigella, Campylobacter*, *Mycobacterium avium* complex, cytomegalovirus, rotavirus, norovirus, and adenovirus.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Center for Food Safety and Applied Nutrition. Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, U.S. Food and Drug Administration
http://vm.cfsan.fda.gov/~mow/intro.html

For more information call (602) 364-3289

Frequently Asked Questions About Cryptosporidiosis

What is Cryptosporidiosis?
Cryptosporidiosis (krip-toe-spo-rid-e-o-sis), is a diarrheal disease caused by a microscopic parasite, *Cryptosporidium parvum*. It can live in the intestine of humans and animals and is passed in the stool of an infected person or animal. Both the disease and the parasite are also known as "Crypto." The parasite is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it very resistant to chlorine disinfection. During the past two decades, Crypto has become recognized as one of the most common causes of waterborne disease (drinking and recreational) in humans in the United States. The parasite is found in every region of the United States and throughout the world.

What are the symptoms of Crypto?
Symptoms include diarrhea, loose or watery stool, stomach cramps, upset stomach, and a slight fever. Some people have no symptoms.

How long after infection do symptoms appear?
Symptoms generally begin 2-10 days after being infected.

How long will symptoms last?
In persons with average immune systems, symptoms usually last about 2 weeks; the symptoms may go in cycles in which you may seem to get better for a few days, then feel worse, before the illness ends.

How is Crypto spread?
Crypto lives in the intestine of infected humans or animals. Millions of Crypto can be released in a bowel movement from an infected human or animal. You can become infected after accidentally swallowing the parasite. Crypto may be found in soil, food, water, or surfaces that have been contaminated with the feces from infected humans or animals. Crypto is not spread by contact with blood. Crypto can be spread:

- By putting something in your mouth or accidentally swallowing something that has come in contact with the stool of a person or animal infected with Crypto.
- By swallowing recreational water contaminated with Crypto. Recreational water is water in swimming pools, hot tubs, jacuzzis, fountains, lakes, rivers, springs, ponds, or streams that can be contaminated with sewage or feces from humans or animals. Note: Crypto is chlorine resistant and can live for days in pools.
- By eating uncooked food contaminated with Crypto. Thoroughly wash with uncontaminated water all vegetables and fruits you plan to eat raw. See below for information on making water safe.
- By accidentally swallowing Crypto picked up from surfaces (such as toys, bathroom fixtures, changing tables, diaper pails) contaminated with stool from an infected person.

I have been diagnosed with Crypto. Should I worry about spreading infection to others?
Yes, Crypto can be very contagious. Follow these guidelines to avoid spreading Crypto to others.

- Wash your hands with soap and water after using the toilet, changing diapers, and before eating or preparing food.
- Avoid swimming in recreational water (pools, hot tubs, lakes or rivers, the ocean, etc.) if you have Crypto and for at least 2 weeks after diarrhea stops. You can pass Crypto in your stool and contaminate water for several weeks after your symptoms have ended. This has resulted in many outbreaks of Crypto among recreational water users. Note: you are not protected in a chlorinated pool because Crypto is chlorine resistant and can live for days in pools.
- Avoid fecal exposure during sex.

Am I at risk for severe disease?
Although Crypto can infect all people, some groups are more likely to develop more serious illness. Young children and pregnant women may be more susceptible to the dehydration resulting from diarrhea and should drink plenty of fluids while ill.

If you have a severely weakened immune system, you are at risk for more serious disease. Your symptoms may be more severe and could lead to serious or life-threatening illness. Examples of persons with weakened immune systems include those with HIV/AIDS; cancer and transplant patients who are taking certain immunosuppressive drugs; and those with inherited diseases that affect the immune system.

How is a Crypto infection diagnosed?
Your health care provider will ask you to submit stool samples to see if you are infected. Because testing for Crypto can be difficult, you may be asked to submit several stool specimens over several days. Because tests for Crypto are not routinely done in most laboratories, your health care provider should specifically request testing for the parasite.

What is the treatment for Crypto?
There is no consistently effective treatment for Crypto. Most people with a healthy immune system will recover on their own. Drinking plenty of fluids will help to prevent dehydration. Antidiarrheal medicine may help slow down diarrhea, but consult with your physician.

Rapid loss of fluids because of diarrhea can be very serious in babies. Parents should consult their health care provider about fluid replacement therapy options for babies. Children should not be given antidiarrheal medicine for severe diarrhea without first consulting their physician.

People who are on medicines that weaken their immune system are at higher risk for more severe and more prolonged illness; treatment for them could include cutting back on these medicines. In addition, patients with HIV infection can develop chronic diarrhea from Crypto; they can be helped by optimizing their antiretroviral medicines.

For more information call (602) 364-3289

EASTERN EQUINE ENCEPHALITIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Eastern Equine Encephalitis (EEE) is a mosquito-borne illness caused by an alphavirus of the *Togaviridae* family.

Routes of Exposure: Humans are primarily exposed to EEE through the bite of an infected mosquito.

Infective Dose & Infectivity: The infective dose is unknown. All people are considered susceptible though children are more likely to be severely affected.

Incubation Period: The incubation period is varies from 5-15 days.

Clinical Effects: The illness is characterized by rapid onset of high fever, vomiting, stiff neck, and drowsiness. Children frequently manifest generalized, facial, or periorbital edema. Motor involvement with paresis is common during the acute phase of the illness. Major disturbances of autonomic function, such as impaired respiratory regulation or excess salivation may dominate the clinical picture. Adults typically exhibit a febrile prodrome for up to 11 days before the onset of neurological disease; however, illness in children exhibits a more sudden onset. Up to 30% of survivors are left with neurological sequelae such as seizures, spastic paralysis, and cranial neuropathies. Cognitive impairment ranges from minimal brain dysfunction to severe dementia.

Lethality: Fatality rates for EEE are estimated to be from 50% to 75%. Mortality rates are highest among young children and the elderly.

Transmissibility: EEE infection occurs when a person is bitten by an infected mosquito. The virus is not directly transmitted from person-to-person.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, EEE would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Secondary transmission does not occur and EEE particles are not considered to be stable in the environment.

Decontamination & Isolation:

Patients – Standard precautions should be practiced and enteric precautions are appropriate until enterovirus meningoencephalitis is ruled out. Specific isolation procedures are not indicated.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: Clinical laboratory findings in patients with EEE often demonstrate an early leukopenia followed by a leukocytosis. Elevated opening pressure is commonly noted on lumbar puncture, and in children, especially, the CSF lymphocytic pleocytosis may reach a cell count of thousands of mononuclear cells per microliter. Specific diagnosis of EEE depends on virus isolation or serologic testing in which rising titers of HI, CF, or neutralizing antibodies are observed. IgM antibodies are usually detectable in acute-phase sera.

Therapeutic Treatment: There is no specific therapy. Patients who develop severe illness may require anticonvulsant and intensive supportive care to maintain fluid and electrolyte balance, adequate ventilation, and to avoid complicating secondary bacterial infections.

Prophylactic Treatment: An investigational formalin-inactivated vaccine is available, but it is poorly immunogenic.

Differential Diagnosis: The differential diagnosis includes a number of infections including cytomegalovirus, herpes simplex encephalitis, St. Louis encephalitis, West Nile encephalitis, Western equine encephalitis, Venezuelan encephalitis, malaria, *Naegleria* infection, leptospirosis, lyme disease, cat scratch disease, bacterial meningitis, tuberculosis, and fungal meningitis.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Smith JF, Davis K, Hart MK, et al. Viral Encephalitides. In: Zajtchuk R, Bellamy RF, eds. Medical Aspects of Chemical and Biological Warfare. Washington, DC: Office of the Surgeon General, U.S. Department of the Army; 1997:561-589.
Available at http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html

For more information call (602) 364-3289

Frequently Asked Questions About Eastern Equine Encephalitis

What is Eastern Equine Encephalitis?
Eastern Equine Encephalitis (EEE) is a mosquito-borne viral disease. As the name suggests, EEE occurs in the eastern half of the US. Because of the high case fatality rate, it is regarded as one of the more serious mosquito-borne diseases in the United States.

How do people become infected with EEE virus?
EEE virus is transmitted to humans through the bite of an infected mosquito. Several species of mosquitoes can become infected with EEE virus. The main EEE transmission cycle is between birds and mosquitoes. Horses can also become infected with, and die from, EEE virus infection.

What causes EEE?
EEE is caused by a virus that is a member of the family *Togaviridae*, genus *Alphavirus*. It is closely related to Western and Venezuelan equine encephalitis viruses.

What type of illness can occur?
Symptoms can range from mild flu-like illness to encephalitis (inflammation of the brain), coma, and death. Among those who are recognized to have infection the death rate is 50-75%, making it one of the most deadly mosquito-borne diseases in the US. It is estimated that 30% of people who survive EEE will have neurologic deficits.

How common is EEE?
Human cases occur relatively infrequently, largely because the cycle of infection between mosquito and birds takes place in swamp areas that humans tend to avoid. There are an average of 4 EEE cases in the US each year. The states with most cases are Florida, Georgia, Massachusetts, and New Jersey.

Who is at risk for developing EEE?
Persons over age 50 and younger than age 15 seem to be at greatest risk for developing severe disease. Residents of and visitors to areas with an established presence of the virus are at increased risk, as are people who engage in outdoor work and recreational activities.

How can people avoid infection with EEE virus?
Though a vaccine is available to protect horses, there is no licensed vaccine for human use.

To avoid infection people should avoid mosquito bites by employing personal and household protection measures, such as using insect repellent containing DEET, wearing protective clothing, taking precautions from dusk to dawn when mosquitoes are most likely to bite, and controlling standing water that can provide mosquito breeding sites.

For more information call (602) 364-3289

EPSILON TOXIN OF CLOSTRIDIUM PERFRINGENS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: *Clostridium perfringens* is a Gram positive, anaerobic, toxin producing spore-forming rod that is commonly found in normal intestinal bacteria. It is a cause of wound infections and food poisoning in humans. *C. perfringens* spores are ubiquitous in the environment. When the spores are injected or inoculated into a wound, bacteria grow and produce toxins.

Epsilon toxin is one of the toxins of type B and type D strains of *C. perfringens*. Epsilon toxin has been suggested as a potential biological weapon. Epsilon toxin damages cell walls and causes potassium and fluid leakage from cells.

Routes of Exposure: *C. perfringens* usually causes infections in humans by contamination of food, or by inoculation into an open wound. Exposure to epsilon toxin could be spread by aerosolization or by adding it to food or water.

Infective Dose & Infectivity: *C. perfringens* is normal flora in the human intestinal tract. However, when large numbers of *C. perfringens* grow in inadequately stored food, or when it contaminates an open wound, clinical symptoms develop.

Incubation Period: The incubation period for gastrointestinal symptoms after oral ingestion of *C. perfringens* is usually 10-12 hours, with a range of 6-24 hours. The incubation period of epsilon toxin after respiratory or oral exposure is not known.

Clinical Effects: *C. perfringens* gastroenteritis can include diarrhea, nausea, severe abdominal cramps and bloating for 1-2 days. Vomiting and fever are not usually seen. Wound contamination can result in clostridial myonecrosis (gas gangrene), or clostridial cellulitis.

Type B and D strains, the strains that produce epsilon toxin, do not usually infect humans. *C. perfringens* type B causes severe gastroenteritis in young calves, foals, lambs and piglets. Type D causes enterotoxemia in sheep and goats. Intravenous injection of epsilon toxin animals has resulted in pulmonary edema and neurologic symptoms.

The symptoms in humans from intentional exposure to epsilon toxin is not known. Extrapolating from animal experiments, pulmonary edema, neurologic symptoms, or gastroenteritis could be seen.

Lethality: Death from naturally occurring *C. perfringens* infection is very rare. It is not known how lethal epsilon toxin would be as a bioterrorism agent.

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Transmissibility: *C. perfringens* is ubiquitous in the environment. Transmission to humans is usually from environmental exposure rather than person-to-person spread. Toxins (such as epsilon toxin) are usually not transmitted from person to person.

Primary contaminations & Methods of Dissemination: In a bioterrorist attack, *C. perfringens* could be used to contaminate food or water supplies. Epsilon toxin could be spread in food, water, or by aerosolization.

Secondary Contamination & Persistence of organism: Since *C. perfringens* is so ubiquitous in the environment yet only causes disease in specific settings, secondary contamination would not be expected to be a problem. *C. perfringens* spores can survive in soil for long periods of time.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Specific isolation procedures are not indicated.

Equipment, clothing & other objects – Methods of decontamination for the epsilon toxin have not been published. Proteins are usually denatured by heat.

Laboratory testing: *C. perfringens* can be isolated from standard bacterial wound and stool cultures. Epsilon toxin can be detected by various assays including enzyme-linked immunosorbent assays (ELISA).

Therapeutic Treatment: Penicillin is the drug of choice for *C. perfringens* gastroenteritis and wound infection. Treatment for toxin exposure would likely be supportive.

Prophylactic Treatment: There is no vaccine available to protect against *C. perfringens* food poisoning or wound infection. There is no preventive measure against epsilon toxin used as a bioterrorism agent.

Differential Diagnosis: The differential diagnosis includes other recognized forms of food poisoning as well as aerosolized toxins and poisons.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Center for Food Safety and Applied Nutrition. Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, U.S. Food and Drug Administration
http://vm.cfsan.fda.gov/~mow/intro.html

Center for Food Security and Public Health. Epsilon toxin of *Clostridium perfringens*, Iowa State University College of Veterinary Medicine
http://www.scav.org/Epsilon-toxin%20Fact%20Sheet.htm

For more information call (602) 364-3289

Frequently Asked Questions About Clostridium Perfringens

What is *Clostridium perfringens*?
Clostridium perfringens are spore-forming bacteria that can be found in soil, feces, and the intestines of healthy people and animals. *Clostridium perfringens* are also often found in raw meat and poultry. The bacteria often cause food poisoning, but can also infect wounds.

How is *Clostridium perfringens* spread?
Eating foods that are served after improper storage can lead to infection. After cooking, small numbers of the organism may still be present. These can grow and produce toxin when the temperature is kept between 70° and 140° F. and air and moisture levels are right. For example, this can occur when foods that are cooked in large quantities are then held at room temperature for a prolonged period of time. *Clostridium perfringens* food poisoning is more common with meat products and gravies. The bacteria can be found in uncooked meat and poultry. It can also be transferred to food from stool bacteria if proper hand washing is not practiced.

What illness does *Clostridium perfringens* cause?
Clostridium perfringens most often causes food poisoning that results in sudden, watery diarrhea and abdominal pain. Usually there is no fever and no vomiting. On very rare occasions *Clostridium perfringens* can cause a more severe infection that causes the intestinal tissue to die and results in an infection of the blood. Wounds that become contaminated with *Clostridium perfringens* can result in tissue decay.

How is *Clostridium perfringens* infection diagnosed?
Clostridium perfringens is initially diagnosed based on symptoms. Laboratory confirmation is made by finding high concentrations of *Clostridium perfringens* in food or stools.

How is the illness treated?
Usually no treatment is needed, other than taking steps to prevent or treat dehydration.

What can be done to prevent *Clostridium perfringens* infection?
Be sure to wash your hands before preparing or serving foods and after handling raw meat or poultry. Meat and poultry based foods should be cooked thoroughly. *Clostridium perfringens* grows best between 45° and 140° F., so it is best to keep hot foods hot (above 140° F.) and cold foods cold (below 40° F.). If you have a large portion of food leftover, divide it into smaller portions not over three inches deep to refrigerate so it cools quickly. Foods should be refrigerated immediately and not left at room temperature to cool. Prepared food should not be left unrefrigerated for more than two hours. Reheat foods to at least that 165° F.

For more information call (602) 364-3289

Escherichia Coli O157:H7

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: *Escherichia coli* serotype O157:H7 is a gram-negative, rod-shaped bacterium that produces Shiga toxin(s). This rare variety of *E.coli* produces large quantities of potent toxins that cause severe damage to the lining of the intestines, leading to hemorrhagic colitis.

Routes of Exposure: Ingestion of contaminated food or water is the main route of exposure, but direct person-to-person contact can also spread infection.

Infective Dose & Infectivity: May be as few as 10 organisms. All people are believed to be susceptible to hemorrhagic colitis, but young children and the elderly appear to progress to more serious symptoms more frequently.

Incubation Period: The incubation can be from 2 to 8 days, but it usually ranges from 3 to 4 days.

Clinical Effects: The illness is characterized by severe cramping (abdominal pain) and diarrhea which is initially watery, but becomes grossly bloody. Occasionally vomiting occurs. Fever is either low-grade or absent. The illness is usually self-limited and lasts for an average of 8 days. Some individuals exhibit watery diarrhea only.

A severe clinical manifestation of *E. coli* O157:H7 infection is hemolytic uremic syndrome (HUS). Up to 15% of those with bloody diarrhea from *E. coli* 0157:H7 can develop HUS, which can lead to permanent kidney failure.

Lethality: The overall mortality rate for *E. coli* O157:H7 is <1%. For those who develop HUS, the death rate is between 3-5%.

Transmissibility: The major source of transmission is the consumption of raw or undercooked ground beef. Other sources of transmission include unpasteurized milk and juice, alfalfa sprouts, lettuce, dry-cured salami, and contact with infected animals. Waterborne transmission can occur by swimming in or drinking inadequately chlorinated water such as that found in contaminated lakes and swimming pools. The organism is easily transmitted from person-to-person when proper hand washing techniques are not used.

Primary Contamination & Methods of Dissemination: In a terrorist attack, *E. coli* would most likely occur due to intentional contamination of food or water supplies. In addition aerosolization could be a possibility.

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Secondary Contamination & Persistence of organism: Secondary transmission can result from exposure to the stool of patients with overt disease. Diarrheal fluids are highly infectious. The period of infectivity of stool is typically a week or less in adults but 3 weeks in one-third of children. Prolonged carriage of *E. coli* O157:H7 in the stool is uncommon.

Decontamination & Isolation:

Patients – No decontamination necessary. Patients can be treated with standard precautions, with contact precautions for diapered or incontinent patients. Hand washing is of particular importance.

Equipment & other objects – 0.5% hypochlorite solution (one part household bleach and nine parts water), EPA approved disinfectants, and/or soap and water can be used for environmental decontamination.

Laboratory Testing: Clinical laboratories can screen for *E. coli* O157:H7 in stool samples by using sorbitol-MacConkey agar.

Therapeutic Treatment: Most people recover without specific treatment in five to ten days. For uncomplicated cases, rehydration may be all that is required. Fluid and electrolyte replacement is important when diarrhea is watery or there are signs of dehydration. Antibiotics are often avoided in *E. coli* O157:H7 infections, since some evidence suggests that antibiotic treatment may precipitate complications such as HUS.

Prophylactic Treatment: No vaccine is available to prevent *E. coli* O157:H7 infections.

Differential Diagnosis: *Salmonella, Shigella, Campylobacter, Yersinia* enterocolitis, and bacterial food poisoning may show similar signs and symptoms.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration http://vm.cfsan.fda.gov/~mow/intro.html

For more information call (602) 364-3289

Frequently Asked Questions About Escherichia Coli O157:H7

What is *Escherichia coli* O157:H7?
Escherichia coli O157:H7 is one of hundreds of strains of the bacterium Escherichia coli. Although most strains are harmless and live in the intestines of healthy humans and animals, this strain produces a powerful toxin and can cause severe illness.

E. coli O157:H7 was first recognized as a cause of illness in 1982 during an outbreak of severe bloody diarrhea; the outbreak was traced to contaminated hamburgers. Since then, most infections have come from eating undercooked ground beef.

The combination of letters and numbers in the name of the bacterium refers to the specific markers found on its surface and distinguishes it from other types of *E. coli.*

How is *E. coli* O157:H7 spread?
The organism can be found on a small number of cattle farms and can live in the intestines of healthy cattle. Meat can become contaminated during slaughter, and organisms can be thoroughly mixed into beef when it is ground. Bacteria present on the cow's udders or on equipment may get into raw milk.

Eating meat, especially ground beef, that has not been cooked sufficiently to kill *E. coli* O157:H7 can cause infection. Contaminated meat looks and smells normal. Although the number of organisms required to cause disease is not known, it is suspected to be very small.

Among other occasional sources of infection are sprouts, lettuce, salami, unpasteurized milk and juice, and swimming in or drinking sewage-contaminated water.

Bacteria in diarrheal stools of infected persons can be passed from one person to another if hygiene or handwashing habits are inadequate. This is particularly likely among toddlers who are not toilet trained. Family members and playmates of these children are at high risk of becoming infected.

What illness does *E. coli* O157:H7 cause?
E. coli O157:H7 infection often causes severe bloody diarrhea and abdominal cramps; sometimes the infection causes nonbloody diarrhea or no symptoms. Usually little or no fever is present, and the illness resolves in 5 to 10 days.

In some persons, particularly children under 5 years of age and the elderly, the infection can also cause a complication called hemolytic uremic syndrome, in which the red blood cells are destroyed and the kidneys fail. About 2%-7% of infections lead to this complication. In the United States, hemolytic uremic syndrome is the principal cause of acute kidney failure in children, and most cases of hemolytic uremic syndrome are caused by *E. coli* O157:H7.

How is *E. coli* O157:H7 infection diagnosed?
Infection with *E. coli* O157:H7 is diagnosed by detecting the bacterium in the stool. All persons who suddenly have diarrhea with blood should get their stool tested for *E. coli* O157:H7.

How is the illness treated?
Most persons recover without antibiotics or other specific treatment in 5-10 days. There is no evidence that antibiotics improve the course of disease, and there is a concern that treatment with antibiotics may lead to kidney complications. Antidiarrheal agents, such as loperamide (Imodium), should also be avoided.

Hemolytic uremic syndrome is a potentially life-threatening. Blood transfusions and kidney dialysis are often required. With intensive care, the death rate for hemolytic uremic syndrome is 3%-5%.

What are the long-term consequences of infection?
Persons who only have diarrhea without HUS usually recover completely. Patients with HUS can develop to high blood pressure or chronic renal failure.

Lethality: The overall mortality rate for *E. coli* O157:H7 is <1%. For those who develop HUS, the death rate is between 3-5%.

What can be done to prevent *E. coli* O157:H7 infection?
There are several things you can do to reduce your risk of infection:

- Cook all ground beef and hamburger thoroughly.
- Keep raw meat separate from ready-to-eat foods.
- Wash hands, counter tops, and utensils with hot soapy water after they touch raw meat.
- Drink only pasteurized milk, juice, or cider.
- Wash fruits and vegetables thoroughly, especially those that will not be cooked.
- Drink municipal water that has been treated with chlorine or other effective disinfectants.
- Avoid swallowing lake or pool water while swimming.
- Make sure that persons with diarrhea, especially children, wash their hands carefully with soap after bowel movements to reduce the risk of spreading infection, and that persons wash hands after changing soiled diapers.
- Anyone with a diarrheal illness should avoid swimming in public pools or lakes, sharing baths with others, and preparing food for others.

For more information call (602) 364-3289

GLANDERS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Glanders is a zoonotic disease caused by the gram-negative bacillus *Burkholderia mallei*. Though primarily a disease of horses, mules, and donkeys, human illness can sometimes occur. Glanders is endemic in parts of Africa, Asia, Europe, and Central and South America.

Routes of Exposure: Humans are primarily exposed to glanders through direct contact with infected animals.

Infective Dose & Infectivity: The infective dose is assumed to be low and all people are considered susceptible.

Incubation Period: The incubation period ranges from 10 to 14 days.

Clinical Effects: Infection with glanders can range from asymptomatic acquisition to life-threatening pneumonia and bacteremia. Pulmonary infection can occur from inhalation or hematogenous spread. Chest radiographs can show lobar pneumonia, pulmonary abscesses, pleural effusions, and/or small military lesions. Bacteremia is accompanied by signs of sepsis and can include abscesses throughout the body and multiple cutaneous pustules. Mucous membrane infection manifests as nasal ulcers and nodules that secrete a bloody discharge. After contamination of broken skin, local ulcerative lesions develop with enlarged regional lymph nodes. Some people develop chronic infection with necrotizing granulomas in the liver and spleen and muscles of the arms and legs.

Lethality: When untreated, septicemia is usually fatal within 7-10 days.

Transmissibility: *B. mallei* is generally transmitted from animals to humans by invasion of nasal, oral, and conjunctival mucous membranes; by inhalation into the lungs; or through lacerated or abraded skin. Additionally, direct contact with an infected person's body fluids can lead to person-to-person transmission.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, glanders would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Secondary cases may occur through improper handling of infected secretions. However, humans have seldom acquired infection from infected animals despite frequent and close contact.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Contact precautions should be used with skin lesions and secretions. Patients with direct exposure to aerosols should be washed with soap and water.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: Gram stain of lesion exudates reveals small gram-negative bacteria. These stain irregularly with methylene blue. *B. mallei* grows slowly on ordinary nutrient agar. Agglutination tests are not positive for 7-10 days, and a high background titer in normal sera (1:320 to 1:640) makes interpretation difficult. Complement fixation tests are more specific and are considered positive if the titer is equal to, or exceeds 1:20. Cultures of autopsy nodules in septicemic cases will usually establish the presence of *B. mallei.*

Therapeutic Treatment: There is little experience in treating glanders in humans; therefore few antibiotics have been evaluated *in vivo*. Treatment varies with the type and severity of the clinical disease. Severe disease requires initial parenteral therapy. Prolonged oral antibiotic therapy for many months is required to prevent relapse. Parenteral regimens have included combinations such as cetazidime and trimethoprim-sulfamethoxazole, or imipenem and doxycycline. Various isolates have markedly different antibiotic sensitivities, so each isolate should be tested for its own individual resistance pattern.

Prophylactic Treatment: There is no vaccine available for human use. Post-exposure chemoprophylaxis has not been established, although it has been suggested that trimethoprim-sulfamethoxazole may be tried.

Differential Diagnosis: The differential diagnosis depends on the clinical manifestations. In addition to common causes of pneumonia, potential agents of bioterroism and zoonotic diseases would include melioidosis, plague, and tularemia. The papular or pustular skin lesions of glanders can resemble the rash of smallpox.

References:

Marty AM. Melioidosis and Glanders In: Physician's Guide to Terrorist Attack. Roy MJ, ed. Physician's Guide to Terrorist Attack. Totowa, NJ: Humana Press, Inc.; 2004:143-159

Kortepeter M, Christopher G, Cieslak T, et al. Medical Management of Biological Casualties Handbook, U.S. Army Medical Research Institute of Infectious Diseases, U.S. Department of Defense; 2001: 37-42
Available at http://www.usamriid.army.mil/education/bluebook.htm

For more information call (602) 364-3289

Frequently Asked Questions About Glanders

What is glanders?
Glanders is an infectious disease that is caused by the bacterium *Burkholderia mallei.* Glanders is primarily a disease affecting horses, but it also affects donkeys and mules and can be naturally contracted by goats, dogs, and cats. Human infection, although not seen in the United States since 1945, has occurred rarely and sporadically among laboratory workers and those in direct and prolonged contact with infected, domestic animals.

Why has glanders become a current issue?
Burkholderia mallei is an organism that is associated with infections in laboratory workers because so very few organisms are required to cause disease. The organism has been considered as a potential agent for biological warfare and of biological terrorism.

How common is glanders?
The United States has not seen any naturally occurring cases since the 1940s. However, it is still commonly seen among domestic animals in Africa, Asia, the Middle East, and Central and South America.

How is glanders transmitted and who can get it?
Glanders is transmitted to humans by direct contact with infected animals. The bacteria enter the body through the skin and through mucosal surfaces of the eyes and nose. The sporadic cases have been documented in veterinarians, horse caretakers, and laboratorians.

What are the symptoms of glanders?
The symptoms of glanders depend upon the route of infection with the organism. The types of infection include localized, pus-forming cutaneous infections, pulmonary infections, bloodstream infections, and chronic suppurative infections of the skin. Generalized symptoms of glanders include fever, muscle aches, chest pain, muscle tightness, and headache. Additional symptoms have included excessive tearing of the eyes, light sensitivity, and diarrhea.

- *Localized infections* – If there is a cut or scratch in the skin, a localized infection with ulceration will develop within 1 to 5 days at the site where the bacteria entered the body. Swollen lymph nodes may also be apparent. Infections involving the mucous membranes in the eyes, nose, and respiratory tract will cause increased mucus production from the affected sites.
- *Pulmonary infections* - In pulmonary infections, pneumonia, pulmonary abscesses, and pleural effusion can occur. Chest X-rays will show localized infection in the lobes of the lungs.
- *Bloodstream infections* - Glanders bloodstream infections are usually fatal within 7 to 10 days.
- *Chronic infections* - The chronic form of glanders involves multiple abscesses within the muscles of the arms and legs or in the spleen or liver.

Where is glanders usually found?
Geographically, the disease is endemic in Africa, Asia, the Middle East, and Central and South America.

How is glanders diagnosed?
The disease is diagnosed in the laboratory by isolating *Burkholderia mallei* from blood, sputum, urine, or skin lesions. Serologic assays are not available.

Can glanders spread from person to person?
In addition to animal exposure, cases of human-to-human transmission have been reported. These cases included two suggested cases of sexual transmission and several cases in family members who cared for the patients.

Is there a way to prevent infection?
There is no vaccine available for glanders. In countries where glanders is endemic in animals, prevention of the disease in humans involves identification and elimination of the infection in the animal population. Within the health care setting, transmission can be prevented by using common blood and body fluid precautions.

Is there a treatment for glanders?
Because human cases of glanders are rare, there is limited information about antibiotic treatment of the organism in humans. Sulfadiazine has been found to be effective in experimental animals and in humans.

For more information call (602) 364-3289

MELIOIDOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Melioidosis is caused by the gram-negative bacillus *Burkholderia pseudomallei*. The bacteria are widely distributed in the soil and water in Southeast Asia and northern Australia. Both humans and other susceptible animals may contract the disease.

Routes of Exposure: Humans are primarily exposed to melioidosis through direct contact with a contaminated source, such as soil or stagnant surface water.

Infective Dose & Infectivity: The infective dose is assumed to be low and all people are considered susceptible. In asymptomatic individuals severe injuries, burns, or debilitating disease may precipitate clinical onset of melioidosis.

Incubation Period: The incubation period can be as short as 2 days. However, years may elapse between the presumed exposure and the appearance of clinical disease.

Clinical Effects: The clinical manifestations of melioidosis include local skin infection, lung involvement, bacteremia, chronic suppurative infection in many organ systems, and neurologic infection. The most likely presentation due to bioterrorism would be pulmonary infection due to aerosolized bacteria. Inhalational melioidosis is an acute pyogenic process that can resemble plague pneumonia, with fever, severe systemic symptoms, and consolidative pneumonia. Secondary bacteremia can result in a papular or pustular rash that resembles smallpox lesions. Chest X-rays can show a variety of infiltrates, often upper lobe infiltrates that cavitate.

Lethality: Mortality from severe pneumonia and septicemia may be as high as 50%. In localized skin disease the mortality is low.

Transmissibility: Infection with *B. pseudomallei* generally occurs when contaminated soil or water comes in contact with lacerated or abraded skin. Melioidosis can also be acquired through aspiration or ingestion of water or inhalation of dust contaminated with the organism. Person-to-person transmission through direct contact may also be possible.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, melioidosis would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Only three cases of secondary infection have been reported. In one case it is thought that a caretaker acquired the disease from a patient with chronic melioidosis. The other two cases are believed to have occurred as a result of sexual contact following a chronic prostate infection.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Contact precautions should be used with sputum, sinus drainage, skin lesions and secretions.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: Gram stain of lesion exudates reveals small gram-negative bacteria. These stain irregularly with methylene blue. A four-fold increase in titer supports the diagnosis of melioidosis. A single titer above 1:160 with a compatible clinical picture suggests active infection.

Therapeutic Treatment: The current treatment of choice for severe melioidosis is cetazidime and trimethoprim-sulfamethoxazole, although other broad spectrum antibiotic regimens are being evaluated. After several weeks of IV therapy, prolonged oral antibiotic treatment of 3-5 months or more is required to decrease the chance of relapse.

Prophylactic Treatment: There is no vaccine available for human use. There is no pre-exposure or post exposure medication for preventing melioidosis, although trimethoprim-sulfamethoxazole has been suggested.

Differential Diagnosis: The differential diagnosis for severe pneumonia should include unusual organisms such as plague, tularemia, and inhalational anthrax. Considerations for acute febile pustular skin lesions include staphylococci, gonorrhea, secondary syphilis, ecthyma gangrenosum, and smallpox.

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Available at http://www.usamriid.army.mil/education/bluebook.htm

For more information call (602) 364-3289

Frequently Asked Questions About Melioidosis

What is melioidosis?
Melioidosis is an infectious disease caused by the bacterium *Burkholderia pseudomallei.* Melioidosis is predominately a disease of tropical climates, especially in Southeast Asia. The bacteria causing melioidosis are found in contaminated water and soil. They are spread to humans and animals through direct contact with the contaminated source. Glanders is spread to humans from infected domestic animals.

Why has melioidosis become a current issue?
Burkholderia pseudomallei is an organism that has been considered as a potential agent for biological warfare and biological terrorism.

How common is melioidosis and where is it found?
Melioidosis is endemic in Southeast Asia, with the greatest concentration of cases reported in Vietnam, Cambodia, Laos, Thailand, Malaysia, Myanmar (Burma), and northern Australia. Additionally, it is seen in the South Pacific, Africa, India, and the Middle East. In many of these countries, *Burkholderia pseudomallei* is so prevalent that it is a common contaminate found on laboratory cultures. Moreover, it has been a common pathogen isolated from troops of all nationalities that have served in areas with endemic disease. A few isolated cases of melioidosis have occurred in the Western Hemisphere in Mexico, Panama, Ecuador, Haiti, Brazil, Peru, Guyana, and in the states of Hawaii and Georgia. In the United States, confirmed cases range from none to five each year and occur among travelers and immigrants.

How is melioidosis transmitted and who can get it?
Besides humans, many animal species are susceptible to melioidosis. These include sheep, goats, horses, swine, cattle, dogs, and cats. Transmission occurs by direct contact with contaminated soil and surface waters. In Southeast Asia, the organism has been repeatedly isolated from agriculture fields, with infection occurring primarily during the rainy season. Humans and animals are believed to acquire the infection by inhalation of dust, ingestion of contaminated water, and contact with contaminated soil especially through skin abrasions, and for military troops, by contamination of war wounds. Person-to-person transmission can occur.

What are the symptoms of melioidosis?
Illness from melioidosis can be categorized as acute or localized infection, acute pulmonary infection, acute bloodstream infection, and chronic suppurative infection. Inapparent infections are also possible. The incubation period (time between exposure and appearance of clinical symptoms) is not clearly defined, but may range from 2 days to many years.

- *Acute, localized infection* - This form of infection is generally localized as a nodule and results from inoculation through a break in the skin. The acute form of melioidosis can produce fever and general muscle aches, and may progress rapidly to infect the bloodstream.

- *Pulmonary infection* - This form of the disease can produce a clinical picture of mild bronchitis to severe pneumonia. The onset of pulmonary melioidosis is typically accompanied by a high fever, headache, anorexia, and general muscle soreness. Chest pain is common, but a nonproductive or productive cough with normal sputum is the hallmark of this form of melioidosis.
- *Acute bloodstream infection* - Patients with underlying illness such as HIV, renal failure, and diabetes are at higher risk for this form of disease, which usually results in septic shock. The symptoms of the bloodstream infection vary depending on the site of original infection, but they generally include respiratory distress, severe headache, fever, diarrhea, development of pus-filled lesions on the skin, muscle tenderness, and disorientation, and abscesses found throughout the body.
- *Chronic suppurative infection* - Chronic melioidosis is an infection that involves the organs of the body. These typically include the joints, viscera, lymph nodes, skin, brain, liver, lung, bones, and spleen.

How is melioidosis diagnosed?
Melioidosis is diagnosed by isolating *Burkholderia pseudomallei* from the blood, urine, sputum, or skin lesions. Detecting and measuring antibodies to the bacteria in the blood is another means of diagnosis.

Can melioidosis be spread from person to person?
Melioidosis can spread from person to person by contact with the blood and body fluids of an infected person. Two documented cases of male-to-female sexual transmission involved males with chronic prostate infection due to melioidosis.

Is there a way to prevent infection?
There is no vaccine for melioidosis. Prevention of the infection in endemic-disease areas can be difficult since contact with contaminated soil is so common. Persons with diabetes and skin lesions should avoid contact with soil and standing water in these areas. Wearing boots during agricultural work can prevent infection through the feet and lower legs. In health care settings, using common blood and body fluid precautions can prevent transmission.

Is there a treatment for melioidosis?
Most cases of melioidosis can be treated with appropriate antibiotics. Treatment should be initiated early in the course of the disease. Although bloodstream infection with melioidosis can be fatal, the other types of the disease are nonfatal.

For more information call (602) 364-3289

PSITTACOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Psittacosis is an avian illness that can also cause disease in humans. It is caused by the rickettsia-like bacteria *Chlamydophila psittaci* (formerly *Chlamydia psittaci*).

Routes of Exposure: Humans are primarily exposed to psittacosis through inhalation of dried secretions from infected birds.

Infective Dose & Infectivity: The infective dose is unknown and all people are considered susceptible, though older adults may be more severely affected.

Incubation Period: The incubation period ranges from 1 to 4 weeks.

Clinical Effects: An acute, generalized chlamydial disease with variable clinical presentations; fever, headache, rash, myalgia, chills, and upper or lower respiratory tract disease are common. Respiratory symptoms are often disproportionately mild when compared with the extensive pneumonia demonstrable by x-ray. Cough is initially absent or nonproductive; when present, sputum is mucopurulent and scant. Pleuritic chest pain and splenomegaly occur infrequently; the pulse may be slow in relation to temperature. Encephalitis, myocarditis, and thrombophlebitis are occasional complications; relapses may occur. Although usually mild or moderate in character, human disease can be severe.

Lethality: The mortality rate for untreated psittacosis ranges from 15-20%. However, with appropriate treatment, the mortality rate drops to less than 1%.

Transmissibility: Infection with *C. psittaci* generally occurs when a person inhales the organism, which has been aerosolized from dried feces or respiratory secretions of infected birds. Psittacosis can also be acquired through mouth-to-beak contact and the handling of infected birds' plumage and tissues. Rare person-to-person transmission has been reported to occur during the acute illness with paroxysmal coughing. However, *Chlamydophila pneumoniae*, rather than *C. psittaci*, organisms may have caused these cases.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, psittacosis would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Secondary cases cannot be proven and are extremely rare. Diseased as well as seemingly healthy birds may shed the agent intermittently, and sometimes continuously, for weeks or months.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Specific isolation procedures are not indicated.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: Most diagnoses are established by using microimmunofluorescence (MIF) to test for antibodies to *C. psittaci* in paired sera. Since there is some antibody cross-reactivity between chlamydial species, polymerase chain reaction (PCR) assays can be used to further distinguish *C. psittaci* infection from other chlamydial species.

Therapeutic Treatment: Tetracyclines are the drugs of choice. Most patients respond to oral therapy, but for severely ill patients doxycycline can be administered intravenously. Though remission of symptoms usually is evident within 48-72 hours, relapse can occur. Therefore, treatment must continue for at least 10-14 days after fever abates. Erythromycin is an alternative when a tetracycline is contraindicated.

Prophylactic Treatment: There is no vaccine available for human use. Post-exposure chemoprophylaxis is not indicated.

Differential Diagnosis: The differential diagnoses should include illnesses with fever and respiratory symptoms including illnesses such as Q fever, mycoplasma, legionnaires' disease, and influenza.

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Available at http://www.avma.org/pubhlth/psittacosis.asp

For more information call (602) 364-3289

Frequently Asked Questions About Psittacosis

What is psittacosis?
Psittacosis is an illness caused by infection with bacteria known as *Chlamydia psittaci*. Also known as parrot fever or ornithosis, it is usually transmitted to humans from birds including parakeets, parrots, pigeons, turkeys, and ducks.

Who gets psittacosis?
Since birds spread the disease, human illness is apt to occur in people who are most likely to be exposed to an infected bird such as pet store workers, pigeon breeders, poultry workers, and people who have recently purchased an infected bird.

How is psittacosis spread?
Psittacosis is usually spread by inhaling bacteria that is in the dust from dried bird droppings of infected birds or by handling infected birds in slaughterhouses. Other potential sources of exposure include bird bites, mouth-to-beak contact and handling feathers and tissue from infected birds. Some birds infected with psittacosis may appear healthy, but can still spread the infection to other birds or humans. Human-to-human spread is very rare.

What are the symptoms of psittacosis?
The symptoms of psittacosis include fever headache, chills, muscle aches, and sometimes pneumonia with a relatively nonproductive cough.

How soon after infection do symptoms occur?
The period between exposure and the beginning of symptoms can range from 5 to 19 days but is usually 10 days.

Does past infection with psittacosis make a person immune?
Infection does not provide permanent immunity form this disease.

How is psittacosis diagnosed?
Psittacosis is usually diagnosed by clinical symptoms and a history of exposure to birds. A blood test to check for antibodies to psittacosis can confirm the diagnosis.

How is psittacosis treated?
Several commonly available antibiotics are used to treat psittacosis in humans. With appropriate treatment, the vast majority of people fully recover.

How can psittacosis be prevented?
Exposed birds should be treated with feed that contains tetracycline to reduce the risk of infection. If birds are kept as pets, clean the cage often so that feces does not accumulate, dry up, and become airborne. Birds should be purchased from a reliable source that adheres to federal recommendations for psittacosis control.

For more information call (602) 364-3289

Arizona Department of Health Services

Q FEVER

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Q fever is a zoonotic disease caused by a rickettsia *Coxiella burnetii*.

Route of Exposure: Humans usually acquire Q fever through the inhalation of airborne particles. Sheep, cattle, and goats can serve as reservoirs for the agent. Consumption of contaminated food or water can also result in infection.

Infective Dose & Infectivity: 1-10 Organisms

Incubation Period: The incubation period ranges from 10 to 40 days.

Clinical Effects: Q fever generally occurs as a self-limiting illness lasting 2 days to 2 weeks. The disease generally presents as an acute non-differentiated febrile illness with headaches, fatigue and myalgias as prominent symptoms. Pneumonia with an abnormal chest X-ray occurs in about 50% of all patients. Non-productive cough and pleuritic chest pain can also occur. Uncommon complications of Q fever infection include: chronic hepatitis, endocarditis, aseptic meningitis, encephalitis, and osteomyelitis.

Lethality: While highly incapacitating, the death rate due to Q fever is very low (<1-3%).

Transmissibility (person to person): Transmission from person-to-person is extremely rare.

Primary Contamination & Methods of Dissemination: The most likely route of intentional dissemination would be through aerosolization. Alternatively, the organism could be disseminated through sabotage of the food supply.

Secondary Contamination & Persistence of Organism: Persons who are exposed to Q fever through the aerosol route do not present a risk for secondary contamination or re-aerosolization of the organism. The organism is highly resistant to many disinfectants.

Decontamination & Isolation:

Patients – Patients can be treated using standard precautions. Gross decontamination is not necessary.

Equipment & other objects – Contaminated surfaces and clothing can be decontaminated with 0. 5% hypochlorite solution (one part household bleach and nine parts water = 0.5% solution) or a 1:100 solution of Lysol.

Outbreak control: Since secondary cases are unlikely, outbreak control measures are not recommended.

Laboratory Testing: Isolation of *C. burnetii* is usually not done due to the risk to laboratory workers. Diagnosis can be made acute and convalescent antibody titers (indirect immunofluorescence antibody or complement fixation antibody), polymerase chain reaction on tissue, or positive immunostaining on a heart valve.

Therapeutic Treatment: Tetracycline or doxycycline is the recommended treatment. A combination of erythromycin plus rifampin is also effective.

Prophylactic Treatment: Treatment with a tetracycline during the incubation period may delay, but will not prevent the onset of symptoms. A vaccine has been developed, but is not licensed for use in the United States.

Differential Diagnosis: Q fever must be differentiated from pneumonias caused by mycoplasma, *Legionella pneumophila*, *Chlamydophila psittaci*, or *Chlamydophila pneumoniae*.

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For more information call (602) 364-3289

Frequently Asked Questions About Q Fever

What is Q fever?
Q fever is a disease caused by the bacteria *Coxiella burnetii*. *C. burnetii* can be found in animals (especially cattle, sheep, and goats) throughout the world.

How do people become infected with the Q fever bacteria?
People usually become infected with Q fever by breathing in airborne particles that contain *C. burnetii* bacteria. This most often occurs in barnyard settings through the inhalation of dust contaminated with dried placental material, birth fluids, and excreta of infected herd animals. In the United States, Q fever outbreaks have resulted mainly from occupational exposure involving veterinarians, meat processing plant workers, sheep and dairy workers, livestock farmers, and researchers at facilities housing sheep. Other modes of transmission, such as tick bites and human-to-human transmission, are very rare.

Why are we concerned about Q fever as a bioweapon?
Coxiella burnetii is a highly infectious agent that is resistant to heat and drying. Humans are often very susceptible to the disease, and very few organisms may be required to cause infection. This agent could be developed for use in biological warfare and is considered a potential terrorist threat.

What are the signs and symptoms of Q fever?
Only about half of all people with Q fever show any symptoms. Acute cases of Q fever begin with a sudden onset of one or more of the following: high fevers (up to 104°-105° F), severe headache, general discomfort and fatigue, muscle pain, confusion, sore throat, chills, sweats, dry cough, nausea, vomiting, diarrhea, stomach pain, and chest pain. Fever usually lasts for 1 to 2 weeks. Weight loss can also occur and may continue for some time. The disease can cause abnormal results on liver function tests and can lead to hepatitis. Additionally, 30% to 50% of people with symptoms may develop pneumonia.

In general, most people will recover to good health within several months without any treatment. Only 1%-2% of people with acute Q fever die from the disease.

Though uncommon, people who have had acute Q fever may develop the chronic form of the disease within 1 to 20 years after first being infected.

How quickly would someone become sick if they were exposed to the Q fever bacteria?
Most people become sick within 2-3 weeks after being exposed to Q fever bacteria, but this depends on how many bacteria have entered the person. The more germs that infect a person, the less time it takes to get sick.

How is Q fever diagnosed?
If the health care provider suspects Q fever, blood samples will be collected and sent to the laboratory to look for antibodies to *Coxiella burnetii* . Because the signs and symptoms of Q fever are similar to other diseases, it is necessary to perform laboratory tests to make an accurate diagnosis.

Can Q fever be treated with antibiotics?
Yes. Q fever can be treated with antibiotics. Treatment is most effective when started early in the course of illness. Doxycycline is the treatment of choice for acute Q fever.

Is a vaccine available to prevent Q fever?
A human vaccine for Q fever has been developed and has successfully protected workers in occupational settings. However, this vaccine is not commercially available in the United States. A vaccine for use in animals has also been developed, but it is not yet available in the United States.

For more information call (602) 364-3289

Arizona Department of Health Services

RICIN

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Potent protein toxin derived from *Ricinis communis*, the castor bean plant

Route of Exposure: Inhalation (the most likely form for bioterrorism) or ingestion

Toxic Dose: The LD_{50} of inhaled ricin is 3-5 μg/Kg.

Incubation Period: The incubation period for symptoms due to oral ingestion is usually less than 6 hours, although symptoms have been reported as quickly as 15 minutes.

Clinical Effects: If the toxin is ingested, there is a rapid onset of nausea, vomiting, abdominal cramping, fever, and severe diarrhea with vascular collapse. Death generally occurs as soon as the third day. The consequences of human inhalation of ricin toxin is not known. However, in animal models, respiratory distress occurs with airway inflammation, pneumonia, and pulmonary edema. Death usually occurs from 36-72 hours after exposure.

Lethality: The mortality rate due to ricin ingestion is 2-6%. The human mortality rate from inhalational ricin is unknown. Careful attention to fluid and electrolyte balance should lessen mortality.

Transmissibility: Ricin intoxication cannot be transmitted from person to person.

Primary Contamination & Methods of Dissemination: Methods of dissemination due to bioterroism could be via aerosolization or sabotage of the food or water supply.

Secondary Contamination & Persistence of Organism: Ricin is not volatile. Risk to health care workers from secondary aerosols would be unlikely.

Decontamination & Isolation:

Patients: Only standard isolation precautions are needed. Skin decontamination can be done with soap and water or a 0.5% hypochlorite solution (one part household bleach & nine parts water = 0.5% hypochlorite solution).

Equipment, clothing & other objects: Surface cleansing can be done with a 0.5% hypochlorite solution.

Laboratory Testing: Ricin can be detected in environmental samples by a fluorescence immunoassay or PCR available at the State Health Lab. Ricin testing in body fluids is experimental, but ricin may be able to be detected in body fluids such as emesis, stools, serum, or on nasopharyngeal swabs.

Therapeutic Treatment: Treatment is supportive. Treatment for inhalational ricin should include management for pulmonary edema. If a patient has ingested ricin, gastric lavage with activated charcoal followed by catharsis with magnesium citrate is recommended. It is also important to replace volume due to GI fluid losses, and to be meticulous in fluid and electrolyte management. Ricin is not dialyzable.

Prophylactic Treatment: There is no known prophylaxis for humans. A vaccine is under development.

Differential Diagnosis: Enteric pathogens can cause fever and gastrointestinal involvement, but vascular collapse would be unusual.

Respiratory symptoms can occur with respiratory infections, Q fever pneumonia, plague pneumonia, tularemia pneumonia, toxin inhalation (such as staphylococcal enterotoxin B or trichothecene mycotoxins), and chemical warfare agents such as phosgene.

Aerosolized ricin is distinguished from routine infections by progressive respiratory symptoms in spite of antibiotics, no widened mediastinum (as in anthrax), progressive worsening (respiratory effects of staphylococcal enterotoxin B tend to stabilize rapidly), fewer systemic effects than trichothecene mycotoxins, and a slower progression in symptoms than phosgene exposure.

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For more information call (602) 364-3289

Frequently Asked Questions About Ricin

What is ricin?
Ricin is a poison that can be made from the waste left over from processing castor beans. It can be made into a powder, a mist, a pellet, or it can be dissolved in water or weak acid. It is a stable substance, which means it is not affected much by extreme conditions such as very hot or very cold temperatures.

Where is ricin found and how is it used?
Ricin is part of the waste "mash" produced when castor oil is made. Since castor beans are processed throughout the world, ricin can be found globally. Though considered a poison, ricin can be used for such medical procedures as bone marrow transplants and cancer treatments.

How can people be exposed to ricin?
Accidental exposure to ricin is extremely unlikely, therefore it would take a deliberate act to make ricin and use it to poison people. There three routes of exposure for ricin: inhalation, ingestion, or injection. People can be poisoned by breathing in ricin mist or powder, swallowing food or water contaminated with ricin, or having a ricin pellet or ricin dissolved in a liquid injected into their bodies. Ricin poisoning is not contagious. It cannot be spread from person to person through casual contact.

How does ricin affect the body?
Ricin affects the body by getting inside the cells and preventing them from making the proteins they need. Without the proteins, cells die. Eventually this is harmful to the whole body, and death may occur. Effects of ricin poisoning depend on whether ricin was inhaled, ingested, or injected.

What are the signs and symptoms of ricin exposure?
The symptoms of ricin poisoning depend on the route of exposure and the dose received. Many organs may be affected in severe cases.

Death from ricin poisoning could take place within 36 to 72 hours of exposure, depending on the route of exposure (inhalation, ingestion, or injection) and the dose received. If death has not occurred in 3 to 5 days, the victim usually recovers.

Inhalation: Initial symptoms of ricin poisoning by inhalation may occur within 8 hours of exposure. The likely symptoms would be respiratory distress (difficulty breathing), fever, cough, nausea, and tightness in the chest. Heavy sweating may follow as well as fluid building up in the lungs (pulmonary edema). This would make breathing even more difficult, and the skin might turn blue. Excess fluid in the lungs would be diagnosed by x-ray or by listening to the chest with a stethoscope. Finally, low blood pressure and respiratory failure may occur, leading to death.

Ingestion: Following ingestion of ricin, initial symptoms typically occur in less than 6 hours. If someone swallows a significant amount of ricin, he or she would develop vomiting and diarrhea that may become bloody. Severe dehydration may be the result, followed by low blood pressure. Other signs or symptoms may include hallucinations, seizures, and blood in the urine. Within several days, the person's liver, spleen, and kidneys might stop working, and the person could die.

Skin and eye exposure: Ricin in the powder or mist form could cause redness and pain of the skin and the eyes.

Note: Showing these signs and symptoms does not necessarily mean that a person has been exposed to ricin.

How is ricin poisoning treated?
There is no antidote for ricin therefore, it is especially important to prevent poisoning by avoiding exposure to ricin. If exposure cannot be avoided, the most important action is to get the ricin off or out of the body as quickly as possible. This may involve flushing the stomach with activated charcoal if the ricin was very recently ingested or washing out the eyes with water if the eyes are irritated.

Ricin poisoning is treated by giving victims supportive medical. The specific treatment depends on how victims were poisoned (inhalation, ingestion, or skin or eye exposure). Care could include such measures as helping victims breathe, giving them intravenous fluids, or giving them medications to treat conditions such as seizures and low blood pressure.

Is there a way to test for ricin?
There is no widely available, reliable test to confirm that a person has been exposed to ricin.

What should people do if they are exposed to ricin?
It is important to get fresh air by leaving the area where the ricin was released. If the ricin release was outside, this means moving away from the area where the ricin was released. If the ricin release was indoors, people should get out of the building. Moving to an area with fresh air is a good way to reduce the possibility of death from exposure to ricin.

If you think you may have been exposed to ricin, you should remove your clothing, rapidly wash your entire body with soap and water, and get medical care as quickly as possible. If someone has ingested ricin, do not induce vomiting or give fluids to drink. Seek medical attention right away.

For more information call (602) 364-3289

SALMONELLOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Several distinct bacteria within the genus *Salmonella* cause diarrheal illness, sometimes with septicemia. *Salmonella enteritidis* has more than 2000 different serotypes and is responsible for many of the foodborne gastrointestinal illnesses commonly found in man and animals. *Salmonella typhi* causes typhoid fever.

Routes of Exposure: Oral - consumption of contaminated food or water

Infective Dose & Infectivity: The infective dose is unknown but the LD_{50} has been reported to be 10 million organisms. The infectivity of *Salmonella* is moderate. A carrier state occurs and is more common among female and elderly patients. It may persist for months to years.

Incubation Period: The incubation can be from 6 to 72 hours, but it usually ranges from 12 to 36 hours.

Clinical Effects: *Salmonella* gastroenteritis typically manifests as nausea, vomiting, abdominal cramps, and diarrhea, which is sometimes bloody. Weakness, chills, and fever may also be present, although there is a wide variability in the severity of symptoms seen. The typhoidal syndrome includes a high spiking fever, abdominal cramps, diarrhea, abdominal distention, septicemia, enlarged spleen, and occasional meningeal signs.

Lethality: The mortality rate of salmonellosis is low to moderate (<1% for most serotypes).

Transmissibility: The fecal-oral route is the most common mode of person-to-person transmission. There is no known transmission by the inhalational or dermal routes.

Primary Contamination & Methods of Dissemination:

In a terrorist attack, salmonellosis would most likely occur due to intentional contamination of food or water supplies.

Secondary Contamination & Persistence of Organism: Secondary transmission can result from exposure to the stool of patients with overt disease and from chronic carriers. Diarrheal fluids are highly infective. Greater than 50% of patients stop excreting nontyphoidal *Salmonella* within five weeks after infection and 90% are culture negative within nine weeks.

Decontamination & Isolation:

Patients – No decontamination necessary. Patients can be treated with standard precautions, with contact precautions for diapered or incontinent patients. Hand washing is of particular importance

Equipment & other objects – 0.5% hypochlorite solution (one part household bleach and nine parts water), other disinfectants, and/or soap and water are effective for environmental decontamination.

Laboratory testing: The stool, blood, and ingested food can be cultured. The best clinical predictor of a positive stool culture for *Salmonella* is the combination of diarrhea persisting for more than 24 hours, fever, and either blood in the stool or abdominal pain with nausea or vomiting.

Therapeutic Treatment: For uncomplicated cases, rehydration may be all that is required. Oral or intravenous routes for rehydration can be used depending on the individual patient's circumstances. Antibiotics are not ordinarily used since they prolong fecal shedding, but they should be considered in infants, the elderly, and those with underlying illnesses. All bacteremic patients should receive antibiotics.

Strains from developing countries are often resistant to many antibiotics, but are usually susceptible to fluoroquinolones (such as ciprofloxacin or levofloxacin) or third generation antibiotics (such as cefotaxime or ceftriaxone). More narrow antibiotics (such as ampicillin, amoxicillin, and trimethprim-sulfamethoxazole) are alternatives choices when the strain is known to be susceptible.

Prophylactic Treatment: A typhoid vaccine exists. It is recommended for travelers to areas where there is a risk of exposure to *Salmonella typhi*, people living in typhoid-endemic areas outside the United states, persons who have continued household contact with a documented typhoid fever carrier, and laboratory workers with frequent contact with *S. typhi*. No prophylaxis is recommended for nontyphoidal *Salmonella* infections.

Differential Diagnosis: *Shigella, Campylobacter*, *Yersinia enterocolitica*, and bacterial food poisoning may show similar signs and symptoms.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

American Academy of Pediatrics. *Salmonella.* In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26 ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003: 541-547.

For more information call (602) 364-3289

Frequently Asked Questions About Salmonellosis

What is salmonellosis?
Salmonellosis is an infection with bacteria called *Salmonella*. Most persons infected with *Salmonella* develop diarrhea, fever, and abdominal cramps 12 to 72 hours after infection. The illness usually lasts 4 to 7 days, and most persons recover without treatment. However, in some persons the diarrhea may be so severe that the patient needs to be hospitalized. In severe cases, *Salmonella* infection may spread from the intestines to the blood stream and other body sites, causing life-threatening illnesses. The elderly, infants, and those with impaired immune systems are more likely to have a severe illness.

What sort of germ is *Salmonella*?
The *Salmonella* germ is a group of bacteria that can cause diarrhea in humans. They are microscopic living creatures that are found in the stools of animal and people. There are many different kinds of *Salmonella* bacteria. *Salmonella* serotype Typhimurium and *Salmonella* serotype Enteritidis are the most common in the United States.

How can *Salmonella* infections be diagnosed?
Many different kinds of illnesses can cause diarrhea, fever, or abdominal cramps. *Salmonella* can be cultured from stool, blood, or other body fluids. Once *Salmonella* has been identified, further testing can determine its specific type, and which antibiotics could be used to treat it.

How can *Salmonella* infections be treated?
Salmonella diarrhea usually resolves in 5-7 days without antibiotics. Persons with severe diarrhea will require rehydration with oral or intravenous fluids. Antibiotics do not shorten the course of most *Salmonella* diarrhea infections, but can contribute to the development of resistant bacteria. However, antibiotics should be considered for certain patients, including people with weak immune systems, infants, and those with serious underlying health problems. Unfortunately, *Salmonella* are becoming more resistant to antibiotics, due to the frequent use of antibiotics to promote growth in food animals.

Are there long-term consequences to a *Salmonella* infection?
Persons with diarrhea usually recover completely, although it may be several months before their bowel habits are entirely normal. Rarely, *Salmonella* can spread to bones, joints, or the brain.

A very small number of persons who are infected with *Salmonella*, will go on to develop pains in their joints, irritation of the eyes, and painful urination. This is called Reiter's syndrome. It can last for months or years, and can lead to chronic arthritis. Antibiotic treatment does not make a difference in whether or not the person later develops this kind of arthritis.

How do people catch Salmonella?
Salmonella live in the intestinal tracts of humans, animals, and birds. *Salmonella* are usually transmitted to humans by when they eat foods contaminated with animal feces. Contaminated foods usually look and smell normal. Foods at higher risk are of animal origin, such as beef, poultry, milk, or eggs. However, all foods may become contaminated, including vegetables. Although many raw foods of animal origin are frequently contaminated, thorough cooking kills *Salmonella*. Food may become contaminated when an infected food

handler does not wash his hands after using the bathroom.

Salmonella may also be found in the feces of some pets, especially those with diarrhea. People can become infected if they do not wash their hands after contact with these animals. Reptiles are particularly likely to harbor *Salmonella*. People should always wash their hands immediately after handling a reptile, even if the reptile seems healthy.

What can a person do to prevent this illness?
There is no vaccine to prevent salmonellosis. People should not eat raw or undercooked eggs, poultry, or meat, and they should not drink raw milk or other unpasteurized dairy products. The source of Salmonella-infected food may not always be apparent. For example, raw eggs may be used in some foods such as homemade hollandaise sauce, Caesar and other salad dressings, tiramisu, homemade ice cream, homemade mayonnaise, cookie dough, and frostings. Poultry and meat should be well cooked (not pink in the middle). Produce should be thoroughly washed before eating.

Cross-contamination of foods should be avoided. Uncooked meats should be kept separate from produce, cooked foods, and ready-to-eat foods. Hands, cutting boards, counters, knives, and other utensils should be washed thoroughly after handling uncooked foods. Hand should be washed before handling any food, and in between handling different food items.

People should wash their hands after contact with animal feces. Since reptiles are particularly likely to have *Salmonella*, everyone should immediately wash their hands after handling reptiles. Reptiles (including turtles) are not appropriate pets for small children and should not be in the same house as an infant.

How common is salmonellosis?
Every year, approximately 40,000 cases of salmonellosis are reported in the United States. Because many milder cases are not diagnosed or reported, the actual number of infections may be much greater. Young children, the elderly, and the immunocompromised are the most likely to have severe infections. It is estimated that 600 persons die each year with acute salmonellosis.

What else is being done to prevent salmonellosis?
State and local public health departments stay informed about cases of salmonellosis. Clinical laboratories send isolates of *Salmonella* to the State Public Health Laboratory for more specific testing. If many similar cases of *Salmonella* occur at the same time, it may mean that a restaurant or other food source has a problem that needs intervention by the public health department.

Pasteurization of milk and treating municipal water supplies reduce the risk of *Salmonella* infection. In 1975, the sale of small turtles was halted in this country to prevent *Salmonella* infections. Improvements in farm animal hygiene, in slaughter practices, in food harvesting, and in packing operations have helped prevent salmonellosis. Food industry workers are taught food safety. Restaurant inspections look for food handling errors that could lead to outbreaks. Future efforts may include meat irradiation reduce *Salmonella* contamination of raw meat.

What is the government doing about salmonellosis?
The Centers for Disease Control and Prevention (CDC) monitors the frequency of *Salmonella* infections in the country and assists the local and State Health Departments to investigate outbreaks and devise control measures. CDC also conducts research to better identify specific types of *Salmonella*. The Food and Drug Administration (FDA) inspects imported foods, milk pasteurization plants, promotes better food preparation techniques in restaurants and food processing plants, and regulates the sale of turtles. The FDA also regulates the use of specific antibiotics to promote growth in food animals. The US Department of

Agriculture monitors the health of food animals, inspects egg pasteurization plants, and is responsible for the quality of slaughtered and processed meat. The US Environmental Protection Agency regulates and monitors the safety of our drinking water supplies.

How can I learn more about this and other public health problems?
You can discuss any medical concerns you may have with your doctor or other heath care provider. Your local Health Department can provide more information about this and other health in your area. Information is available on the website of the Arizona Department of Health Services at , and on the website of the Centers for Disease Control and Prevention at .

What can I do to prevent salmonellosis?

- Cook poultry, ground beef, and eggs thoroughly before eating.
- Do not eat or drink foods containing raw eggs, or raw unpasteurized milk.
- If you are served undercooked meat, poultry or eggs in a restaurant, don't hesitate to send it back to the kitchen for further cooking.
- Always wash your hands before handling any food
- Wash hands, kitchen work surfaces, and utensils with soap and water immediately after they have been in contact with raw meat or poultry.
- Be particularly careful with foods prepared for infants, the elderly, and the immunocompromised.
- Wash hands with soap after handling reptiles or birds, or after contact with pet feces.
- Avoid direct or even indirect contact between infants or immunocompromised persons and reptiles (turtles, iguanas, other lizards, snakes).
- Drinking pasteurized milk prevents salmonellosis and many other health problems.

For more information call (602) 364-3289

Arizona Department of Health Services

SHIGELLOSIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: *Shigella* are gram-negative, nonmotile, nonsporeforming, rod-shaped bacteria that are comprised of four species or serogroups which are further divided into serotypes and subtypes. Shigellosis is caused when virulent *Shigella* organisms attach to and penetrate epithelial cells of the intestinal mucosa. After invasion, they multiply intracellularly, and spread to contiguous epithelial cells resulting in tissue destruction. Some strains produce enterotoxin and Shiga toxin.

Routes of Exposure: Fecal-oral transmission through direct and indirect person-to-person contact is the main route of exposure. Ingesting contaminated foods and beverages can also spread infection.

Infective Dose & Infectivity: *Shigella* bacteria are highly infectious. The ingestion of very few organisms (10-100) is sufficient to cause infection. Though all people are believed to be susceptible to some degree, infants, the elderly, and the infirm are most likely to experience severe symptoms of disease.

Incubation Period: The incubation is usually between 1 and 3 days, but can range from 12 to 96 hours for most strains. Some strains have incubation periods of up to one week.

Clinical Effects: The illness is characterized by diarrhea accompanied by fever, nausea, toxemia, vomiting, cramps, and tenesmus. Though cases may also present with watery diarrhea, typical stools contain blood, mucus, or pus, which is the result of mucosal ulcerations and confluent colonic crypt microabscesses caused by the invasive organisms. Bacteremia is uncommon. Mild and asymptomatic infections can occur. Illness is usually self-limited, lasting an average of 4-7 days. Severe complications can include toxic megacolon, the hemolytic uremic syndrome, and Reiter syndrome. Convulsions, which could be the result of rapid temperature elevation or metabolic alterations, may occur in young children.

Lethality: Although the mortality rate for some strains of *Shigella* may be as high as 10-20%, it is generally quite low. Two-thirds of the cases, and most of the deaths are in children under 10 years old.

Transmissibility: *Shigella* infection is caused by fecal-oral transmission. Individuals primarily responsible for transmission are those who do not practice proper hand washing techniques, especially after defecating. Infection may be spread to others directly through physical contact or indirectly through contaminated food and beverages. Unsanitary food handling is the most common cause of contamination. Flies can also transfer organisms from latrines to uncovered food items.

Primary Contamination & Methods of Dissemination: In a terrorist attack, *Shigella* would most likely be disseminated through the intentional contamination of food or water supplies.

Secondary Contamination & Persistence of organism: Secondary transmission can result from exposure to the stool of infected individuals. Diarrheal fluids are highly infectious. In households, secondary attack rates can be as high as 40%. Following illness, stool typically remains infectious for 4 weeks, though the bacteria can persist for months or longer in asymptomatic carriers. Antimicrobial treatment can reduce the period of infectivity to a few days.

Decontamination & Isolation:

Patients – No decontamination necessary. Patients can be treated with standard precautions, with contact precautions for diapered or incontinent patients. Hand washing is of particular importance.

Equipment & other objects – 0.5% hypochlorite solution (one part household bleach and nine parts water), EPA approved disinfectants, and/or soap and water can be used for environmental decontamination.

Laboratory Testing: Diagnosis is made by isolation of *Shigella* from feces or rectal swabs. Prompt laboratory processing of specimens and use of appropriate media increase the likelihood of *Shigella* isolation. Infection is usually associated with the presence of copious numbers of fecal leukocytes detected by microscopic examination of stool mucus stained with methylene blue or gram stain. .

Therapeutic Treatment: Fluid and electrolyte replacement is important when diarrhea is watery or there are signs of dehydration. Antibacterial therapy shortens the duration and severity of illness and the duration of *Shigella* excretion.

Multidrug resistance is common; the choice of empiric antibiotics is best determined by local susceptibility patterns. Usually effective antibiotics include fluoroquinolones, third generation cephalosporins, and trimethoprim-sulfamethoxazole. Antimotility agents such as loperamide are not approved for children under 2 years old. Their use is generally discouraged in bacterial infections as these drugs may prolong the illness. Nevertheless, if they are administered in an attempt to alleviate the severe cramps that often accompany shigellosis, they should never be given without concomitant antimicrobial therapy.

Prophylactic Treatment: Prophylactic administration of antibiotics is not recommended.

Differential Diagnosis: *Salmonella, E. coli* O157:H7*, Campylobacter, Yersinia enterocolitca*, and bacterial food poisoning may show similar signs and symptoms.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Center for Food Safety and Applied Nutrition. Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, U.S. Food and Drug Administration
http://vm.cfsan.fda.gov/~mow/intro.html

For more information call (602) 364-3289

Frequently Asked Questions About Shigellosis

What is shigellosis?
Shigellosis is an infectious disease caused by a group of bacteria called *Shigella*. Most people who are infected with *Shigella* develop diarrhea, fever, and stomach cramps starting a day or two after they are exposed to the bacterium. The diarrhea is often bloody. Shigellosis usually resolves in 5 to 7 days. In some persons, especially young children and the elderly, the diarrhea can be so severe that the patient needs to be hospitalized. A severe infection with high fever may also be associated with seizures in children less than 2 years old. Some persons who are infected may have no symptoms at all, but may still pass the *Shigella* bacteria to others.

What sort of germ is *Shigella*?
The *Shigella* germ is actually a family of bacteria that can cause diarrhea in humans. They are microscopic living creatures that pass from person to person. There are several different kinds of *Shigella* bacteria: *Shigella sonnei*, also known as "Group D" *Shigella*, accounts for over two-thirds of the shigellosis in the United States. A second type, *Shigella flexneri*, or "group B" *Shigella*, accounts for almost all of the rest. Other types of *Shigella* are rare in this country, though they continue to be important causes of disease in the developing world. One type found in the developing world, *Shigella dysenteriae* type 1, causes deadly epidemics there.

How can *Shigella* infections be diagnosed?
Many different kinds of diseases can cause diarrhea and bloody diarrhea, and the treatment depends on which germ is causing the diarrhea. Determining that *Shigella* is the cause of the illness depends on laboratory tests that identify *Shigella* in the stools of an infected person. These tests are sometimes not performed unless the laboratory is instructed specifically to look for the organism. The laboratory can also do special tests to tell which type of *Shigella* the person has and which antibiotics, if any, would be best to treat it.

How can *Shigella* infections be treated?
Shigellosis can usually be treated with antibiotics. Appropriate treatment kills the *Shigella* bacteria that might be present in the patient's stools, and shortens the illness. Unfortunately, some *Shigella* bacteria have become resistant to antibiotics. Using antibiotics to treat shigellosis may contribute to make the germs more resistant in the future. Persons with mild infections will usually recover quickly without antibiotic treatment. Therefore, when many persons in a community are affected by shigellosis, antibiotics are sometimes used to treat only the more severe cases. Antidiarrheal agents such as loperamide (Imodium) or diphenoxylate with atropine (Lomotil) are likely to make the illness worse and should be avoided.

Are there long term consequences to a *Shigella* infection?
Persons with diarrhea usually recover completely, although it may be several months before their bowel habits are entirely normal. About 3% of persons who are infected with one type of Shigella, *Shigella flexneri*, will later develop pains in their joints, irritation of the eyes, and painful urination. This is called Reiter's syndrome. It can last for months or years, and can lead to chronic arthritis which is difficult to treat. Reiter's syndrome is caused by a reaction to *Shigella* infection that happens only in people who are genetically predisposed to it.

Once someone has had shigellosis, they are not likely to get infected with that specific type again for at least several years. However, they can still get infected with other types of *Shigella*.

How do people catch *Shigella*?
The *Shigella* bacteria pass from one infected person to another. *Shigella* are present in the diarrheal stools of infected persons while they are sick and for a week or two afterwards. Most *Shigella* infections are the result of the bacterium passing from stools or soiled fingers of one person to the mouth of another person. This happens when basic hygiene and handwashing habits are inadequate. It is particularly likely to occur among toddlers who are not fully toilet-trained. Family members and playmates of such children are at high risk of becoming infected.

Shigella infections may be acquired from eating contaminated food. Contaminated food may look and smell normal. Food may become contaminated by infected food handlers do not wash their hands after using the bathroom. Vegetables can become contaminated if they are harvested from a field with sewage in it. Flies can breed in infected feces and then contaminate food. *Shigella* infections can also be acquired by drinking or swimming in contaminated water. Water may become contaminated if sewage runs into it, or if someone with shigellosis swims in it.

What can a person do to prevent this illness?
There is no vaccine to prevent shigellosis. However, the spread of *Shigella* from an infected person to other persons can be stopped by frequent and careful handwashing with soap. Frequent and careful handwashing is important among all age groups. Frequent, supervised handwashing of all children should be followed in day care centers and in homes with children who are not completely toilet-trained (including children in diapers). When possible, young children with a *Shigella* infection who are still in diapers should not be in contact with uninfected children.

If a child in diapers has shigellosis, everyone who changes the child's diapers should be sure the diapers are disposed of properly in a closed-lid garbage can, and should wash his or her hands carefully with soap and warm water immediately after changing the diapers. After use, the diaper changing area should be wiped down with a disinfectant such as household bleach, Lysol or bactericidal wipes.

For more information call (602) 364-3289

Arizona Department of Health Services

STAPHYLOCOCCAL ENTEROTOXIN B

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Staphylococcal enterotoxin B (SEB) is one of seven enterotoxins produced by strains of *Staphylococcus aureus*.

Routes of Exposure: Humans are primarily exposed to SEB by consuming contaminated food.

Infective Dose & Infectivity: Minute concentrations are able to cause incapacitation. All people are considered susceptible.

Incubation Period: The incubation period ranges from 4-10 hours after ingestion and 3-12 hours after inhalation.

Clinical Effects: Symptoms of SEB intoxication are abrupt and include nonspecific flu-like symptoms (fever, chills, headache, myalgias), and specific features dependent on the route of exposure. Gastrointestinal exposure results in severe nausea, vomiting, abdominal cramps, and prostration often accompanied by diarrhea. Inhalation exposures produce respiratory symptoms including nonproductive cough, retrosternal chest pain, and dyspnea. Gastrointestinal symptoms may accompany respiratory exposure due to inadvertent swallowing of the toxin after normal mucocilliary clearance. The fever may last up to five days and range from 103 to 106 degrees F, with variable degrees of chills and prostration. The cough may persist up to four weeks.

Physical examination in patients with SEB intoxication is often unremarkable. Conjunctival injection may be present, and postural hypotension may develop due to fluid losses. Chest examination is unremarkable except in the unusual case where pulmonary edema develops. The chest X-ray is also generally normal, but in severe cases increased interstitial markings, atelectasis, and possibly overt pulmonary edema or an ARDS picture may develop. Intoxication is usually self-limiting though, presumably, severe exposure could lead to septic shock and death.

Lethality: SEB intoxication is rarely fatal, though at higher exposures death is possible.

Transmissibility: SEB is usually transmitted by ingesting a contaminated food product. When contaminated foods remain at room temperature for several hours before being eaten, toxin-producing staphylococci multiply and elaborate the heat stable toxin. SEB could also be transmitted through inhalation during an aerosolized release.

Primary contaminations & Methods of Dissemination: In a terrorist attack, SEB intoxication would most like occur due to an aerosolized release. In addition, intentional contamination of food or water supplies could be a possibility.

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Secondary Contamination & Persistence of organism: Secondary transmission does not occur. SEB is relatively stable and resistant to temperature fluctuations.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Specific isolation procedures are not indicated.

Equipment, clothing & other objects – 0.5% sodium hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: Laboratory findings are not very helpful in the diagnosis of SEB intoxication. A nonspecific neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate may be seen, but these abnormalities are present in many illnesses. Toxin is difficult to detect in the serum by the time symptoms occur; however, toxin accumulates in the urine and can be detected for several hours post exposure. Therefore, urine samples should be obtained and tested for SEB. Because most patients will develop a significant antibody response to the toxin, acute and convalescent serum should be drawn which may be helpful retrospectively in the diagnosis.

Therapeutic Treatment: Treatment is limited to supportive care. Artificial ventilation might be needed for SEB inhalation. Attention to fluid management is important.

Prophylactic Treatment: There is no vaccine available to prevent SEB intoxication.

Differential Diagnosis: The differential diagnosis of gastrointestinal SEB includes other recognized forms of food poisoning. The differential diagnosis of a rapid onset of respiratory distress would include ricin, mycotoxins, chemical poisons, Hantavirus pulmonary syndrome, and routine bacterial and viral respiratory infections.

References:

Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Kortepeter M, Christopher G, Cieslak T, et al. Medical Management of Biological Casualties Handbook, U.S. Army Medical Research Institute of Infectious Diseases, U.S. Department of Defense; 2001: 80-83
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For more information call (602) 364-3289

Frequently Asked Questions About Staphylococcal Enterotoxin B

What is Staphylococcal Enterotoxin B?
Staphylococcal Enterotoxin B (SEB) is one of several toxins produced by the *Staphylococcus aureus* bacteria. The toxin commonly causes unintentional outbreaks of food poisoning.

How is SEB spread?
SEB thrives in unrefrigerated meats, dairy, and bakery products. Therefore, SEB is generally transmitted by eating contaminated foods. If SEB were used as a biological weapon, it could be aerosolized and thus inhaled. It is not possible to spread SEB from person-to-person.

What are the symptoms of SEB exposure?
Symptoms differ depending on the type of exposure. After eating contaminated foods, symptoms with usually start within 4-10 hours and include nausea, vomiting, stomach cramps, and diarrhea. Symptoms of inhaled SEB include a sudden high fever (103º F. to 106º F.), chills, headache, muscle aches, and a dry cough and will usually appear within 3-12 hours after breathing in SEB.

How is SEB exposure diagnosed?
SEB is initially diagnosed based on symptoms. Laboratory confirmations can be made by testing blood and urine samples.

How is the illness treated?
Usually treatment of foodborne disease is not needed, other than taking steps to prevent or treat dehydration. For respiratory distress from inhaled SEB, ventilation may be required.

What can be done to prevent SEB food poisoning?
By properly preparing meat products and using appropriate refrigeration techniques to store meat and dairy products you can greatly reduce your risk of SEB food poisoning. It is also important to wash your hands before preparing or serving foods and after handling raw meat.

Why are we concerned about SEB as a biological weapon?
We know that in the past SEB has been studied as a biological weapon and even stockpiled by the United States during its old biological weapons program, which ended in 1969. SEB is considered an effective biological weapon because it can be easily aerosolized and is very stable. Though death is possible after exposure to large amounts of the toxin, fatalities are rare. Since SEB is much more likely to cause illness that death, it is classified as an “incapacitating agent.”

Is a vaccine available for SEB?
No vaccine or antitoxin is available to treat SEB before or after exposure.

For more information call (602) 364-3289

TRICHOTHECENE MYCOTOXINS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Tricothecene mycotoxins (T-2 mycotoxins) are nonvolatile compounds produced by filamentous fungi primarily of the genera *Fusarium*, *Myrotecium*, *Trichoderma*, and *Stachybotrys*.

Routes of Exposure: Inhalation, Dermal, and Oral.

Toxic Dose:
Inhalation – Unknown.
Dermal – Unknown.
Oral – Leukopenia seen with as little as 0.1mg/kg/day for several weeks.

Incubation Period:
Inhalation – Minutes
Dermal – Minutes to hours
Oral – Minutes to days

Clinical Effects: Mycotoxins act by inhibition of protein synthesis. Symptoms start within minutes to hours after exposure, and involve eyes, skin, respiratory and gastrointestinal tracts.

Eyes – Eye pain, excessive lacrimation, visual blurring and scleral injection.

Inhalation – Nasal itching and pain, epistaxis, rhinorrhea, cough, dyspnea, wheezing.

Dermal – Burning skin, redness, blistering progressing to necrosis, skin sloughing.

Oral – Anorexia, mouth pain, nausea, vomiting, hematemesis, abdominal pain, watery or bloody diarrhea, abdominal cramps.

Early systemic effects – Weakness, loss of coordination, dizziness, ataxia, tachycardia, hypothermia, hypotension or death.

Late systemic effects – Two to eight weeks after ingestion on contaminated food, bone marrow suppression occurs with with severe neutropenia and hemorrhagic syndromes such as diffuse bleeding into skin with petechiae, melena, hematuria, hematemesis, epistaxis, and vaginal bleeding. Other common problems include fever, oral and GI ulceration, and secondary sepsis. These effects are similar to the effects seen with exposure to radiation.

Lethality: There is a death rate of 10-20% with ingestion of contaminated food.

Transmissibility: Person-to-person transmission of intoxication does not occur, although exposure could occur by contact with contaminated objects and surfaces that had not bee appropriately decontaminated.

Primary dissemination: There were reports that mycotoxins may have been used in the past as bioterrorism weapons in Iran and Southeast Asia. These were described as aerosol attacks in the form of “yellow rain” with droplets of yellow fluid contaminating clothes and the environment.

Secondary Contamination: There is no person-to-person transmission but contaminated fomites, such as clothing, could be a source of exposure.

Decontamination & Isolation:

Patients – Outer clothing should be removed and exposed skin decontaminated by washing thoroughly with soap and water. Eye exposure should be treated with copious saline or water irrigation. Once decontamination is complete, isolation is not required.

Equipment, clothing & other objects – T-2 mycotoxins are stable in the environment, resistant to heat and ultraviolet light. Environmental decontamination requires the use of a chlorine bleach solution under alkaline conditions such as a 1% sodium hypochlorite (1 part bleach + 4 parts water) and 0.1M sodium hydroxide solution with one hour contact time.

Personal Protective Equipment: Respiratory, skin and eye protection are required since toxin can be absorbed by the respiratory, gastrointestinal, dermal and ocular routes.

Health Care Facility: There is no person-to-person transmission. However, avoid contact with contaminated clothing. If a contaminated person arrives fully clothed, protective clothing should be worn until decontamination of the patient is completed and contaminated clothing discarded.

Identification of Exposure: Exposure to T-2 mycotoxins should be suspected if an aerosol attack occurs in the form of "yellow rain". Currently, there are no commercially available rapid field diagnostic tests available. Confirmation requires testing of blood, tissue, and environmental samples using gas liquid chromatography-mass spectrometry techniques.

Laboratory testing: Serum, nasopharyngeal swab, and urine can be sent for toxin.

Therapeutic Treatment: Superactivated charcoal should be administered to persons who may have ingested T-2 mycotoxins in order to adsorb the toxin. There is no vaccine and no specific antidote or therapeutic regimen. Treatment is symptomatic and supportive.

Prophylactic Treatment: None

Differential Diagnosis: Mustard gas has a delay of several hours before symptoms start. Staphylococcus enterotoxin B can cause fever, cough, dyspnea and wheezing but does not involve the skin. Ricin can cause severe respiratory distress, and gastrointestinal symptoms, but does not involve the skin.

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Chin J. Control of Communicable Diseases Manual, Seventeenth Edition, American Public Health Association; 2000.

Kortepeter M, Christopher G, Cieslak T, et al. Medical Management of Biological Casualties Handbook, U.S. Army Medical Research Institute of Infectious Diseases, U.S. Department of Defense; 2001: 78-85
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For more information call (602) 364-3289

Frequently Asked Questions About Trichothecene Mycotoxins

What are trichothecene mycotoxins?
Trichothecene mycotoxins, biological toxins, are a group of 40 compounds produced by a common grain mold. Biological toxins are harmful substances that are produced by living organisms such as fungi.

Why are we concerned about trichothecene mycotoxins as a biological weapon?
We are concerned about trichothecene mycotoxins, especially T-2, as a biological weapon because they are very stable, resistant to disinfectants, easy to produce in large quantities, and can be dispersed through a number of different ways. Additionally, there is strong evidence to suggest that they have been used as biological warfare agents in the past.

How are trichothecene mycotoxins transmitted?
Trichothecene mycotoxins can be inhaled, ingested, or absorbed through the skin. The T-2 mycotoxins are the only potential biological agent that can adhere to and penetrate intact skin. Trichothecene mycotoxins cannot be transmitted person to person.

Can trichothecene mycotoxin exposure occur naturally?
Yes. This usually occurs when contaminated foods, such as moldy grain, are eaten.

What are the symptoms of trichothecene mycotoxin exposure?
After exposure early symptoms begin within 5 to 60 minutes. Symptoms are dependant on the route of exposure.

Inhalational exposure results in nasal itching, pain, sneezing, bloody and runny nose, difficulty breathing, wheezing, cough, and blood-tinged saliva and sputum.

Exposure through ingestion causes loss of appetite, nausea and vomiting, stomach cramping, and watery and/or bloody diarrhea.

Skin symptoms include burning, tender and reddened skin, swelling, and blistering progressing to death of skin tissues and, in lethal cases, sloughing of large areas of skin. After exposure to the eyes, pain, tearing, redness, and blurred vision occur.

Exposure through any route can lead to full body illness, the symptoms of which include weakness, fatigue, dizziness, lack of muscular coordination, irregular heartbeat, hyperthermia or hypothermia, extensive bleeding, and low blood pressure.

How is exposure to trichothecene mycotoxins diagnosed?
A diagnosis is generally made based on the symptoms the patient is experiencing and the results from blood and urine tests. Environmental tests may also be done to help support the diagnosis. Additionally, if the exposure were the result of a bioterrorism event, many patients may report seeing a “yellow rain” or a smoke attack.

How can trichothecene mycotoxin exposure be treated?
There is no antitoxin for the trichothecene mycotoxins therefore, the only thing that can be done is to provide supportive care and treat the symptoms that occur. If given early, superactivated charcoal can be useful in treating patients who have ingested trichothecene mycotoxins.

What should people do if they are exposed to trichothecene mycotoxins?
People who are known have been exposed to trichothecene mycotoxins should seek immediate medical. Exposed skin should be washed thoroughly with soap and water and eyes should be flooded with saline or water.

How can trichothecene mycotoxin exposure be prevented?
The only way to prevent exposure is to avoid contact with the trichothecene mycotoxins. The can be done by wearing protective clothing and a mask.

For more information call (602) 364-3289

TYPHUS FEVER

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Typhus fever is a rickettsial disease caused by the organism *Rickettsia prowazekii*, a Gram negative, obligate intracellular bacterium.

Routes of Exposure: Humans are exposed to epidemic typhus through arthropod vectors, primarily the human body louse.

Infective Dose & Infectivity: The infective dose is unknown. All people are considered susceptible, though older adults may be more severely affected.

Incubation Period: The incubation period ranges from 1 to 2 weeks, but is usually 12 days.

Clinical Effects: Illness usually starts suddenly with headache, chills, prostration, fever, and generalized body aches. A macular eruption appears in four to seven days, initially on the upper trunk, followed by spread to the entire body, but usually not to the face, palms, or soles. The rash starts as maculopapular, becomes petechial or hemorrhagic, then develops into brownish-pigmented areas. The rash may be more concentrated in the axillae. Changes in mental status are common with delirium or coma. Toxemia is usually pronounced. Myocardial and renal failure can occur when the disease is severe. When untreated, the fever and illness last for 2 weeks.

Lethality: The death rate for untreated epidemic typhus increases with age and varies from 10% to 40%.

Transmissibility: Typhus fever is transmitted from person to person by the body louse, which feeds on the blood of humans. Infected lice excrete rickettsiae in their feces and usually defecate at the time of feeding. People are infected when they rub feces or crush lice in the bite, superficial abrasions, or mucous membranes. Inhalation of infective louse feces in dust may account for some infections. Transmission has also been associated with contact with infected flying squirrels in the United States, their nests, or their ectoparasites.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, *R. prowazekii* would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Direct person-to-person spread of the disease does not occur in the absence of the vector. Rickettsia can remain viable in a dead louse for weeks.

Decontamination & Isolation:

Patients – Standard precautions should be practiced with patients with typhus. Louse-infected people should be treated with pediculocides containing pyrethrins (0.16-33%), piperonyl butoxide (2-4%), crotamiton (10%), or lindane (1%). Several applications may be needed because lice eggs are resistant to most insecticides.

Equipment, clothing & other objects: Washing clothes in hot water kills lice and eggs. Insecticides dusted onto clothing has been effective in epidemics.

Laboratory testing: Culture isolation of *R. prowazekii* is rarely attempted. The preferred serology for acute and convalescent antibodies is the IFA test, although ELISA, microagglutination and latex agglutination are also available. Antibody tests usually become positive in the second week. Rickettsiae an be detected in tissue biopsies by PCR or immunohistochemical assays.

Therapeutic Treatment: Doxycycline is the treatment of choice for epidemic louseborne typhus fever. Therapy should be administered until the patient is afebrile for at least 3 days and clinical improvement is documented; the usual duration of therapy is 7 to 10 days. Severe disease can require a longer course of treatment.

Despite concerns regarding dental staining after use of a tetracycline-class antimicrobial agent in children 8 years of age or younger, doxycycline provides superior therapy for this potentially life-threatening disease. In people who are intolerant of tetracyclines, intravenous chloramphenicol or fluoroquinolones can be considered. Fluoroquinolones are not recommended for people younger than 18 years of age. When faced with a seriously ill patient with possible typhus, suitable therapy should be started without waiting for laboratory confirmation.

Prophylactic Treatment: Vaccine is no longer available in the United States and post-exposure chemoprophylaxis is not indicated. Apply residual insecticide to those who are subject to risk.

Differential Diagnosis: The differential diagnoses should includes febrile illnesses such as anthrax, dengue fever, infectious mononucleosis, leptospirosis, malaria, meningitis, meningococcemia, relapsing fever, Rocky Mountain spotted fever, syphilis, toxic shock syndrome, tularemia, typhoid fever, rubella, measles, and other rickettsial diseases.

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For more information call (602) 364-3289

Frequently Asked Questions About Typhus Fever

What is typhus fever?
Typhus fever is a potentially fatal, infectious disease caused by the bacterium *Rickettsia prowazekii*. Also known as epidemic typhus, this disease is transmitted to humans by body lice. Though it has occurred on all continents throughout the world except Australia, typhus fever is not common in the United States.

Who gets typhus fever?
Anyone can get typhus fever, though it is most likely to occur among people living in overcrowded, dirty conditions, with few opportunities to wash themselves or their clothing. As a result typhus fever often occurs when cold weather, poverty, war, and other disasters result in close living conditions where body lice can thrive and spread.

How is typhus fever transmitted?
Typhus fever is transmitted by body lice, which become contagious by feeding on the blood of infected humans. The lice then defecate will feeding on another person and the feces, which contains the typhus fever bacteria, can get rubbed into small wounds such as those caused by scratching lice-infected areas. It is the feces, not the bite of the louse that transmits the illness to humans. It is also possible to become infected through contact with the mucous membranes of the mouth and eyes or by inhaling the dust of dried lice feces. Typhus fever is not spread directly from person-to-person.

Could terrorists use typhus fever?
Typhus fever is considered dangerous and could be used as a biological weapon. However, because it would be difficult to deliver and easy to treat it is not considered a very likely agent.

What are the symptoms of typhus fever?
Symptoms of typhus fever will usually appear within one to two weeks after exposure. Common symptoms include fever, headache, weakness, and muscle aches. Typhus fever also causes a rash composed of both spots and bumps. The rash starts on the back, chest, and stomach, then spreads to the arms and legs. The worst types of complications involve infection in the heart muscle (myocarditis) or brain (encephalitis).

Is typhus fever fatal?
Most people do not die from typhus fever. Patients usually recover with early detection and treatment. However, if left untreated, the death rate can be as high as 10 to 40 percent.

How is typhus fever diagnosed?
Typhus fever is usually diagnosed through blood tests. The organism can also be identified in tissue samples.

Is there treatment for typhus fever?
Effective treatment is possible with antibiotics such as doxycycline, chloramphenicol., or ciprofloxacin.

For more information call (602) 364-3289

VENEZUELAN EQUINE ENCEPHALITIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Venezuelan Equine Encephalitis (VEE) is a mosquito-borne illness caused by an alphavirus of the *Togaviridae* family.

Routes of Exposure: Humans are primarily exposed to VEE through the bite of an infected mosquito.

Infective Dose & Infectivity: The infective dose is considered to be 10-100 organisms. All people are considered susceptible though children are more likely to be severely affected.

Incubation Period: The incubation period is usually 2-6 days; though it can be as short as 1 day.

Clinical Effects: VEE is characterized by inflammation of the meninges of the brain and of the brain itself, thus accounting for the predominance of CNS symptoms in the small percentage of infections that develop encephalitis. The disease is usually acute, prostrating and of short duration. Illness begins suddenly with generalized malaise, spiking fevers, rigors, severe headache, photophobia, and myalgias. Nausea, vomiting, cough, sore throat, and diarrhea may follow. Full recovery takes 1-2 weeks.

Lethality: The overall mortality rate for VEE is less than 1%, but is somewhat higher among children and older adults.

Transmissibility: VEE infection generally occurs when a person is bitten by an infected mosquito. VEE is highly infectious when aerosolized. There is no evidence of human-to-human transmission, even though VEE virus can be found in human throat swabs.

Primary contaminations & Methods of Dissemination: As a bioterrorism weapon, VEE would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of organism: Secondary transmission does not occur and VEE particles are not considered to be stable in the environment.

Decontamination & Isolation:

Patients – Standard precautions should be practiced. Specific isolation procedures are not indicated.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution), other EPA approved disinfectants, and heat are effective for environmental decontamination.

Laboratory testing: Virus can be isolated from serum, and in some cases throat swab specimens. An increase in VEE IgG antibody in paired sera, or VEE specific IgM present in a single serum sample indicate recent infection.

Therapeutic Treatment: There is no specific therapy. Patients with uncomplicated VEE infection may be treated with analgesics to relieve headache and myalgia. Patients who develop encephalitis may require anticonvulsant and intensive supportive care to maintain fluid and electrolyte balance, adequate ventilation, and to avoid complicating secondary bacterial infections.

Prophylactic Treatment: A live, attenuated vaccine is available as an investigational new drug. A second, formalin-inactivated, killed vaccine is available for boosting antibody titers in those initially receiving the live vaccine.

Differential Diagnosis: The differential diagnosis includes a number of viral and bacterial infections including arenaviruses, cytomegalovirus, dengue fever, viral hepatitis, herpes simplex encephalitis, influenza, leptospirosis, malaria, bacterial meningitis, Q fever, St. Louis encephalitis, West Nile encephalitis, yellow fever, Colorado tick fever, and the early prodrome of measles.

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Available at http://www.usamriid.army.mil/education/bluebook.htm

For more information call (602) 364-3289

Frequently Asked Questions About Venezuelan Equine Encephalitis

What is Venezuelan Equine Encephalitis?
Venezuelan Equine Encephalitis (VEE) is a mosquito-borne viral disease. It is common in South America, Trinidad, Central America, Mexico, and Florida.

How do people become infected with VEE virus?
VEE virus is transmitted to humans through the bite of an infected mosquito. Horses can also become infected with, and die from, VEE virus infection. There is no evidence that VEE has been directly transmitted from person-to-person.

What causes VEE?
VEE is caused by a virus that is a member of the family *Togaviridae*, genus *Alphavirus*. It is closely related to Eastern and Western equine encephalitis viruses.

Where is VEE found?
VEE is found in northern South America (Colombia, Peru, Brazil, Venezuela, French Guiana, Guyana, and Suriname) and Trinidad. It also causes rare cases of human encephalitis in Central America, Mexico, and Florida.

Why are we concerned about VEE as a biological weapon?
VEE could possibly be used as a biological weapon. The virus is stable in the environment and can survive the storage and manipulation procedures necessary for making it into a weapon. Since it may take no more that 10-100 organisms to cause disease, it is considered to be a potentially effective bioterrorism weapon.

Who is at risk for developing VEE?
Anyone can get VEE, but those at increased risk of developing severe disease include young children and older adults. Pregnant women may also develop complications.

What are the signs and symptoms of VEE?
Most VEE infections are mild with only a small percentage of the infected population developing encephalitis. Persons with the mild form of illness may describe only minimal flu-like symptoms of low-grade fever, muscular pain, or headache. Patients with moderate disease may experience fever, chills, muscle pain, back pain, headache, sensitivity to light, vomiting, and sore throat. Among severe cases symptoms include a sudden high fever, severe muscle and back pain, headache, sensitivity to light, vomiting, weakness, exhaustion, and confusion. Though rare, seizures, paralysis, tremors, coma, and severe encephalitis can also occur.

How soon after exposure do symptoms appear?
Symptoms usually appear in 2 to 6 days after the bite of an infected mosquito.

How is VEE diagnosed?
VEE is often diagnosed based on symptoms and travel history. Blood samples to test for the virus are used to confirm the diagnosis.

Is there treatment for VEE?
No specific treatment other than supportive care is available.

Is there a vaccine for VEE?
Although two vaccines are being developed and tested, there is currently no licensed vaccine for human use.

For more information call (602) 364-3289

WESTERN EQUINE ENCEPHALITIS

Bioterrorism Agent Profiles for Health Care Workers

Causative Agent: Western Equine Encephalitis (WEE) is a mosquito-borne illness caused by an alphavirus of the *Togaviridae* family.

Routes of Exposure: Humans are primarily exposed to WEE through the bite of an infected mosquito.

Infective Dose & Infectivity: The infective dose is unknown. All people are considered susceptible though children are more likely to be severely affected.

Incubation Period: The incubation period is usually 5-10 days.

Clinical Effects: Most infections are asymptomatic. Mild cases often present with a nonspecific febrile illness or aseptic meningitis. Severe infections are usually marked by acute onset, headache, high fever, meningeal signs, stupor, disorientation, coma, tremors, occasional convulsions (especially infants) and spastic (but rarely flaccid) paralysis. Physical examination typically reveals nuchal rigidity, impaired sensorium, and upper motor neuron deficits with pathologically abnormal reflexes.

Lethality: The overall mortality rate for WEE is less than 3-4%, but is closer to 10% among children and older adults.

Transmissibility: WEE infection occurs when a person is bitten by an infected mosquito. The virus is not directly transmitted from person-to-person.

Primary Contamination & Methods of Dissemination: As a bioterrorism weapon, WEE would most likely be delivered via aerosolization.

Secondary Contamination & Persistence of Organism: Secondary transmission does not occur and WEE particles are not considered to be stable in the environment.

Decontamination & Isolation:

Patients – Standard precautions should always be practiced. Enteric precautions are appropriate for aseptic meningitis of unknown etiology until enterovirus meningoencephalitis is ruled out. When the diagnosis of WEE is known, specific isolation procedures are not indicated.

Equipment, clothing & other objects – 0.5% hypochlorite solution (one part household bleach and 9 parts water = 0.5% solution) is effective for environmental decontamination.

Laboratory testing: By the end of the first week of illness IgM, hemagglutination inhibition antibodies, and neutralizing antibodies can generally be found. During the next week they increase in titer. Complement fixation responses generally appear in the second week and rise thereafter. Four-fold titer rises are diagnostic, but because of serologic cross-reactions with other alphaviruses, neutralization tests are preferred. Examination of the CSF reveals a lymphocytic pleocytosis ranging from 10 to 400 mononuclear cells per microliter. WEE virus may occasionally be isolated from the CSF or throat swabs taken within the first 2 days of illness and is frequently recovered from brain tissue on postmortem examination.

Therapeutic Treatment: There is no specific therapy. Patients who develop severe illness may require anticonvulsant and intensive supportive care to maintain fluid and electrolyte balance, adequate ventilation, and to avoid complicating secondary bacterial infections. The extremes of high fever occasionally produced by WEE infection may require aggressive antihyperthermia measures.

Prophylactic Treatment: An investigational formalin-inactivated vaccine is available, but it is poorly immunogenic.

Differential Diagnosis: The differential diagnosis includes a number of infections including cytomegalovirus, herpes simplex encephalitis, St. Louis encephalitis, West Nile encephalitis, eastern equine encephalitis, Venezuelan encephalitis, leptospirosis, lyme disease, cat scratch disease, bacterial meningitis, tuberculosis, fungal meningitis, malaria, and *Naegleria* infection.

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Available at http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html

For more information call (602) 364-3289

Frequently Asked Questions About Western Equine Encephalitis

What is Western Equine Encephalitis?
Western Equine Encephalitis (WEE) is a mosquito-borne viral disease that can affect the central nervous system and cause severe complications and death.

How do people become infected with WEE virus?
WEE virus is transmitted to humans through the bite of an infected mosquito. The main WEE transmission cycle is between birds and mosquitoes. Horses can also become infected with, and die from, WEE virus infection.

What causes WEE?
WEE is caused by a virus that is a member of the family *Togaviridae*, genus *Alphavirus*. It is closely related to Eastern and Venezuelan equine encephalitis viruses.

Where is WEE found?
WEE is found in North, Central, and South America, but most cases have been reported from the plains regions of the western and central United States.

What are the signs and symptoms of WEE?
Infection can cause a range of illnesses, from no symptoms to fatal disease. People with mild illness often have only a headache and sometimes fever. People with more severe disease can have sudden high fever, headache, drowsiness, irritability, nausea, and vomiting, followed by confusion, weakness, and coma. Young infants often suffer seizures.

How soon after exposure do symptoms appear?
Symptoms usually appear in 2 to 10 days after the bite of an infected mosquito.

How common is WEE?
Human cases occur relatively infrequently and can occur in isolated cases or in epidemics. Human cases in the US are usually first seen in June or July.

Who is at risk for developing WEE?
Anyone can get WEE, but those at increased risk include people who engage in outdoor work and recreational activities and people living in or visiting areas where the disease is common. WEE occurs in all age groups.

How can people avoid infection with WEE virus?
Though a vaccine is available to protect horses, there is no licensed vaccine for human use.

To avoid infection people should avoid mosquito bites by employing personal and household protection measures, such as using insect repellent containing DEET, wearing protective clothing, taking precautions from dusk to dawn when mosquitoes are most likely to bite, and controlling standing water that can provide mosquito breeding sites.

For more information or call (602) 364-3289

Section 6:
CDC Smallpox Resources

SMALLPOX FACT SHEET

Smallpox Overview

The Disease

Smallpox is a serious, contagious, and sometimes fatal infectious disease. There is no specific treatment for smallpox disease, and the only prevention is vaccination. The name *smallpox* 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.

There are two clinical forms of smallpox. Variola major is the severe and most common form of smallpox, with a more extensive rash and higher fever. There are four types of variola major smallpox: ordinary (the most frequent type, accounting for 90% or more of cases); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic (both rare and very severe). Historically, variola major has an overall fatality rate of about 30%; however, flat and hemorrhagic smallpox usually are fatal. Variola minor is a less common presentation of smallpox, and a much less severe disease, with death rates historically of 1% or less.

Smallpox outbreaks have occurred from time to time for thousands of years, but the disease is now eradicated after a successful worldwide vaccination program. The last case of smallpox in the United States was in 1949. The last naturally occurring case in the world was in Somalia in 1977. 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.

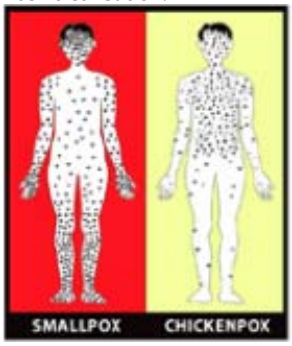
Where Smallpox Comes From

Smallpox is caused by the variola virus that emerged in human populations thousands of years ago. Except for laboratory stockpiles, the variola virus has been eliminated. However, in the aftermath of the events of September and October 2001, there is heightened concern that the variola virus might be used as an agent of bioterrorism. For this reason, the U.S. government is taking precautions for dealing with a smallpox outbreak.

Transmission

Generally, direct and fairly prolonged face-to-face contact is required to spread smallpox from one person to another. Smallpox also can be spread through direct contact with infected bodily fluids or contaminated objects such as bedding or clothing. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains. Humans are the only natural hosts of variola. Smallpox is not known to be transmitted by insects or animals.

A person with smallpox is sometimes contagious with onset of fever (prodrome phase), but the person becomes most contagious with the onset of rash. At this stage, the infected person is usually very sick and not able to move around in the community. The infected person is contagious until the last smallpox scab falls off.

Smallpox Disease	
Incubation Period **(Duration: 7 to 17 days)** ***Not contagious***	**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)*** **(Duration: 2 to 4 days)** ***Sometimes contagious****	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 on their normal activities. This is called the *prodrome*phase and may last for 2 to 4 days.
Early Rash **(Duration: about 4 days)** ***Most contagious*** **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 becomes **most contagious**. Around the time the sores in the mouth break down, a rash appears on the skin, starting on the face and 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 the third day of the rash, the rash becomes raised bumps. By the fourth day, the bumps fill with a thick, opaque fluid and often have a depression in the center that looks like a bellybutton. (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 **(Duration: about 5 days)** ***Contagious***	The bumps become **pustules**—sharply raised, usually round and firm to the touch as if there's a small round object under the skin. People often say the bumps feel like BB pellets embedded in the skin.
Pustules and Scabs **(Duration: about 5 days)** ***Contagious***	The pustules begin to form a crust and then **scab**. By the end of the second week after the rash appears, most of the sores have scabbed over.
Resolving Scabs **(Duration: about 6 days)** ***Contagious***	The scabs begin to fall off, leaving marks on the skin that eventually become pitted **scars**. Most scabs will have fallen off three weeks after the rash appears. The person is contagious to others until all of the scabs have fallen off.
Scabs resolved ***Not contagious***	Scabs have fallen off. Person is no longer contagious.

Smallpox Case Definitions

Introduction

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% of smallpox cases in previously unvaccinated individuals and 70% of cases that occurred in previously vaccinated individuals who were no longer fully protected by vaccination.

Because the likelihood of reintroduction of smallpox is extremely low, and acknowledging that there are many other causes of vesicular and pustular rash illnesses, healthcare providers evaluating such cases should also familiarize themselves with diseases that can be confused with smallpox (e.g., varicella, herpes simplex, drug reactions, erythema multiforme), as well as the clinical manifestations of smallpox disease. In this way, in the unlikely event of a smallpox case, the disease will be clearly and quickly recognized.

Case definition

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*

- 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.

*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.

Note: 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.

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 (www.bt.cdc.gov/agent/smallpox/diagnosis/evalposter.asp).

Case classification

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:

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 1-4 days.

Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States

Introduction

This protocol has been developed to illustrate the types of laboratory testing to be undertaken in different situations involving patients with acute, generalized vesicular or pustular rash illness. The protocol is composed of four charts, each illustrating a different set of symptoms or circumstances. It has been designed to correlate with .Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol.

Chart 1 lists the symptoms associated with acute, generalized vesicular or pustular rash illness and categorizes the risk of smallpox according to the patient.s signs and symptoms.

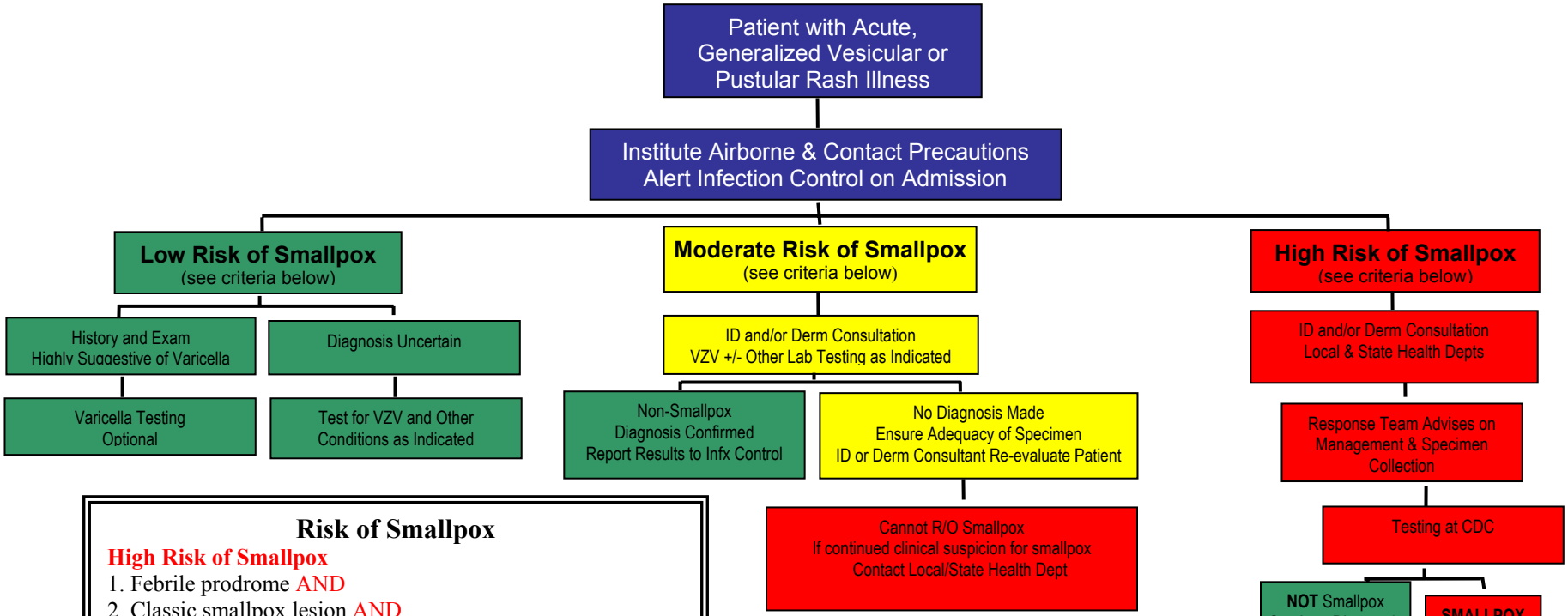
Chart 2 presents a flow chart for laboratory testing of specimens from patients presenting with acute generalized vesicular or pustular rash illness. A two-armed algorithm is presented to reduce the time to receive results and to ensure that testing of high-risk specimens is confined to laboratories with appropriate biosafety levels and expertise. The two arms of the testing algorithm are for 1) specimens from individuals with low- and moderate-risk symptoms and 2) specimens from individuals with high-risk symptoms.

Chart 3 presents a testing algorithm that should be used when a smallpox vaccine adverse event or monkeypox infection is suspected.

Chart 4 presents an orthopoxvirus testing algorithm for environmental samples.

The testing protocols are supported at Laboratory Response Network (LRN) reference laboratories. Details for performance and interpretation of each assay are specified in each LRN procedure.

Chart 1. Acute, Generalized Vesicular or Pustular Rash Illness Protocol



Risk of Smallpox

High Risk of Smallpox
1. Febrile prodrome AND
2. Classic smallpox lesion AND
3. Lesions in same stage of development

Moderate Risk of Smallpox
Febrile prodrome AND one other MAJOR smallpox criterion
OR
Febrile prodrome AND ≥4 MINOR smallpox criteria

Low Risk of Smallpox
No febrile prodrome
OR
Febrile prodrome AND <4 MINOR smallpox criteria

Major smallpox criteria:
- Febrile prodrome
  - >101F, 1-4 days prior to rash onset
  - with headache, back ache, or abdominal pain
- Firm, deep seated, well circumscribed vesicles/pustules
- Lesions in the same stage of development in any one area of the body

Minor smallpox criteria:
- Centrifugal distribution
- First lesions in the pharynx, oral mucosa
- Patient appears "toxic"
- Slow evolution of rash
  - ➤ 1-2 days each stage: macule, papule, vesicle
- Lesions on the palms and soles

Chart 2. Laboratory Testing for Acute, Generalized Vesicular or Pustular Rash Illness in the United States

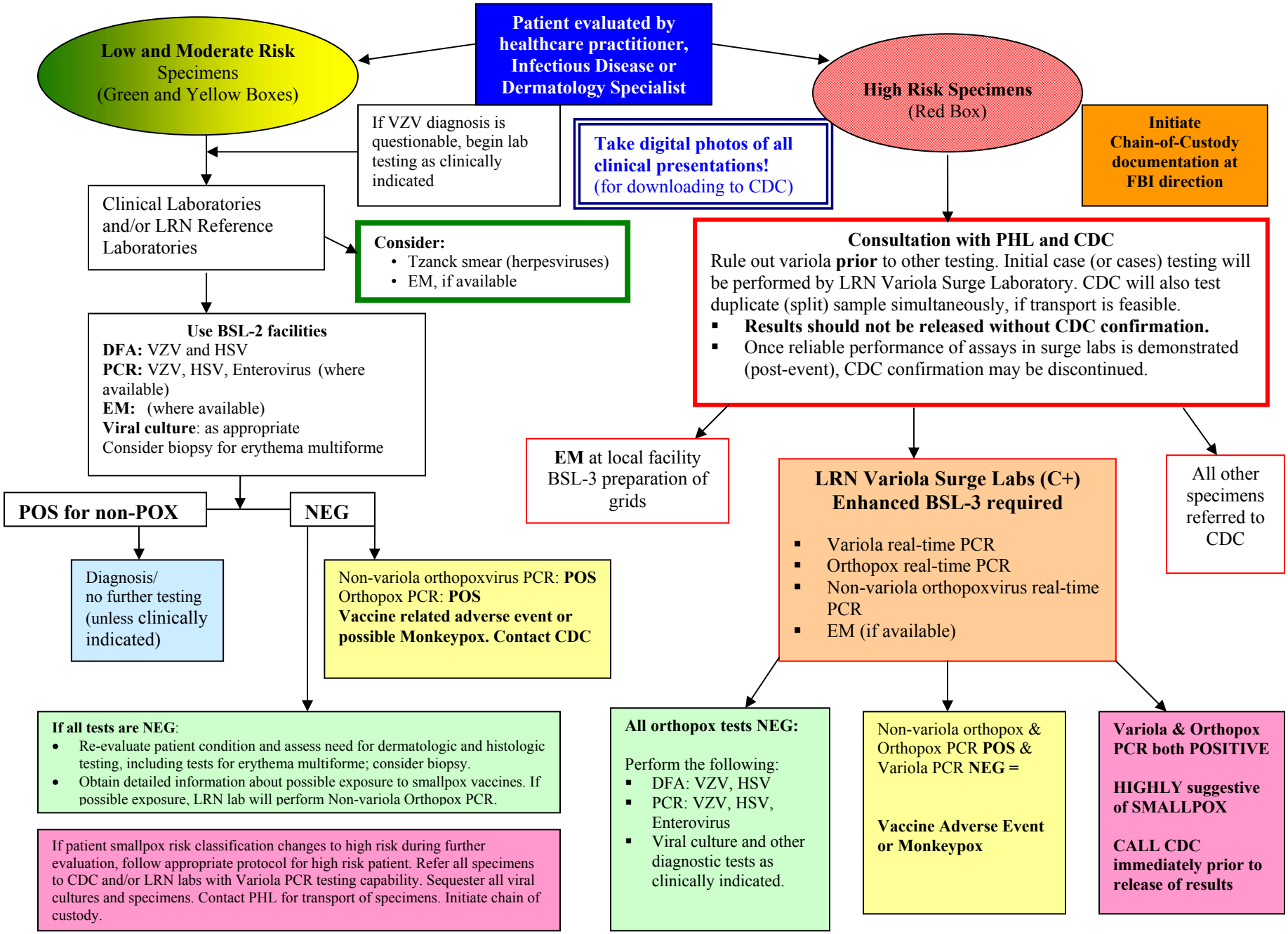


Chart 3. Laboratory Testing for Suspected Smallpox Vaccine (Vaccinia) Adverse Events or Monkeypox in the United States

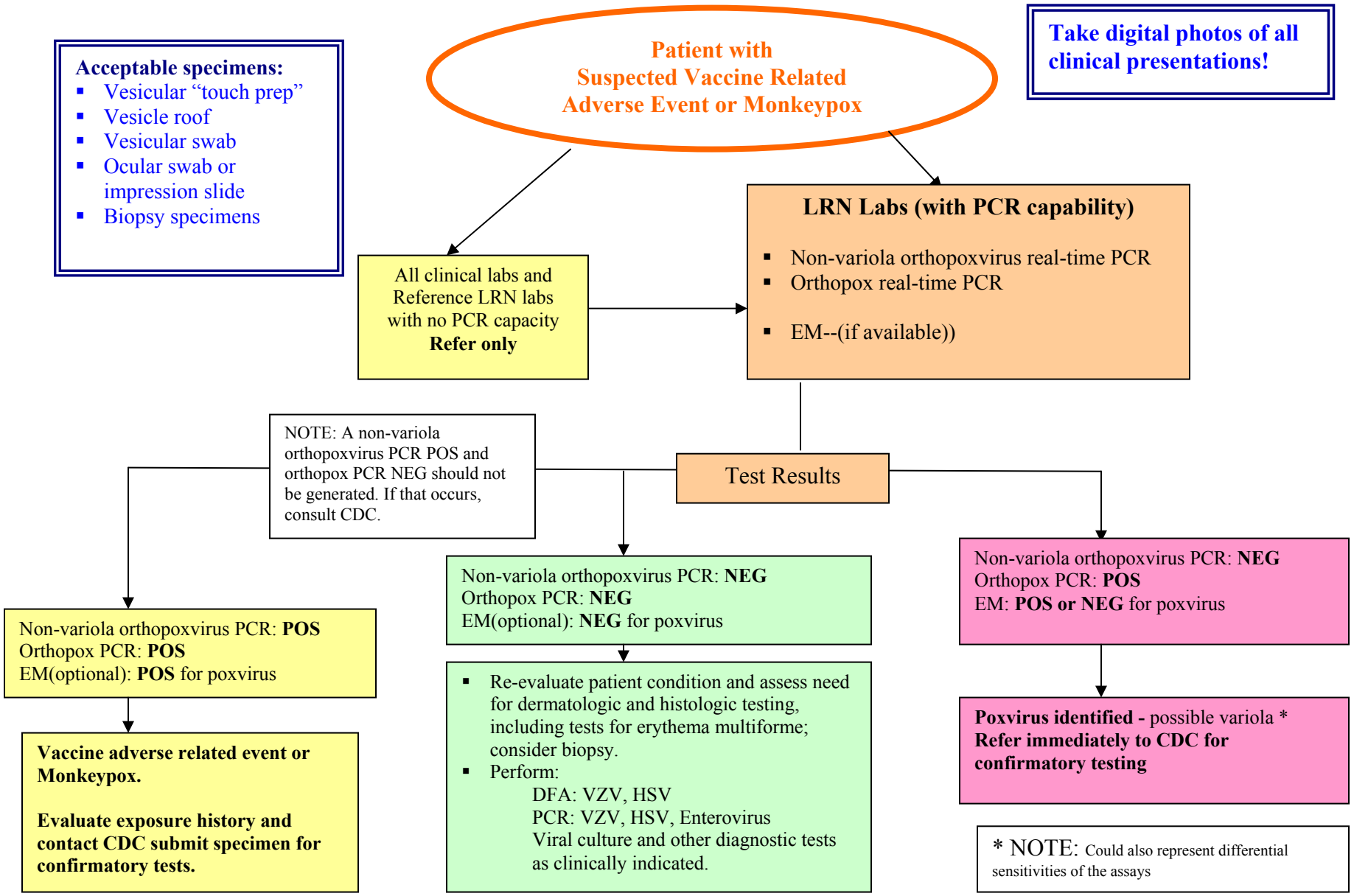
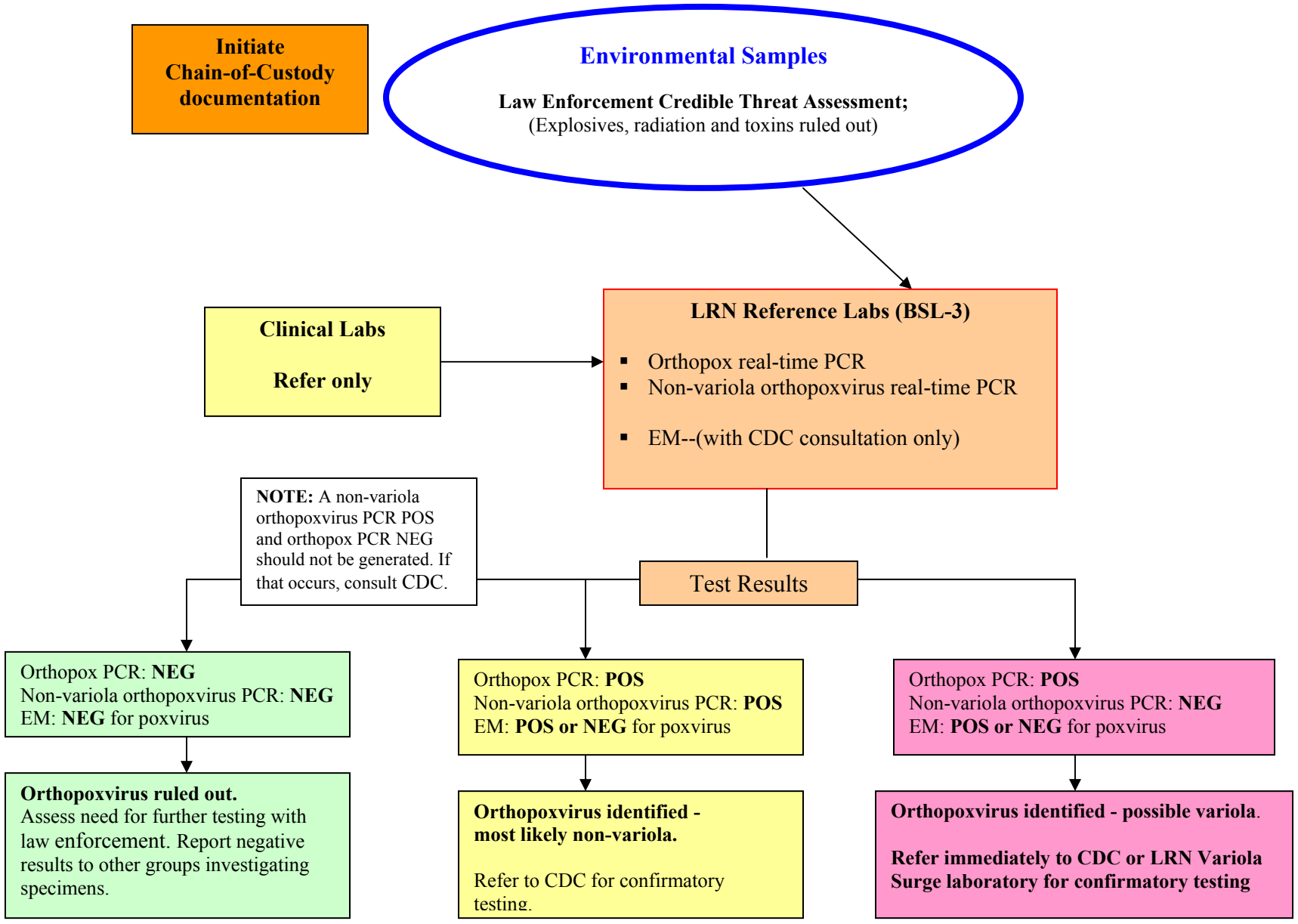


Chart 4. Laboratory Testing for Environmental Samples in the United States



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

CLINICAL NOTES

SOURCE / EXPOSURE INFORMATION

Is chickenpox (varicella) occurring in the community? ☐ Yes ☐ No ☐ Unknown

Has the patient had contact with a person with chickenpox or shingles 10-21 days before rash onset? ☐ Yes ☐ No ☐ Unknown

If *Yes*, give date(s) and type of contact: _____

In the 3 weeks before onset of illness: *(applies to remainder of section)*

Has the patient been in contact with a person with any other rash illness? ☐ Yes ☐ No ☐ Unknown

If *Yes*, please specify, with date: _____

Has the patient traveled? ☐ Yes ☐ No ☐ Unknown

If *Yes*, please provide locations and dates of travel:

Place: _____ Dates: _____

Place: _____ Dates: _____

Has the patient had contact with mice? ☐ Yes ☐ No ☐ Unknown

Has the patient been camping, hiking, or exposed to woods before onset of illness? ☐ Yes ☐ No ☐ Unknown

If *Yes*, please provide details and dates:

_____ Dates: _____

_____ Dates: _____

Has the patient received insect bites? ☐ Yes ☐ No ☐ Unknown

Has the patient been exposed to ticks? ☐ Yes ☐ No ☐ Unknown

VACCINATION HISTORY

Has the patient received chickenpox (varicella) vaccine? ☐ Yes ☐ No ☐ Unknown
(Chickenpox vaccine was licensed in the United States in 1995.)

If *Yes*, dose #1 date ____/____/____ or age _____

dose #2 date ____/____/____ or age _____
(only persons >13 years receive a second dose)

Has the patient ever received smallpox vaccine? ☐ Yes ☐ No ☐ Unknown
(The smallpox vaccine was routinely given in the U.S. until 1972, was recommended for health care providers until 1976, was administered in the military until 1990.)

If *Yes*, when was the most recent vaccination? ____/____/____
or at what age? _____

MEDICAL HISTORY

Has the patient ever had chickenpox or shingles? ☐ Yes ☐ No ☐ Unknown

If *Yes*, when? ____/____/____ or at what age? _____

Is the patient immunocompromised? ☐ Yes ☐ No ☐ Unknown

If *Yes*, specify type of illness *(e.g., cancer, HIV/AIDS)* _____

Does the patient have any other serious underlying medical illnesses? *(e.g., asthma)* ☐ Yes ☐ No ☐ Unknown

If *Yes*, please list: _____

Is the patient sexually active? ☐ Yes ☐ No ☐ Unknown

Is the patient pregnant? ☐ Yes ☐ No ☐ Unknown

MEDICATIONS

Is the patient on medications that suppress the immune system? *(e.g., steroids, chemotherapy, radiation)* ☐ Yes ☐ No ☐ Unknown

If *Yes*, name of medication: _____
Dosage: _____
Method of administration: _____

Is the patient taking antiviral medications? ☐ Yes ☐ No ☐ Unknown

If *Yes*, name of medication: _____
Dosage: _____
Method of administration: _____

Please list all prescription and non-prescription medications that the patient has taken in the past three weeks. *(List drug, dosage, route, dates)*

Is there a history of illicit drug use? ☐ Yes ☐ No ☐ Unknown

If *Yes*, please specify drug, amount (if known), route, and dates:

DIFFERENTIAL DIAGNOSIS

LABORATORY

Other lab testing — Please complete last page

Have you tested the patient for chickenpox? ☐ Yes ☐ No ☐ Unknown

If *Yes*, what type of test? _____

Results of tests: _____

Date: ____/____/____

Other comments: _____

DISPOSITION

Risk of smallpox
using CDC criteria (available at www.cdc.gov/nip/smallpox):

☐ **Low** ☐ **Moderate** ☐ **High*** ☐ **Unknown**
**If checked, see contact checklist below in Immediate Response Information*

IMMEDIATE RESPONSE INFORMATION

☐ Institute airborne and contact precautions
☐ Alert infection control
☐ Take digital photographs of rash
☐ Consult ID and/or dermatology

IF THE PATIENT IS AT HIGH RISK:

☐ Contact local health department

Name: _____ Phone: _____

E-mail: _____ Phone: _____

☐ Contact state epidemiologist

Name: _____ Phone: _____

E-mail: _____ Phone: _____

☐ Contact state BT coordinator

Name: _____ Phone: _____

E-mail: _____ Phone: _____

☐ Contact CDC BT coordinator

Name: _____ Phone: _____

E-mail: _____ Phone: _____

24-HOUR FOLLOW-UP INFORMATION

Date of follow -up: ____/____/____

Person making follow-up: _____

Condition of patient: _____

Risk of smallpox 24 hours later: ☐ Low ☐ Moderate ☐ High ☐ Unkn

Action taken: _____

Diagnosis: _____

Was diagnosis confirmed? ☐ Yes ☐ No ☐ Unknown

How was diagnosis confirmed? _____

48-HOUR FOLLOW-UP INFORMATION

Date of follow -up: ____/____/____

Person making follow-up: _____

Condition of patient: _____

Risk of smallpox 48 hours later: ☐ Low ☐ Moderate ☐ High ☐ Unkn

Action taken: _____

Diagnosis: _____

Was diagnosis confirmed? ☐ Yes ☐ No ☐ Unknown

How was diagnosis confirmed? _____

72-HOUR FOLLOW-UP INFORMATION

Date of follow -up: ____/____/____

Person making follow-up: _____

Condition of patient: _____

Risk of smallpox 72 hours later: ☐ Low ☐ Moderate ☐ High ☐ Unkn

Action taken:

Diagnosis: _____

Was diagnosis confirmed? ☐ Yes ☐ No ☐ Unknown

How was diagnosis confirmed? _____

www.cdc.gov/smallpox

CLINICAL NOTES

PLEASE LIST ALL LABORATORY TESTS ORDERED OR PERFORMED REGARDING THIS ILLNESS

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

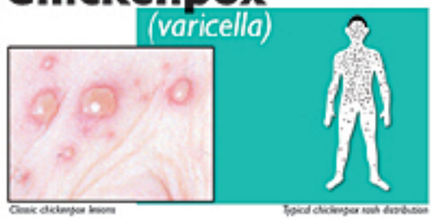
Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Date: ______/______/______ Results: ____________________
Disease: ____________________
Test: ____________________
Laboratory: ☐ State
☐ Other ____________________

Evaluating Patients for Smallpox

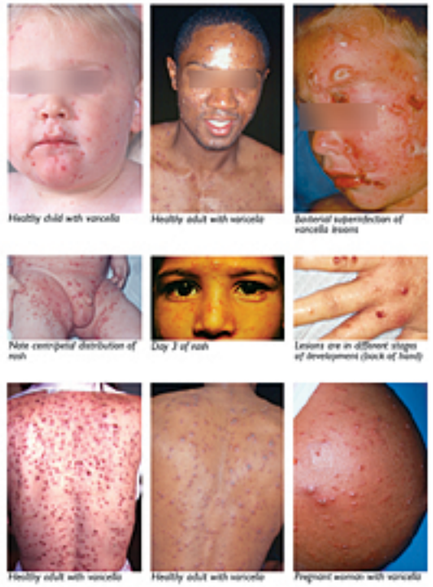
Acute, Generalized Vesicular or Pustular Rash Illness Protocol

Chickenpox (varicella)



Classic chickenpox lesions — Typical chickenpox rash distribution

Images of Chickenpox (Varicella)



Healthy child with varicella — Healthy adult with varicella — Bacterial superinfection of varicella lesions

Note centripetal distribution of rash — Day 3 of rash — Lesions are in different stages of development (back of hand)

Healthy adult with varicella — Healthy adult with varicella — Pregnant woman with varicella

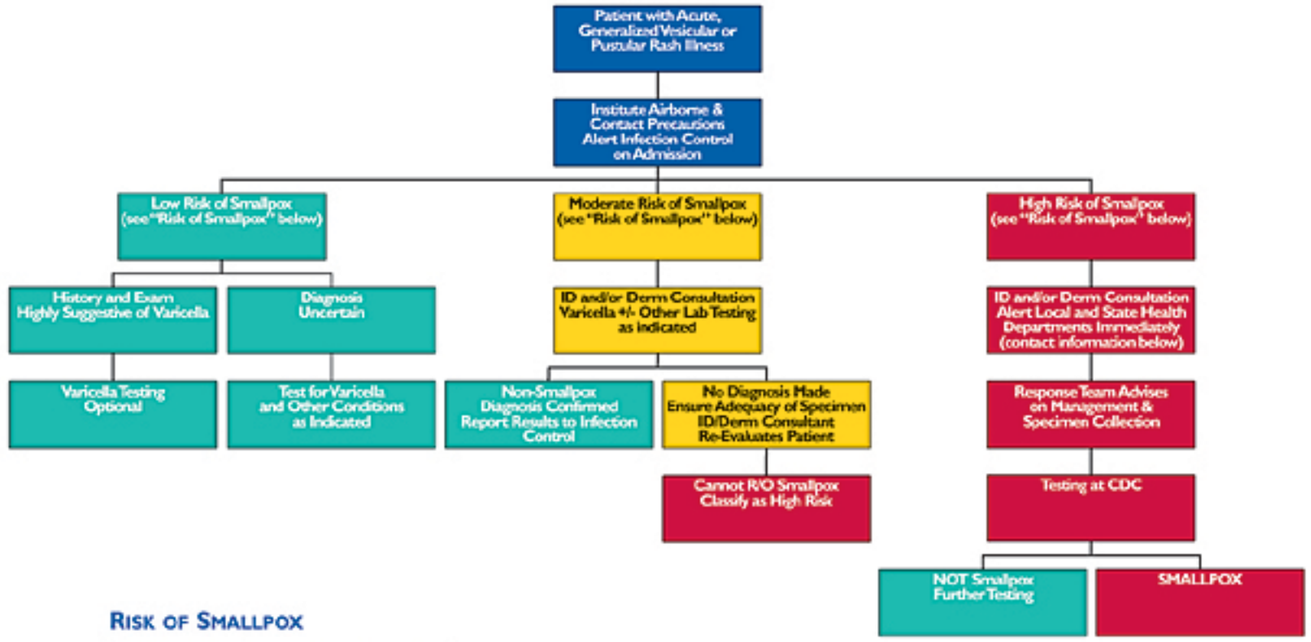
Differentiating Chickenpox from Smallpox

Chickenpox (varicella) is the most likely condition to be confused with smallpox.

In chickenpox:

- No or mild prodrome
- Lesions are superficial vesicles: "dewdrop on a rose petal" (see photo at top)
- Lesions appear in crops; on any one part of the body there are lesions in different stages (papules, vesicles, crusts)
- Centripetal distribution: greatest concentration of lesions on the trunk, fewest lesions on distal extremities. May involve the face/scalp. Occasionally entire body equally affected.
- First lesions appear on the face or trunk
- Patients rarely toxic or moribund
- Rapid evolution: lesions evolve from macules => papules => vesicles => crusts quickly (<24 hours)
- Palms and soles rarely involved
- Patient lacks reliable history of varicella or varicella vaccination
- 50-80% recall an exposure to chickenpox or shingles 10-21 days before rash onset

Photo Credits: Dr. Thomas Mack, Dr. Barbara Watson, Dr. Scott A. Norton, Dr. Patrick Algaire, World Health Organization, American Academy of Pediatrics, American Academy of Dermatology



Risk of Smallpox

High Risk of Smallpox => Report Immediately

1. Febrile prodrome (defined below) **AND**
2. Classic smallpox lesion (defined below & photo at top right) **AND**
3. Lesions in same stage of development (defined below)

Moderate Risk of Smallpox => Urgent Evaluation

1. Febrile prodrome (defined below) **AND**
2. One other **MAJOR** smallpox criterion (defined below)

OR

1. Febrile prodrome (defined below) **AND**
2. ≥4 **MINOR** smallpox criteria (defined below)

Low Risk of Smallpox => Manage as Clinically Indicated

1. No febrile prodrome

OR

1. Febrile prodrome **AND**
2. <4 **MINOR** smallpox criteria (defined below)

There have been no naturally occurring cases of smallpox anywhere in the world since 1977. A high risk case of smallpox is a public health and medical emergency.

Report ALL HIGH RISK CASES immediately (without waiting for lab results) to:

1. Hospital Infection Control _____ ( ) _____-_____
   _____ ( ) _____-_____
2. _____ health department ( ) _____-_____
   ( ) _____-_____
3. _____ health department ( ) _____-_____
   ( ) _____-_____

MAJOR Smallpox Criteria

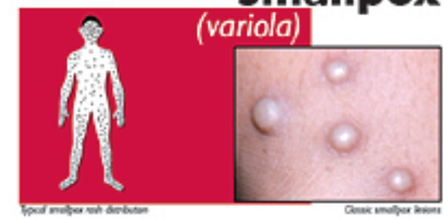
- **FEBRILE PRODROME:** occurring 1-4 days before rash onset: fever ≥101°F and at least one of the following: prostration, headache, backache, chills, vomiting or severe abdominal pain.
- **CLASSIC SMALLPOX LESIONS:** deep-seated, firm/hard, round well-circumscribed vesicles or pustules; as they evolve, lesions may become umbilicated or confluent
- **LESIONS IN SAME STAGE OF DEVELOPMENT:** on any one part of the body (e.g., the face, or arm) all the lesions are in the same stage of development (i.e., all are vesicles, or all are pustules)

MINOR Smallpox Criteria

- Centrifugal distribution: greatest concentration of lesions on face and distal extremities
- First lesions on the oral mucosa/palate, face, or forearms
- Patient appears toxic or moribund
- Slow evolution: lesions evolve from macules to papules => pustules over days (each stage lasts 1-2 days)
- Lesions on the palms and soles

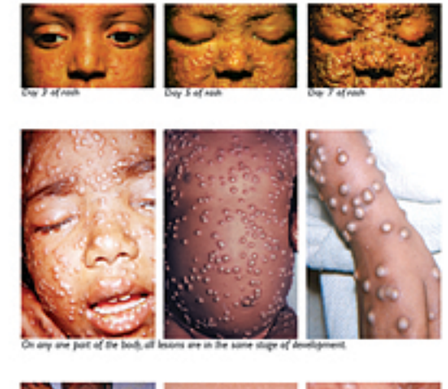
Department of Health and Human Services
Centers for Disease Control and Prevention

Smallpox (variola)



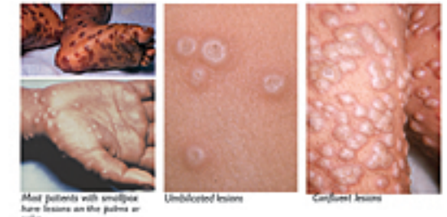
Typical smallpox rash distribution — Classic smallpox lesions

Images of Smallpox



Day 3 of rash — Day 5 of rash — Day 7 of rash

On any one part of the body, all lesions are in the same stage of development.



Most patients with smallpox have lesions on the palms or soles — Umbilicated lesions — Confluent lesions

Common Conditions That Might Be Confused with Smallpox

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

For more information, please go to the CDC website http://www.cdc.gov/nip/smallpox and http://www.bt.cdc.gov/Erv/ContactIndex.asp

Smallllpox Vaccine Components

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

Smallpox

Guidelines for Smallpox Vaccine Packing & Shipping

DISCLAIMER

The use of proprietary names and description of specific manufacturers' products does not imply endorsement by the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

Table of Contents

1. INTRODUCTION

Vaccines protect children and adults from potentially disabling and sometimes fatal diseases. If vaccines are improperly handled, they can lose their potency and must be replaced. Replacing vaccines can be costly — a shipment of vaccines can be worth hundreds, thousands or tens of thousands of dollars. It can also be costly to the providers' confidence in having properly immunized patients, and the patients' trust of the provider and of vaccines.

Every site that ships smallpox vaccines and their diluents should have its own standard operating procedures (SOPs), which describe procedures, training, supervision and record keeping to ensure continuous quality assurance year after year. In order to help you develop your procedures, the National Immunization Program of the Centers for Disease Control and Prevention has prepared the following guidelines for smallpox vaccine packing and shipping. These guidelines are based in part on CDC's research on different shipping and handling methods under strenuous test conditions. These guidelines are not intended to be rules and regulations. They are suggestions written primarily for personnel who pack and ship vaccines.

If you desire additional information on shipping and shipping materials, contact the National Immunization Program at CDC, at the following address:

Attention: Program Support Branch, Immunization Services Division
Mailstop E–52, 1600 Clifton Road
Atlanta, Georgia 30333
Telephone: (404) 639-8222

2. PROTECTING SMALLPOX VACCINES & DILUENT

The individual smallpox vaccine vial, the appropriate amount of reconstituting diluent in a syringe, and the appropriate number of bifurcated needles for administering the vaccine are usually combined ("kitted") as a single packet ("kit"). As needed, one or more "kits" is then packed and shipped to a designated receiver (clinic).

Smallpox vaccine should always be protected from heat, and should never be frozen.

Diluents should not be frozen.

Smallpox vaccine must be kept at appropriate temperatures to retain effectiveness. There are two major problems in storing and handling vaccines which can rapidly reduce their potency: either 1) freezing vaccines that should not be frozen, or 2) letting infectious (live) vaccines warm.

Smallpox vaccine, like DTaP, Hep A, Hep B, Hib, PCV and IPV, should never be frozen and should be kept between 2°– 8°C (36° – 46°F)

THE "COLD CHAIN"

Keeping vaccines at the proper temperature at all times is called **maintaining the cold chain.** The cold chain starts at the manufacturer, and continues until the vaccine is used at the clinic or physician's office. Remember that it is as important to keep smallpox vaccine from freezing as it is to keep other vaccines from getting too warm. It's up to you to see that the "cold chain" isn't broken.

Cold storage unit monitors should have their temperatures certified annually against reference thermometers. Storage temperatures should be maintained between 2°– 8°C (36° – 46°F) for smallpox and other non-frozen vaccines. Since, in any 24-hour period, the temperature in the refrigerator will often rise or fall a few degrees, it is a good idea to set the temperature at mid-range, about 5°C (40°F). You need a continuous temperature monitor that gives a visual record of the temperature fluctuations in the refrigerator (Figure 1).

An example of a temperature chart is shown on the next page. You will usually need to change the graph paper weekly. (Digital monitors that record data directly into a computer database are also available.) You should keep the temperature records for three years to prove that your refrigerator performed correctly over time.

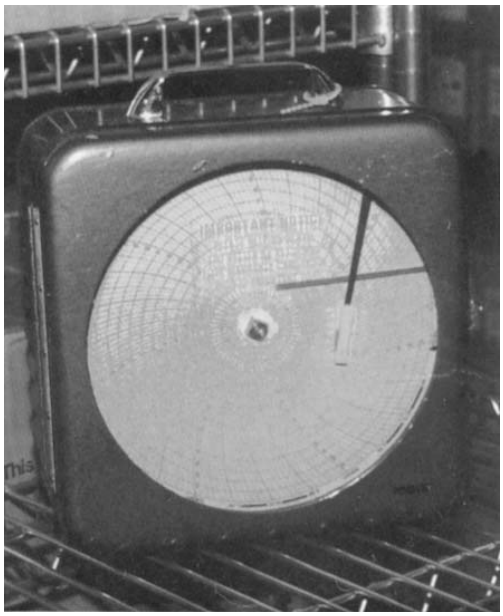
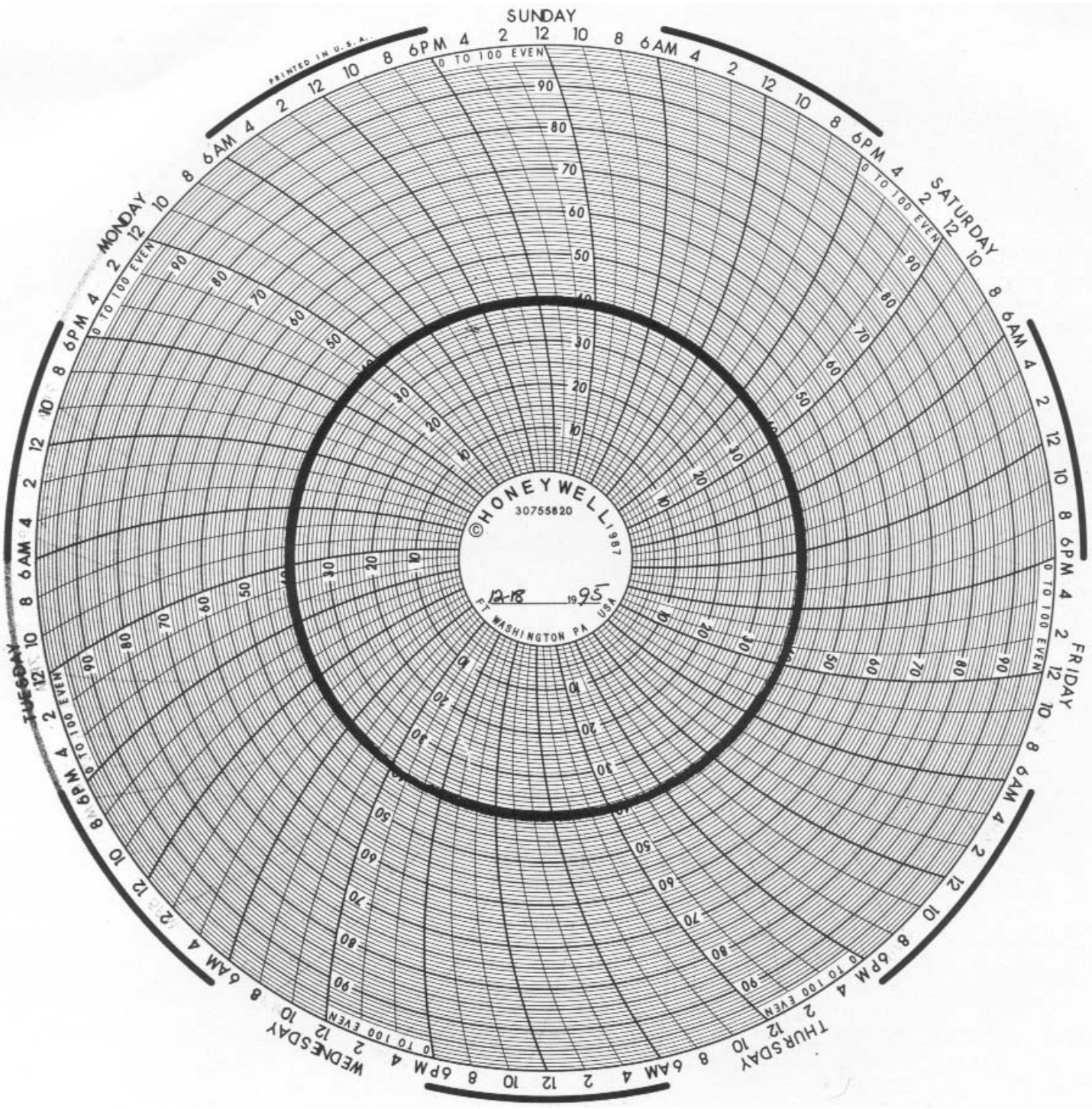


Figure 1 A continuous temperature monitor



This sample chart shows the evenness of temperatures in a cold room during one week. Note the temperature is set at mid-range, about 5°C (40°F).

Consider a security system for the cold unit which will give a local and a remote warning if there are problems with the power or temperature (Figure 2). There should be a regular, and a back-up, alarm in distribution centers where the smallpox vaccine is stored. Such an alarm system must alert a guard, or call a certain phone number in case of a power failure or temperature problem. Be sure everyone knows how the system works, and how to reach someone responsible for the vaccines. It's correct procedure to have a written emergency plan ("Disaster Recovery Plan") posted, so staff know what to do if the power is out in the cold facility or there is a mechanical failure.

Figure 2 An alarm system that calls you or a guard if there is a temperature malfunction.

All deviations from normal temperatures or procedures should be reported in writing to supervisors and managers, and any responses taken should be recorded, also.

Other tips are:

- Have a back-up generator in case of a power failure (Figure 3). Routine testing (weekly) assures the generator will work if needed. Critical spare parts should be available on demand for rapid repairs.

- After installing or repairing a refrigerator, allow time (~ 72 hours) for the temperature to stabilize before loading vaccines into it.

Your vaccine storage area, or cold facility, should be physically secure at all times. It's a good idea to keep the vaccine facility locked. A designated person, and a back-up person, should have access to the facility. A "Restricted to Authorized Personnel" sign may be helpful. (See **Appendix I** for Vaccine Do's.)

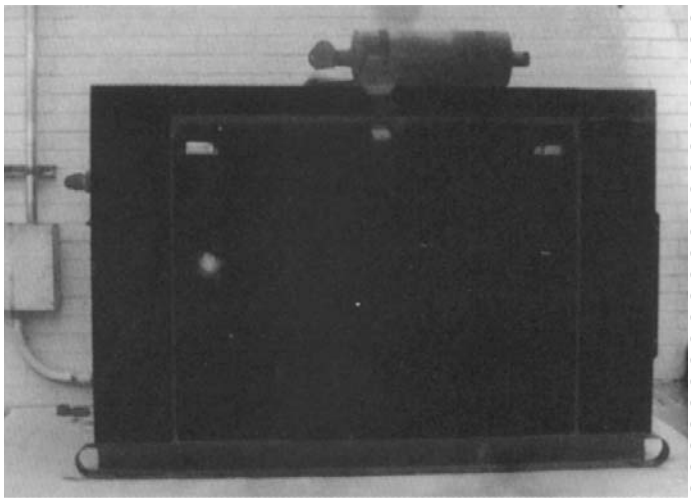


Figure 3 A back-up generator takes over if the power fails. However, it should be tested and serviced regularly so that it will start when you need it.

3. SHIPPING MATERIALS

SHIPPING BOXES

Boxes should be sturdy and the right size for shipping the amount of vaccines needed. It's a good idea to have several sizes of insulated boxes on hand (Figure 4). You might code those sizes (e.g., A, B, C) and note that size on the shipping label. That way, if a box is lost in transit, you and the shipping company will know which size box you're looking for.

INSULATION

There are a number of ways to insulate your vaccine shipment. Types of insulation are:

- Molded polystyrene boxes which may be shipped inside a cardboard box. (See Figure 5.)
- Isocyanurate panels of foil and plastic with mitered corners inside a cardboard box. These have the advantage of folding flat for storage. (See Figure 6.)
- Polyurethane foam molded between cardboard formers (may be damaged by water. See Figure 7.) Plastic-coated boxes are more durable, but more expensive.

The insulating quality ("R Value") depends on the material and its thickness. Polystyrene boxes with walls approximately 2 inches thick, or isocyanurate panels approximately 1 inch thick, may provide a suitable balance between price and performance.

Figure 4 Various sized boxes for vaccine shipping.

Figure 5 Expanded polystyrene box inside a cardboard box.

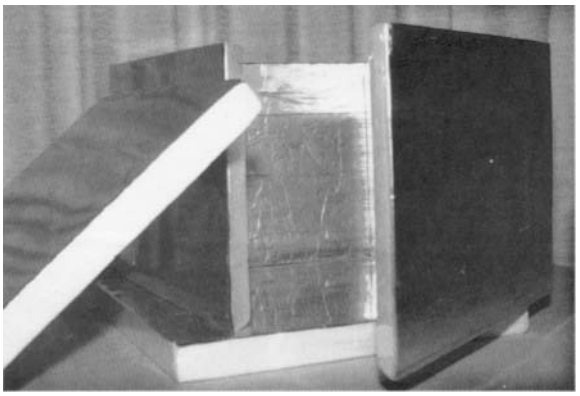


Figure 6 Isocyanurate panels covered with foil and plastic, having mitered corners..

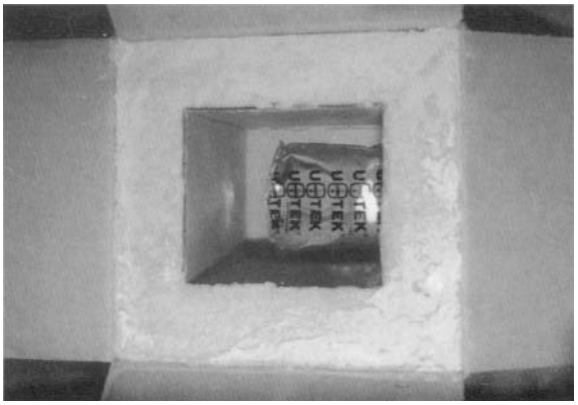


Figure 7 Polyurethane foam between cardboard formers.

FILLERS

Fillers are used in empty spaces to prevent shifting of vaccines and cold packs during shipment. They do not provide reliable insulation.

Fillers include:

- Brown packing paper. CDC tested 2-ply layers of crumpled brown paper; one ply was a "30-lb" face, the second ply was a "50-lb" face (Figure 8).

- Styrofoam pellets or "peanuts" or bubble wrap or similar materials (Figure 9).

Fillers are also used to separate frozen cold packs from the vaccines to prevent freezing.

Figure 8 Paper filler which has been crumpled before use.

Figure 9 Styrofoam "peanuts" are also used as filler.

COLD PACKS AND COOL PACKS

To maintain the cold chain when shipping vaccines, a cold source (or sometimes a "cool" source) is needed. Cold (or cool) sources are:

- Permanently sealed, thin-walled "gel packs" or "blue-ice." These can be reused, but may leak slightly if damaged. They are flexible when not frozen. (See Figure 10)

- Capped plastic bottles filled with a frozen liquid (water or chemical). Those tested by the World Health Organization (WHO) have special sealing plugs and caps that do not leak, except under exceptional conditions. These bottles can be emptied and refilled. (See Figure 11)

In CDC's tests, the pac performance of gel packs and bottles was similar on a weight to weight basis. Gel packs (or blue-ice) are usually kept in a freezer until they are ready to be included in a shipment. For conditions that need frozen cold packs, it's best that they are "warmed" at room temperature until they are at about -5°C (23°F).

This may take 15 minutes or more, depending on how cold the packs are to begin with, and how they are placed for warming.

Figure 10 Permanently sealed, thin-walled "gel packs."

Warming will be quicker when the frozen packs are separated from each other with good circulation of room temperature air than if they are stacked together. For simplicity and consistency, freezing cold packs in a special freezer at -5°C (23°F) might be helpful in some facilities.

The choice of cold pack is best determined by the convenience of fit into the shipping package; for example, which size is easiest to use.*

* In CDC's tests, a single 24 oz. pack covered the top or bottom of a "small" box (about 5"x6"), and 4 packs completely covered the top or bottom of a "large" box (about 12" square).

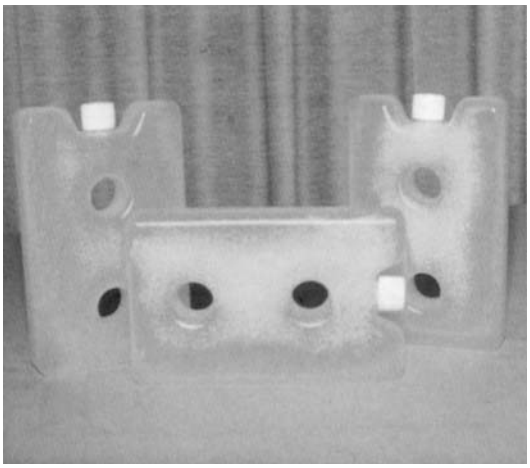


Figure 11 WHO-tested, thick-walled plastic bottles with leak-proof caps.

TEMPERATURE MONITORS

There are a number of monitors that can measure the temperature inside your packages. You may consider including at least one heat indicator and one cold indicator in every box, with instructions on how to interpret them. More monitors may be useful to measure temperatures in different places inside larger boxes.

CDC tested the following monitors:

- Time/temperature tags which monitor temperatures warmer than 10°C (50°F). After pulling the activation tab, an irreversible blue dye is released in the windows as they are exposed to temperatures warmer than 10°C(50°F). The more blue windows, the higher the temperature reached inside the box or the longer the time at temperatures warmer than 10°C (50°F) (Figure 12).

- Color-change monitors, which detect exposure to temperatures colder than 0°C (32°F), by releasing a red dye marker into a visible bulb. Particularly useful in very cold weather (Figure 13).

- Analog disposable recording temperature monitors which produce linear strip charts over a 4-day period. They may be appropriate for large, expensive shipments (Figure 14). (Electronic, digital recording thermometers are available, also.)

(See **Appendix 2A** for instructions on using monitors, and **Appendix 2B** for instructions on reading monitors when received in vaccine shipments.)

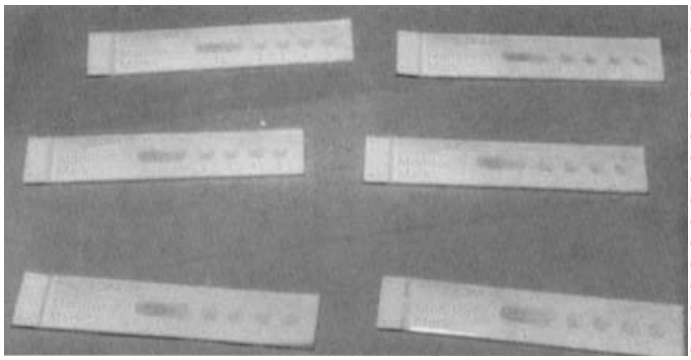


Figure 12 The windows in a time/temperature tag turn blue as the temperature inside the package reaches more than 10°C (50°F).

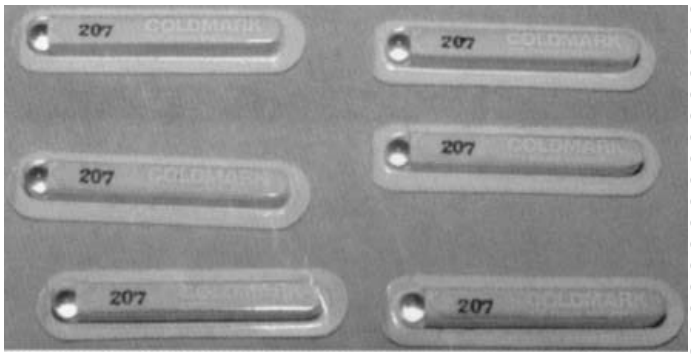


Figure 13 A color-change monitor releases an irreversible red dye if the temperature inside the package reaches the freezing point of water.

Figure 14 Analog disposable recording temperature monitors which use a battery powered motor to pull a strip chart. The chart is obtained by breaking open the recorder box.

INSERTS/INFORMATION

A packing slip with the contents and a telephone number to call with vaccine inquiries should be included.

SEALERS

To assure that the package is tightly sealed and that the vaccines don't spill or shift during shipping, seal the packages well with tape or strapping.

Sealers include:

- Self-adhesive tape which can be used to seal all lids very tightly on polystyrene containers and to seal the top flaps on outer cardboard boxes of all packages.

- Plastic strapping machines are also used to seal outer boxes.

LABELS

After the boxes are sealed, it is important to mark the boxes as clearly as possible to designate the contents – valuable and fragile vaccines. A variety of stickers are available. (See **Appendix 3** for samples of labels.)

COMMERCIAL CARRIERS

It is important that commercial carriers charged with getting your vaccines to the provider fully understand their responsibility. The more clearly you can specify your requirements and work with the contractor(s) of choice, the better the results, and the more likely you and the recipient will be satisfied.

(See **Appendices 4 and 5** for a list of packing materials you will need and examples of sources.)

4. THE PACKING PROCESS

ESTABLISHING A ROUTINE — THE NEED FOR STANDARD OPERATING PROCEDURES

It is important to establish a routine, systematic process for handling smallpox vaccine orders. Many facilities find that an "assembly line-type" procedure works best. It helps avoid confusion, protects the cold chain, and helps ensure that the order is filled properly.

We suggest that only one box be packed at a time at each packing station. (See **Appendix 6** for a sample procedure. You may want to adapt this system to fit your needs, or you may want to devise a totally different program.)

Each facility should develop its own standard operating procedures (SOPs), covering every aspect of work; receiving, storing, and packing and shipping smallpox vaccines. You may want to test various materials and packing configurations to see what works best for your situation. The following "How-to's" are examples of packing based on tests by CDC.

In order to comply with good manufacturing practices, written SOPs should also exist, and be followed, for training and monitoring staff performing the work. Otherwise, there can be no assurance that procedures will continue to be followed, and problems identified, reported, and corrected.

COOLING REQUIREMENTS FOR SMALLPOX VACCINE SHIPMENTS

Smallpox vaccine should never be frozen.

Cold packs (i.e., # 0°C, 32°F) should be used to keep smallpox vaccine temperature at 2°– 8°C (36° – 46°F) during shipping to ensure potency.

Temperature monitors should normally be used.

To keep vaccines from freezing while also keeping them from getting too warm during shipping, you can: 1) vary the temperature of the "cold" packs, and/or 2) vary the number of "cold" packs used, based on the outside temperature. The quality of the insulation will also affect the internal package temperatures. When using boxes of similar quality as those tested by CDC, the following guidelines are suggested.

Example 1 — "hot weather"
In "hot weather," temperatures warmer than 25°C (75°F), use enough cold packs to fully cover two or more faces (e.g., top and bottom or front and back) of the inside of the package. These "cold" packs should be at 0°C (32°F). This should maintain internal temperatures for up to 48 hours.

Example 2 — "temperate weather"
In "temperate weather," 0° – 24°C (32° – 75°F), either pack vaccines as you would for hot conditions, with the "cool" packs at -5°C (23°F), or use enough cool packs to fully cover four sides of the inside of the package.

These "cool" packs should be at +5°C (41°F) for short-term delivery of less than 24 hours.

Example 3 — "cold weather"
In "cold weather," vaccine packages may be exposed to temperatures colder than 0°C (32°F) outside, but also, to temperatures of 24°C (75°F) in a heated indoor area. There is a significant risk that vaccines will freeze when left in unheated locations outdoors. Therefore, use enough cool packs to fully cover all six sides of the inside of the package. These "cool" packs may be at +10°C (50°F) for short-term delivery up to 24 hours. Protection against freezing during extended outdoor exposure can be obtained with "cool" packs initially at 15°– 20°C (59°– 68°F). (See **Appendix 7** for a climate chart.)

HOW TO PACK SHIPMENTS OF NON-FROZEN VACCINES

Example 1 — small box
(Inside dimensions about 6"x6"x8")
For a small shipment of smallpox vaccine and diluent:

- put one 24 oz (600 gm) cold pack on the bottom (See Figure 15)
- use 4 layers of crumpled 2-ply brown paper or bubble wrap to separate the cold packs from the vaccine kits at the bottom of the package (See Figure 16)
- put the vaccine kits in the center of the vaccine load and close to the cold packs in order to maintain the desired internal temperature range (See Figure 17)
- if the vaccine has been reconstituted, ship the vial inside the stability block. Place additional brown paper around the stability block to assure the vaccine does not tip over. Ship the bifurcated needles with the vaccine.
- place a heat monitor closest to the vaccine (but away from the cold packs) so the receiver can tell if the temperature stayed within the acceptable range during transit
- place a freezing temperature indicator near the outside of the vaccines in winter, or near a cold pack (summer and winter)
- use more brown paper or bubble wrap on top of the vaccines (See Figure 18)
- put one "cold" pack on the top
- add filler, if needed
- enclose a packing list
- seal the box and add labels
- store in the cold unit when there will be a delay (more than 4 hours), or at room temperature (less than 4 hour delay), until the commercial carrier picks it up

Figure 15 Put one cold pack on the bottom of a small box.

Figure 16 Put crumpled brown paper between cold packs and the vaccines.

Figure 17 Put the vaccines close to the cold pack. Put a heat monitor on top of the vaccines, but not adjacent to the cold pack.

Example 2 — medium box
(Inside dimensions about 10"x10"x7")
For a medium shipment of smallpox vaccine and diluent:

- put one 24 oz (600 gm) cold pack on each of two facing sides (See Figure 19)
- use 4 layers of crumpled 2-ply brown paper to separate the vaccines from the bottom and all sides of the box (See Figure 20)
- put the vaccine at the "cold" sides or near the top in order to maintain the desired internal temperature range (See Figure 21)
- place a heat monitor close to the vaccine (but away from the cold packs) so the receiver can tell if the temperature stayed within the acceptable range during transit
- place a freezing temperature indicator near the outside of the vaccines in winter, or near a cold pack (summer and winter).
- use more crumpled brown paper (4 layers of 2-ply) or bubble wrap on top of the vaccines
- put one "cold" pack on the top
- add filler, if needed
- enclose a packing list
- seal the box and add labels
- store in the cold unit or in normal ambient temperature until the commercial carrier picks it up

Example 3 — large box
(Inside dimensions about 12"x12"x12")
For a large shipment of smallpox vaccine and diluent:

- put four 24 oz (600 gm) cold packs on the bottom (See Figure 22)
- use 8 layers of crumpled 2-ply brown paper to separate the cold packs from the vaccine (See Figure 23)

Figure 18 Put more brown paper on top of the vaccines, and put a cold pack on top of the paper.

Figure 19 Put two cold packs on the sides of a medium box for "warm" weather shipping of non-frozen vaccines.

Figure 20 Put crumpled brown paper between the cold packs and the vaccines.

Figure 21 Put the vaccines close to the cold packs. Add more brown paper, and an additional cold pack on top.

- put the vaccines adjacent to the cold packs in order to maintain the desired internal temperature range
- place a heat monitor close to the vaccines (but away from the cold packs) so the receiver can tell if the temperature stayed within the acceptable range during transit (See Figure 24)
- place a freezing temperature indicator near the outside of the vaccines (See Figure 25)
- use more brown paper on top of the vaccines
- put four "cold" packs on the top (See Figure 26)
- enclose a packing list (See Figure 26)
- seal the box and add labels
- store in the cold unit or in an area with normal ambient temperatures until the commercial carrier picks it up

Figure 22 Put 4 cold packs on the bottom of a large box for warm weather shipping of the vaccine.

Figure 23 Put crumpled brown paper between the cold packs and the vaccines.

Figure 24 Place a heat monitor (outlined in black) close to the vaccines, but away from the cold packs.

Figure 25 Put in next layer of vaccines. Particularly in winter, put a freezing temperature indicator (outlined in black) next to the side of the box, close to the vaccines which would be damaged by freezing.

Figure 26 Add more brown paper, 4 more cold packs on top of the paper, and any inserts you use.

PLACEMENT OF TEMPERATURE MONITORS

Where monitors are placed within the package is important since temperatures vary inside the box. Placing monitors next to the "cold" packs does not give an accurate measure of the temperature of the vaccines that are farther from the "cold" packs. Color-change monitors have adhesive backs and may be attached to vaccine cartons, or walls of the box to prevent them from moving.

A heat monitor (e.g., 3M time-temperature tag), placed at the point of greatest heat exposure (usually near a side, away from cold packs) may have up to, but no more than, four windows blue at the time of unpacking.

A freezing temperature indicator (e.g., ColdMark 32°F monitor), placed with vaccines near cold packs in summer and, also, near a side but away from "cold" packs in winter, should remain clear. (See **Appendices 2A and 2B** for instructions for how to use and read temperature monitors.)

Analog recording monitors are relatively large, and "best judgement" must be used regarding where they should be placed (e.g., in the center or on the outside of the vaccines in a large shipment).

Temperature Chart

Fahrenheit	Celsius
- 20	- 29
- 15	- 26
- 10	- 23
- 5	- 21
0	- 18
5	- 15
10	- 12
15	- 9
20	- 7
25	- 4
30	- 1
32	0
34	1
36	2
38	3
40	4
42	6
44	7
46	8
48	9
50	10
52	11
54	12
56	13
58	14
60	16
65	18
70	21
75	24
80	27
85	29
90	32
95	35
100	38
105	41
110	43
115	46
120	49

5. APPENDICES

APPENDIX 1

SMALLPOX VACCINE DO'S FOR DISTRIBUTION FACILITIES

- Do prevent freezing of Smallpox vaccine and its diluent. Keep them at 2°– 8°C (36°– 46°F).
- Do check the refrigerator unit monitor at least twice daily to be sure the temperature stays between 2° – 8°C (36° – 46°F).
- Do change the graph paper in the refrigerator monitors as needed (usually weekly). Also check the ink!
- Do ensure the cold facility and refrigerator are locked.
- Do get a security system for the cold facility and train everyone on its use.
- Do have a written plan in case of an emergency power outage.
- Do have a back-up generator and test it regularly.
- Do let the temperature in a new, or newly repaired refrigerator stabilize (~72 hours) before putting vaccines in it.
- Do have standard operating procedures covering the use of every item of equipment and all steps for receipt, storage, and distribution in place; train staff in their use; and continually check for compliance.
- Do have phone numbers of key people available for handling emergencies.

APPENDIX 2A — INFORMATION FOR SHIPPERS

HOW TO USE TEMPERATURE MONITORS

Time/temperature tags must be kept refrigerated until the moment of use. Pull the tab to activate the monitor. As the temperature inside the package rises to warmer than 10°C (50°F), the windows in the monitor turn blue. The more windows that have turned blue, the higher the temperatures reached inside the box or the longer the time warmer than 10°C. If no windows are blue, then check whether the monitor was activated. If all five windows are blue, then contact the manufacturer.

The ColdMark Freeze Indicators detects exposure to temperatures under 0°C by releasing a red dye marker into a visible bulb. These are usually placed adjacent to cold packs in the summer, and also near a wall in the winter. If the bulb is red, smallpox vaccine may not be usable. Contact the manufacturer.

Analog disposable recording temperature monitors are available which produce linear strip charts over a 4 day period. They may be appropriate for large, expensive shipments. They should be kept refrigerated until used. To start the temperature monitor: fill out the tag with a ball point pen, press hard; peel off the top tag; pull up on the start tab and remove completely. Confirm the unit is ticking. To remove the chart: cut the tamper evident seal; press end and pry up on cassette; remove chart.

All monitors have adhesive backs which can be used to prevent them from moving.

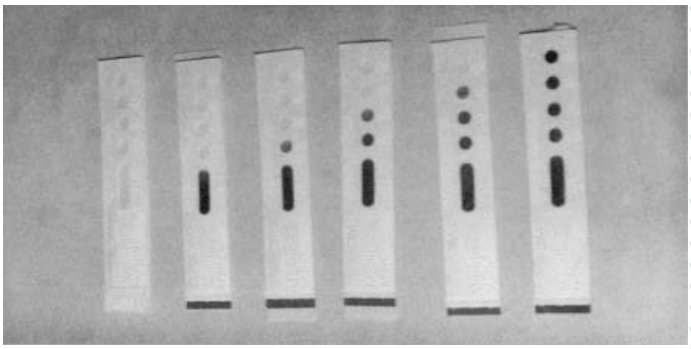


Figure 27 Time/temperature monitor (far left) has not been activated. The monitor (far right) with all five windows blue, means the vaccine manufacturer should be contacted. (See text for more information.)

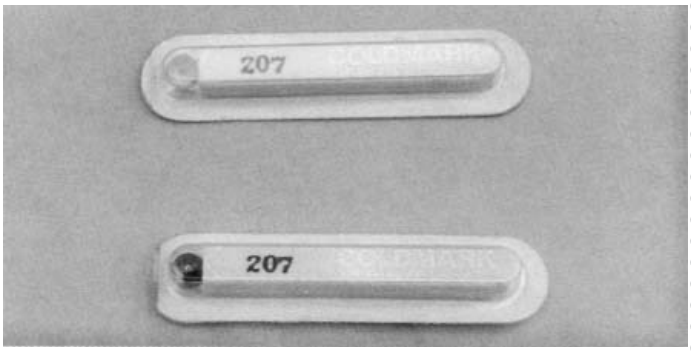


Figure 28 The top indicator is clear, the bottom indicator means the vaccines have been too cold at some point during shipping. (See accompanying text for more information.)

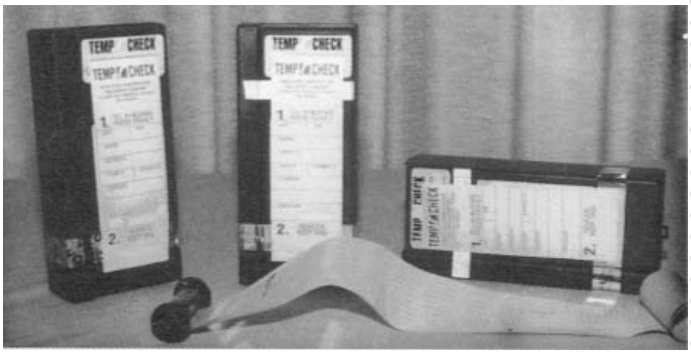


Figure 29 The box must be broken open and the strip chart removed to determine the temperatures reached during shipping. (See accompanying text.)

APPENDIX 2B — INFORMATION FOR RECEIVERS

READING TEMPERATURE MONITORS IN VACCINE SHIPMENTS

Time/temperature tags. As the temperature inside the package rises to warmer than 10°C (50°F), the windows in the monitor turn blue. The more windows that have turned blue, the higher the temperatures reached inside the box or the longer the time above 10°C.

If no windows are blue, check whether the monitor was activated. If all five windows are blue, contact the manufacturer.

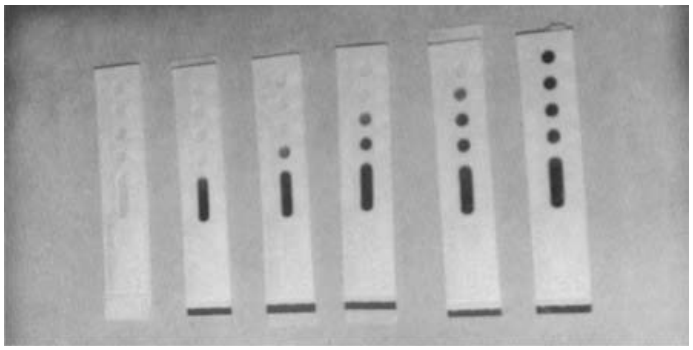


Figure 30 Time/temperature tags showing all windows are clear, and one to five windows blue.

Color-change monitors, also called a "Freeze Watch" monitor, detects exposure to temperatures under 0°C by releasing a red dye marker into a visible bulb. These are usually placed adjacent to cold packs in the summer, and on an inside wall in the winter.

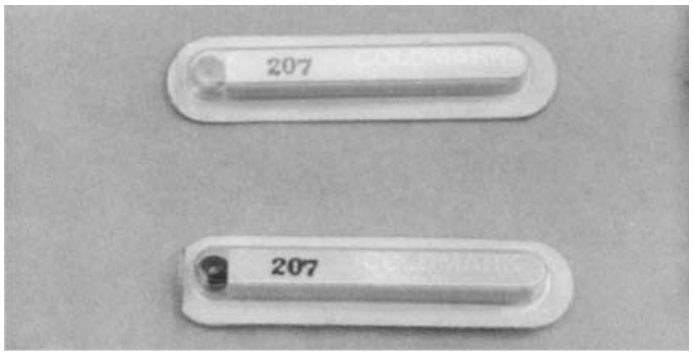


Figure 31 A color-change monitor that has not been exposed to temperatures below 0°C (32°F) stays clear. When exposed to temperatures below 0°C (32°F), the bulb turns red.

Analog disposable recording temperature monitors produce linear strip charts over a 4-day period. They may be appropriate for large, expensive shipments. The monitor should be ticking when you receive it. To remove the temperature chart: cut the tamper evident tape seal; press the end and pry up on the cassette; remove the chart.

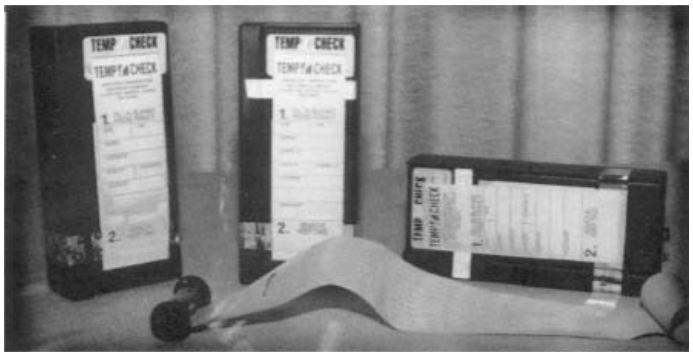
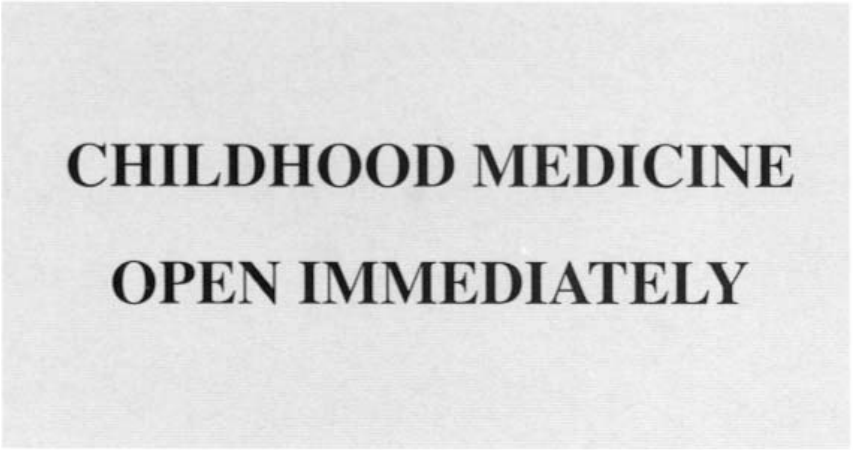


Figure 32 Analog disposable recording temperature monitors. The monitor must be broken open to get the chart strip inside.

APPENDIX 3

SAMPLE LABELS



Various labels that identify your package as valuable cargo.

APPENDIX 4

MATERIALS YOU WILL NEED FOR YOUR PACKING AREA

- Insulated boxes: small, medium and large
- Vaccine: directly from the cold room
- Fillers: crumpled brown paper, styrofoam "peanuts", or bubble wrap
- Cool packs: either permanently sealed or plastic bottles with leak-proof caps
- Temperature monitors: e.g., analog disposal recording monitors, color-change monitors, time/temperature tags
- Insert: packing list
- Sealers: tape or plastic straps
- Labels: content, value, caution

Record-keeping sheets and log books or computer terminals need to be provided in the packing area to record any deviations from standard procedures, including storage temperature units going outside established temperature ranges. Records of all such deviations should be filed with supervisory/managerial staff for at least three years and responses to each situation recorded.

APPENDIX 5

WHERE CDC OBTAINED MATERIALS FOR TESTING PACKING METHODS

Cardboard-covered insulated boxes

Molded polystyrene, Polyfoam Packers Corp., Wheeling, Illinois
Isocyanurate, True pack Ltd, Wilmington, Delaware
Molded polyurethane, Normco Inc, Beltsville, Maryland

Cold packs

Chemical gel packs, U-TEC, manufactured by Polyfoam Packers Corp., Wheeling, Illinois.

Plastic Bottles

WHO-approved, capped bottles, Electrolux, Vianden, Luxembourg

Monitors

Analog temperature recorders, Marathon Temperature Recorder Co., Modesto, California
Color-change monitors "ColdMark Freeze indicator", IntroTech Inc, St. Paul, Minnesota
"MonitorMark Time/Temperature Tag, model 10-I" indicators, 3M Specialty Packaging Department, St. Paul, Minnesota

Fillers and Sealers

Brown paper, styrofoam peanuts, bubble wrap, tape or plastic straps - office or packaging suppliers.

Samples of any materials received should be tested to verify they meet specifications and function as required under local circumstances.

DISCLAIMER

The use of proprietary names and description of specific manufacturers' products does not imply endorsement by the Centers for Disease Control and Prevention, or the U.S. Department of Health and Human Services.

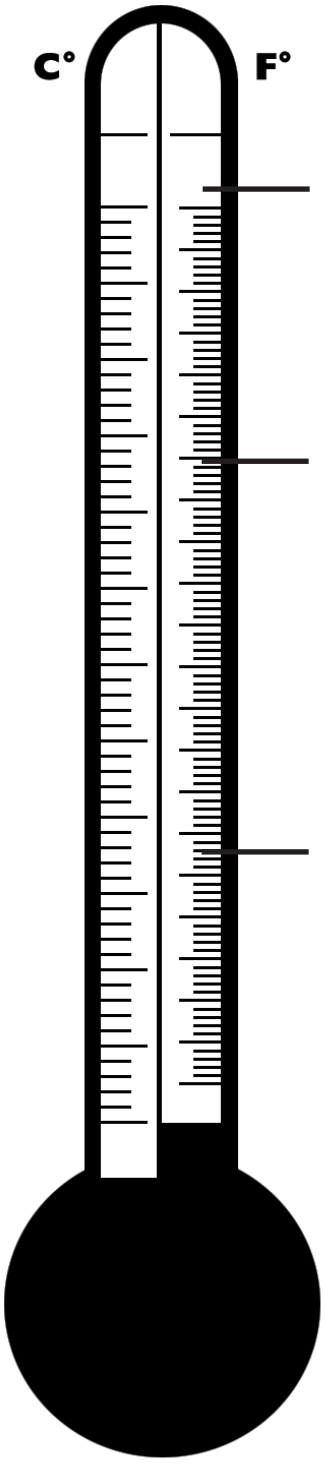
APPENDIX 6

SMALLPOX VACCINE ORDERING AND SHIPPING PROCESS

- The order is received in the shipping department. Inventory controls identify which smallpox vaccines will be selected.
- Smallpox vaccines are pulled from systematically organized smallpox vaccine stocks.
- Vaccines are set on a work counter and checked carefully against the order need.
- The appropriate sized box is selected, based on the quantity of vaccine being shipped.
- Smallpox vaccine packed with enough cold packs to keep the appropriate internal temperatures throughout the shipping process.
- Temperature monitors are placed in appropriate locations in the package to detect potentially harmful temperature exposures during shipping.
- All remaining empty space in the box is filled with some kind of filler material.
- A packing list is enclosed.
- The box is sealed with tape or plastic straps to insure that it remains tightly closed.
- A shipping label, coded for the size of the box being shipped, is affixed, so that if the box is misplaced, it will be easier to locate.
- Labels are applied so that they are clearly visible on the outside of the box, to let everyone know that the contents include vaccines which must be handled properly.
- Once the box is packed, sealed, and labeled, it is stored until it is picked up by the commercial carrier or designated clinic personnel. Other packages may be similarly stored or placed in a refrigerated area, if space is available, or at ambient temperature, depending on when the carrier picks up packages.

APPENDIX 7

CHART OF COLD PACK NEEDS FOR DIFFERENT CLIMATES



Outside Temperature	No. faces covered with cold packs	Temperature of cold/cool packs	Comment*
110°F			
	2§	-5°C (25°F)	up to 48 hrs delivery with 10hrs at 110°F
>75°F			
75°F			
	2§	-5°C (25°F)	48 hrs delivery
	4	+5°C (45°F)	up to 24 hrs
32°F			
<32°F			
	4 – 6¶	+5°C (50°F)	about 24 hours exposure to mix of outdoors & heated areas
0°F or colder 24–48hrs	6¶	+20°C (68°F)	prolonged, continuous exposure to 0°F (-20°C)

* Applies when high quality insulated boxes with walls of 1:" to 23" expanded polystyrene, 1" isocyanurate, or 3" polyurethane insulation were used.

§ 3 for the medium box tested by CDC.

¶ Essentially the entire surface area is covered with "cool" packs

SMALLPOX VACCINE

WHAT YOU NEED TO KNOW

1 WHAT IS SMALLPOX?

Smallpox is a serious disease that can kill up to 3 out of 10 people who get it.

Smallpox can also cause—

- a severe rash, which can leave scars when healed.
- high fever.
- tiredness.
- severe headaches and backache.
- blindness.

Smallpox is caused by a virus called "**variola**," which spreads from person to person. Usually, face-to-face contact lasting 3 or more hours is needed to spread smallpox from one person to another. Smallpox can also be spread through direct contact with infected body fluids or objects such as bedding or clothing that have smallpox virus on them.

Smallpox killed millions of people over the centuries. Smallpox vaccination was developed in 1796. As a result, the last outbreak of smallpox in the United States was in 1949. The world's last case of naturally occurring smallpox was in 1977. Routine vaccination of the American public against smallpox ended in 1972.

2 WHAT IS THE SMALLPOX VACCINE?

Smallpox vaccine is made from a living virus called "**vaccinia**." Vaccinia virus is like smallpox virus, but less harmful.

The smallpox vaccine can ***NOT*** give you smallpox.

The vaccine is not a shot like other vaccines. The needle is pricked into the skin a number of times in a few seconds (usually in the upper arm). The pricking is not deep, but will cause one or two small drops of blood to form. The place on the skin where the vaccine is given is called the "vaccination site."

Getting the vaccine—

- *before exposure* will protect most people from smallpox (the vaccine is about 95% effective).
- *up to 3 days after exposure* can prevent the disease or at least make it less severe.
- *4-7 days after exposure* can still make the disease less severe and decrease the chance of death.

Smallpox vaccine protects people from getting smallpox for 3 to 5 years. Protection from severe illness and death can last 10 years or more.

3 WHY GET VACCINATED NOW?

Smallpox vaccine protects people from smallpox.

Some people should get the vaccine because they work with smallpox or related viruses in laboratories.

Others are being offered the vaccine so they can assist in responding to a smallpox outbreak. Smallpox virus is kept in two approved laboratories in the United States and Russia. There is concern that terrorists may have obtained the smallpox virus and could use it as a weapon. If this happened, many people could become ill and many could die.

The U.S. needs teams of health care providers and others to be vaccinated so they can respond quickly if a smallpox attack happens. These teams will do many things to help control a smallpox outbreak, including quickly vaccinating people who have been exposed to the disease.

4 WHO SHOULD GET SMALLPOX VACCINE AND WHEN?

When There is *NO* Smallpox Outbreak—

You should get the smallpox vaccine if you—

- Are a lab worker who works with smallpox or viruses like it.
- Are a member of a smallpox response team.

When There *IS* a Smallpox Outbreak—

You should get the smallpox vaccine if you—

- Are directly exposed to smallpox virus.

If there is a smallpox outbreak, public health experts will say who else should get the vaccine.

Vaccinated persons may need to get the vaccine again at least every 3-10 years, depending on their risk of exposure to smallpox or related viruses.

5 WHO SHOULD *NOT* GET THE SMALLPOX VACCINE, OR SHOULD WAIT?

When There is *NO* Smallpox Outbreak—

You should *NOT* get the smallpox vaccine if you—

- **Have Skin Problems**
  People with skin problems are at risk of developing rashes which can be severe if they get the smallpox vaccine.
  - Anyone who has atopic dermatitis (often called eczema) or had it in the past, should not get the smallpox vaccine.
  - Anyone who has Darier's disease (a skin disease that usually begins in childhood) should not get the smallpox vaccine.
  - Anyone who has a skin problem that has made many breaks in the skin (such as an allergic rash, bad burn, impetigo, psoriasis, pityriasis rosea, poison oak, poison ivy, chickenpox, shingles, herpes, or very bad acne) should not get the vaccine now. They should wait until the skin heals before getting the smallpox vaccine.
- **Have Immune System Problems**
  Rarely, when a person with a weakened immune system gets the smallpox vaccine, their vaccination site does not heal. Instead, it spreads to other parts of the body. This reaction can be life-threatening. Anyone with a weakened immune system should ***NOT*** get the smallpox vaccine, including anyone who:
  - Has HIV/AIDS, primary immune deficiency disorders, humoral (antibody) immunity problems (such as agammaglobulinemia or lack of normal antibodies), or other diseases that affect the immune system.
  - Has lupus or another severe autoimmune disease that weakens the immune system.
  - Has leukemia, lymphoma, or most other cancers.
  - Is taking cancer treatment with radiation or drugs, or has taken such treatment in the past 3 months.
  - Is taking, or has recently taken, drugs that affect the immune system. These include high-dose steroids (for 2 weeks or longer within the past month), some drugs for autoimmune disease, or drugs taken for an organ or bone marrow transplant.
- **Have Heart Problems**
  Smallpox vaccination may cause heart inflammation that can be mild to life-threatening. It is not known who is at risk for this problem. As a precaution, anyone who has been told by a doctor that they have a heart condition should ***NOT*** get the smallpox vaccine, even if they feel well. This includes anyone who has:
  - Known heart disease, such as past heart attack or angina (chest pain caused by lack of blood to the heart).
  - Congestive heart failure
  - Cardiomyopathy (heart muscle becomes enlarged and does not work as well as it should)
  - Stroke or transient ischemic attack (a "mini-stroke" that causes stroke-like symptoms, but no lasting damage)
  - Chest pain or shortness of breath with activity (such as walking up stairs)
  - Other heart conditions that require the care of a doctor

In addition, anyone with **3 or more** of the following risk factors should ***NOT*** get the smallpox vaccine:

- Have been told by a doctor that you have high blood pressure.
- Have been told by a doctor that you have high blood cholesterol.
- Have been told by a doctor that you have diabetes or high blood sugar.
- Have a first degree relative (for example, mother, father, sister or brother) who had a heart condition before the age of 50.
- Smoke cigarettes now

Are Pregnant or Breastfeeding

Babies of mothers who have been vaccinated while pregnant or during the month before they become pregnant can get a very rare but serious infection from the vaccine.

- Do ***NOT*** get the smallpox vaccine if you are pregnant, think there is a chance you are pregnant, or think you might become pregnant within 4 weeks after vaccination.
- Sexually active women are encouraged to take a pregnancy test before getting the vaccine. The test should be done the day their vaccination is scheduled. But be aware that even the best tests may not detect early pregnancies (those less than 2 weeks).
- Take steps to prevent pregnancy during the month before and the month after vaccination:
  - Do not have sex, **or**
  - Use effective birth control **every time** you have sex. Effective birth control methods include male or female sterilization, hormonal methods (such as birth control pills, implants, patches or injections) and intrauterine devices (IUDs). Condoms and the use of spermicide with diaphragms, sponges, or cervical caps are also acceptable methods, although they are less effective. Do ***NOT*** rely solely on the rhythm or 'natural family' planning method.
- Do ***NOT*** get the smallpox vaccine if you are breastfeeding. Follow this advice even if you are pumping and then bottle-feeding breast milk. It is not known if smallpox vaccine virus or antibodies can be passed to babies through breast milk.

Other Reasons—Do ***NOT*** Get the Smallpox Vaccine if You—

- Are very allergic to polymyxin B, streptomycin, chlortetracycline, neomycin, or latex.
- Had a bad reaction the last time you got the smallpox vaccine.
- Are using steroid drops in your eyes.
- Are moderately or severely ill the day of your vaccination appointment. Wait until you are better before getting the smallpox vaccine.

You should ***NOT*** get the smallpox vaccine if you live with or have close physical contact with anyone (such as a sex partner) who—

- Has any of the skin problems listed above.
- Has any of the immune system problems listed above.
- Is pregnant or may become pregnant within 4 weeks of your vaccination.

The smallpox vaccine may pose a similar risk to them.

Smallpox vaccine is not routinely recommended for anyone under 18 years of age or for older people. People age 65 or older who do not have any of the conditions listed above should talk to their health care provider before getting the vaccine.

If There *IS* a Smallpox Outbreak—

These restrictions may not apply. Public health experts will say who should get the vaccine at that time.

6 What should you expect after vaccination?

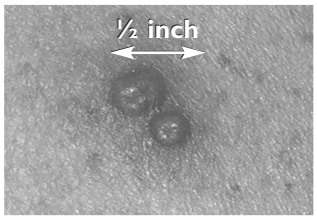
Normal Reactions

Week 1: Three or 4 days after vaccination, a red, itchy bump will form at the "vaccination site". Most times, this spot is about the size of a dime. It can be larger than 3 inches. The bump becomes a blister. It will fill with pus and then start to drain.

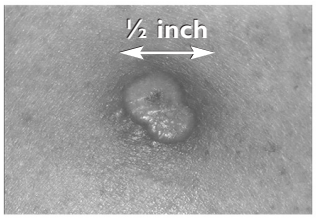
A health care provider should check your vaccination site 6–8 days after you get the vaccine to make sure the vaccination worked and everything is o.k.

Week 2: The blister will dry up and a scab will form.

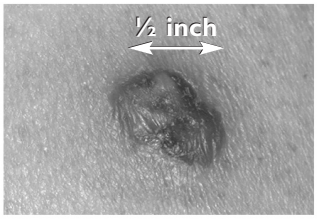
Week 3: The scab will fall off. It will leave a small scar.



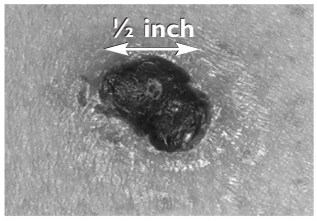
Day 4



Day 7



Day 14



Day 21

The lymph nodes under your arm may swell and be sore. The vaccination site may itch. You may also feel tired, have a mild fever, headache, or muscle aches.

You may not get a blister if the vaccine did not work properly or if you are already immune to smallpox. In this case, you will need to get the vaccine again. If you still do not get a blister after getting the vaccine a second or third time, a health care provider will tell you if you are, or are not, considered immune.

What You Will Need to Do

The virus in the vaccine is alive. It can be spread from the vaccination site to other parts of your body or to other people through close physical contact. This can happen until the scab falls off.

In the past, the vaccine virus was spread from vaccinated people to others about 2 to 6 times out of every 100,000 people vaccinated for the first time (this usually happened between people who lived together).

To Help Prevent Spread of the Virus:

- **Cover the area** loosely with a gauze bandage held in place with first aid tape. While at work, health care workers should also cover the gauze with a semi-permeable bandage (this type of bandage allows air to flow through but not fluids).
- Change the bandage often (at least every 3 days).
- **Try not to touch your vaccination site.**
- Do not let others touch the site or items that have touched it such as bandages, clothes, sheets, or towels.
- Always **wash your hands** with soap and water or alcohol-based hand wash if you touch the site or if you touch bandages, clothes, sheets, or towels that have touched the site.
- Keep the vaccination site dry. If the gauze bandage gets wet, change it right away. Cover your vaccination site with a waterproof bandage while bathing.
- Don't scratch or put ointment on the vaccination site.
- Don't touch your eyes, any part of your body, or another person after changing the bandage or touching the vaccination site until you have washed your hands.
- Wear a shirt that covers the vaccination site and bandage. This helps protect those you have close contact with such as young children or the person you share a bed with.
- Don't share towels.
- Do your own laundry. Use a separate laundry hamper for clothes, towels, sheets, and other items that may come into contact with your vaccination site or pus from the site. Machine wash items that have touched the vaccination site in hot water with detergent and/or bleach.
- Put used bandages in plastic zip bags, then throw them away in the regular trash.
- After the scab falls off, put it in a plastic zip bag and throw it away.

If you do not feel like you can follow these instructions, do not get vaccinated.

7 WHAT ARE THE RISKS FROM THE SMALLPOX VACCINE?

A vaccine, like any medicine, can cause serious problems. There is a very small risk of smallpox vaccine causing serious harm, or death.

The following information is about known reactions to smallpox vaccine. There may be other unknown side effects.

People who did not get the vaccine can also have the side effects described below if they touch someone's vaccination site or items that have touched the site (like bandages, clothes, sheets, or towels). Following instructions on how to care for the vaccination site (such as covering the site and washing hands) can help prevent spread of the vaccine virus to others.

MILD TO MODERATE PROBLEMS	**HOW OFTEN DID IT HAPPEN IN THE PAST?**
Feel sick enough to miss work	About 1 out of 10 to 20 people vaccinated
Fever of over 100°F	About 1 out of 10 people vaccinated
Mild rash that gets better without medicine	About 1 out of 12 people vaccinated
Blisters on other parts of the body	About 1 out of 10,000 people vaccinated
MODERATE TO SEVERE PROBLEMS ***CALL OR VISIT A HEALTH CARE PROVIDER***	**HOW OFTEN DID IT HAPPEN IN THE PAST?**
Eye infection from touching your eye if you have vaccine virus on your hand. This can lead to a loss of vision in the infected eye.	About 1 out of 45,000 people vaccinated
Rash on entire body which usually goes away without problems	About 1 per 15,000 people vaccinated
Inflamed heart (can be mild to life-threatening)	About 1 out of 10,000 people vaccinated for the first time
SEVERE OR LIFE-THREATENING PROBLEMS ***GET TO A HEALTH CARE PROVIDER IMMEDIATELY***	**HOW OFTEN DID IT HAPPEN IN THE PAST?**
Severe rash on people with eczema or atopic dermatitis, which can lead to scarring or death.	About 1 out of 26,000 people vaccinated
Encephalitis (severe brain swelling), which can lead to permanent brain damage or death.	About 1 out of 83,000 people vaccinated
Skin and tissue destruction starting at the vaccination site and spreading to the rest of the body, which can lead to scarring or death (usually happens in people with very weakened immune systems).	About 1 out of 667,000 people vaccinated
Vaccinia virus infection in unborn child that can lead to premature delivery, skin rash with scarring, stillbirth, or death of the child after delivery	Very rare, less than 50 cases have been reported throughout the world in the last 100 years

For every million people vaccinated in the past, up to 52 people had a life-threatening reaction to smallpox vaccine and up to 2 people died.

The numbers provided above for severe or life-threatening problems are from studies done in the 1960's when the smallpox vaccine was still routinely used in the U.S. The numbers reflect how often the problems occurred in infants, children, and adults.

The numbers provided for all other problems are from recent studies and experiences vaccinating members of response teams and the military.

8 What if someone has a moderate, severe or life-threatening problem?

Within a Few Minutes to a Few Hours of Getting the Vaccination, Watch For—

- Trouble breathing, hoarseness or wheezing.
- Hives, pale skin, weakness, a fast heart beat, or dizziness.

These could be signs that you are having an allergic reaction to the vaccine.

For the Next 3 to 4 Weeks, Keep Watching For—

- A vaccination site that is not healing.
- A rash or sore on other parts of your body.
- An eye infection.
- A lasting headache or fever.
- Confusion, seizures, or trouble staying awake.
- Chest pain, shortness of breath, rapid or unusual heartbeat or unusual fatigue.
- Any unexpected health problem.

What Should You Do?

If you or a close contact have any of these problems, or if you are concerned about any health problem that you have after vaccination—

- Call or go to a health care provider right away.
- Tell the health care provider that you received the smallpox vaccine and when.
- Ask your doctor or nurse to file a Vaccine Adverse Event Report (VAERS form) and contact the health department. You can also file a report yourself by visiting the VAERS website at **www.vaers.org** or by calling **1-800-822-7967**.

Treating Serious Problems

There are two drugs that may help people who have certain serious side effects from the vaccine: Vaccinia Immune Globulin (VIG) and cidofovir. These drugs are not licensed for this purpose, and may also cause side effects.

Cost of Treating Serious Problems

In the rare event that you have a serious reaction to the smallpox vaccine, a federal program has been created to help pay for related costs of medical care and lost wages. This program was created to compensate certain people, such as health care workers and emergency responders, injured by the vaccine. It will also cover certain people injured as the direct result of exposure to vaccinia through contact with certain people who received the smallpox vaccine (or with the contacts of such vaccine recipients). The program covers related costs of medical care and lost wages (usually starting after the first five days of missed work) after other available coverage, such as workers' compensation or health insurance, has been used.

The Department of Health and Human Services will make more information about this program available soon, including how to request benefits and/or compensation. For more information contact Paul T. Clark, Director, Smallpox Vaccine Injury Compensation Program, Office of Special Programs, **888-496-0338** or go to **www.hrsa.gov/smallpoxinjury.**

9 How can you learn more?

- Ask your health care provider. They can give you more information, show you the vaccine package insert or suggest other sources of information.
  - Call your local or state health department.
  - Visit the Centers for Disease Control and Prevention (CDC) smallpox website at **www.cdc.gov/smallpox**
  - Contact the (CDC):
    - Call **1-888-246-2675** (English)
    - Call **1-888-246-2857** (Español)
    - Call **1-866-874-2646** (TTY)

If you decide to get the smallpox vaccine, please **KEEP THIS DOCUMENT** for one month following vaccination.

Vaccination Contraindication: Previous Allergic Reaction to Smallpox Vaccine or Any of the Vaccine's Components

- Vaccinia vaccine (Dryvax®) contains small amounts of polymyxin B sulfate, streptomycin sulfate, chlortetracycline hydrochloride, neomycin sulfate, and phenol. 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.
- **General precaution:** 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.

SMALLPOX FACT SHEET . *Information for Clinicians*

Smallpox (Vaccinia) Vaccine Contraindications

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

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.

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). 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.
- HIV testing should be readily available to all persons considering smallpox 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 vaccine before the planned date of vaccination. Persons with a positive test result should be told not to present to the vaccination clinic for immunization.

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., ≥ 2 mg/kg body weight or 20 mg/day of prednisone for ≥ 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. Persons undergoing other treatments which cause immunosuppression or who have household contacts undergoing such treatment should not receive smallpox vaccine until they or their household contact have been off immunosuppressive treatment for 3 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 4 weeks; those who respond positively should not be vaccinated. In addition, women who are vaccinated should be counseled not to become pregnant during the 4 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.
- Any woman who thinks she could be pregnant or who wants additional assurance that she is not pregnant should perform a urine pregnancy test using a .first morning. void urine on the day scheduled for vaccination. 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 4 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.

The contraindications above apply to potential vaccinees and their household contacts. The following additional contraindications apply only to potential vaccinees:

Previous allergic reaction to smallpox vaccine or any of the vaccine.s components

- Vaccinia vaccine (Dryvax®) contains small amounts of polymyxin B sulfate, streptomycin sulfate, chlortetracycline hydrochloride, neomycin sulfate, and phenol. 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.

Infants and children

- Smallpox vaccine is contraindicated for children under 12 months of age.
- The Advisory Committee on Immunization Practices (ACIP) advises against non-emergency use of smallpox vaccine in persons younger than 18 years of age.

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.

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.

Contraindications to Vaccination During a Smallpox Emergency

- During a smallpox emergency, all contraindications to vaccination would be reconsidered in the light of the risk of smallpox exposure. Persons would be advised by public health authorities on recommendations for vaccination.

Careful screening is essential to minimize complications from the smallpox vaccine. If you have any questions about whether or not someone should receive the smallpox vaccine, visit the CDC website at www.cdc.gov/smallpox.

For more information, visit www.cdc.gov/smallpox, or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY)

March 28, 2003

SMALLPOX FACT SHEET

What to Do After You've Gotten the Smallpox Vaccine

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:

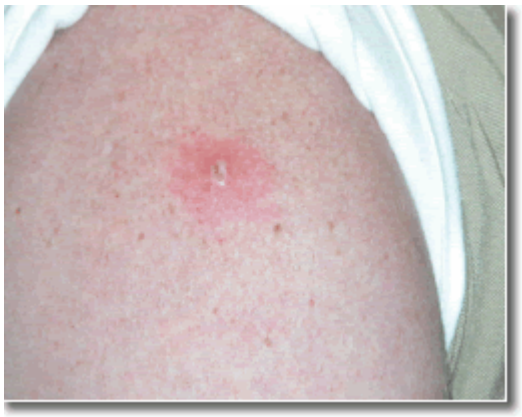
- ***Don't use a bandage that blocks all air from the vaccination site.*** This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.
- ***Don't put salves or ointments on the vaccination site.***
- ***Don't scratch or pick at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

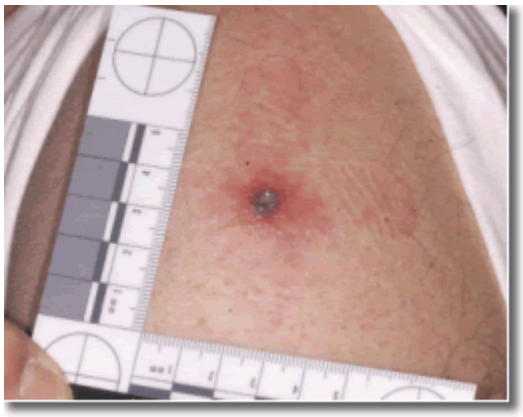
Evaluation of Takes and Non-Takes

A “take” or “major reaction” indicates successful vaccination and is characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer. All other responses should be considered “non-takes.” “Non-takes” can be caused by improper vaccination technique, use of vaccine that has lost its potency, or residual vaccinial immunity among previously vaccinated persons. Persons with a “non-take” cannot be presumed to be immune to smallpox, and revaccination is recommended.

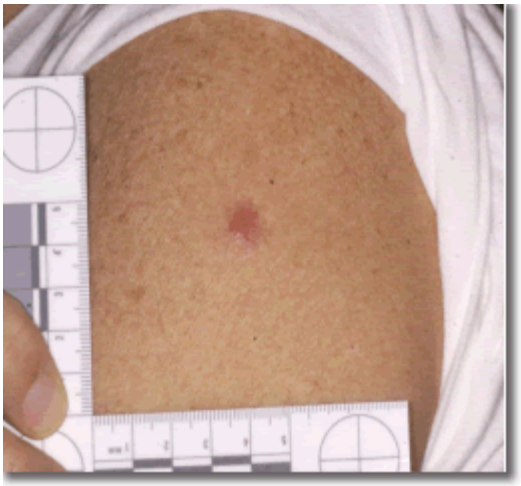
It is recommended that “take” evaluation for both first-time vaccinees and revaccinees be done on day 6, 7, or 8 following vaccination. Vaccine site evaluations on other days may not be reliable. If the evaluation is done too early (e.g., <6 days postvaccination), certain “non-takes” may look reactive because of dermal hypersensitivity to vaccinial proteins. These reactions are sometimes referred to as immediate reactions but are not successful “takes.” If “take” evaluation is done too late (e.g., >8 days postvaccination), the vaccination “take” might be missed among previously vaccinated persons who can experience an accelerated successful take reaction at the vaccination site if they still have partial immunity to vaccinia.

The two images below both clearly demonstrate a central lesion and thus qualify as “takes.”

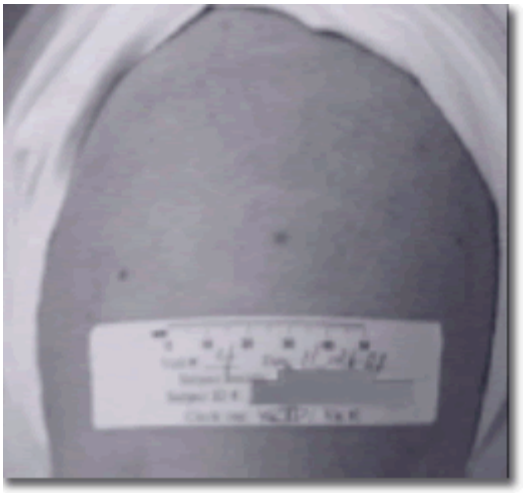




The image below has an area of erythema but no central lesion and is classified as a “non-take.”



The image below has neither erythema nor a central lesion and is classified as a “non-take.”



Source: Color Images: Ramzy Azar, LTJG, MSC, United States Navy: National Naval Medical Center, Bethesda, MD; Black and white image: Stephen Heyse, MD, National Institutes of Health
Page last reviewed August 5, 2004

Normal Primary Vaccination Reactions

A normal primary vaccination appears as a papule in 3-4 days, and rapidly progresses to a vesicle with the surrounding erythema by the 5th-6th day. The vesicle center becomes depressed and progresses to a well-formed pustule by the 8th-9th day. By the twelfth day, or soon thereafter, the pustule crusts over forming a brown scab, which progresses from the center of the pustule to the periphery. After 2.5 to 3 weeks, the scab detaches and a well-formed scar remains.

Normal Reaction Time

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

Rarely, in some first-time or distantly vaccinated (re-vaccinee) individuals, seemingly appropriate vaccination techniques may result in no reaction. One should assume that the individual is not immune and repeat attempts should be made to achieve a major response or “take.” At least one repeat vaccination with a different vaccine vial should be given, switching skin sites on the same arm or using the other arm. If the second vaccination is unsuccessful, consultation should be obtained to determine if the vaccination technique was flawed (primary or re-vaccinee), the vaccine was non-viable (first-time or re-vaccinee), or the vaccinee still had immunity from a previous vaccination (re-vaccinee).

Systemic symptoms: Systemic symptoms are expected and usually occur between 8 -10 days after vaccination when the vaccine site reaction reaches the peak of the inflammatory response. These include:

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

Historically, the occurrence of these normal reactions varied considerably from study to study as shown in ranges demonstrated in the table below. They also varied between primary vaccinees (higher rates of symptoms) and revaccinees (lower rates of symptoms).

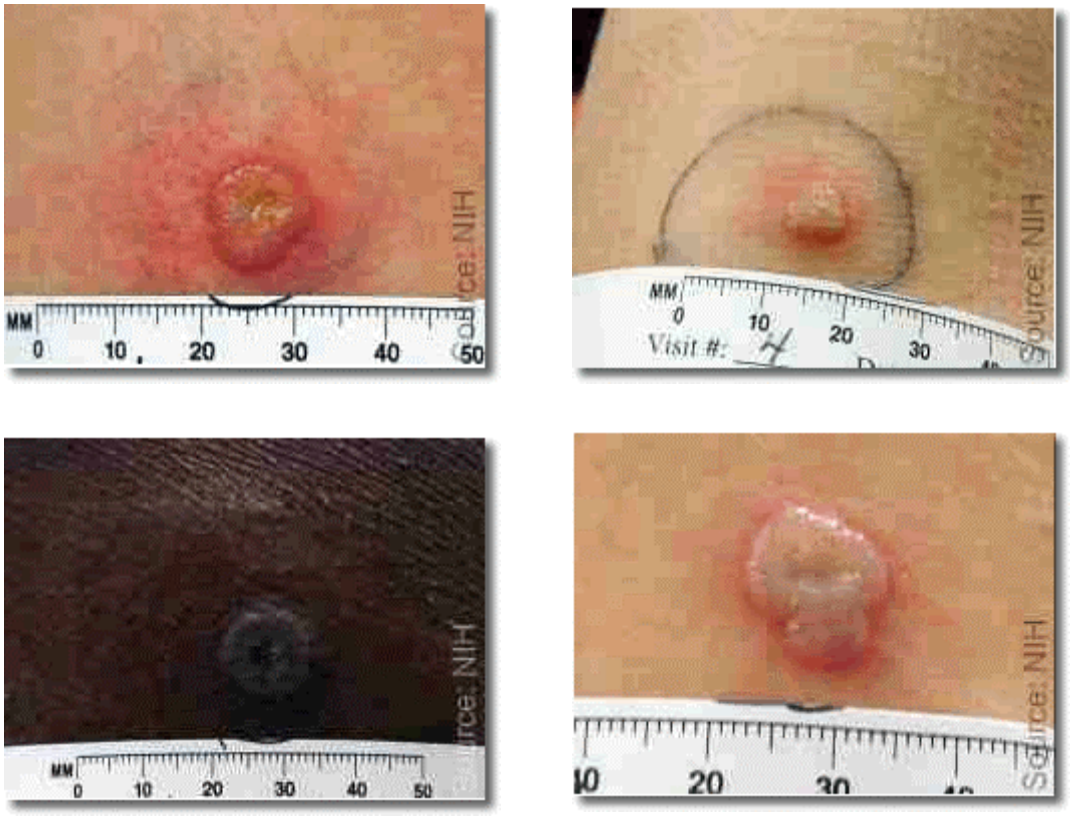
• Lymphadenopathy	25.0 - 50.0 %
• Myalgia, headache, chills, nausea, fatigue	0.3 - 37.0 %
• Fever > 37.7° C	2.0 - 16.0 %

A recent NIH study, evaluating diluted and undiluted smallpox vaccine in adults receiving their first vaccination, reported the following symptom rates during the 14 days following vaccination. These rates are similar to those seen in previous studies.

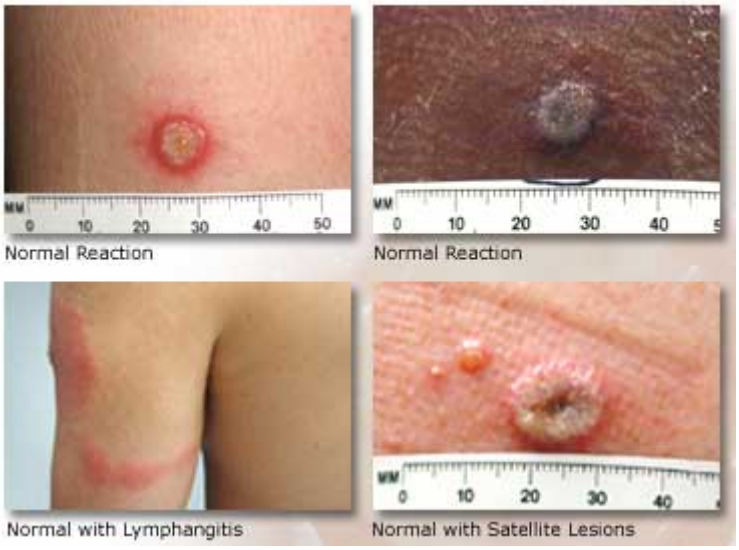
- Lymphadenopathy 54%
- Myalgia and chills, 20%
- Headache 40%
- Nausea 20%
- Fatigue 50%
- Fever > 37.7° C 10%

More Examples of Major or "Take" Reactions to Smallpox Vaccination

Formation by days 6-8 post-vaccination of a papule, vesicle, ulcer, or crusted central lesion, surrounded by an area of induration signifies a response to vaccination; this event is referred to as a major reaction or a "take," and usually results in a scar.



Normal reactions include a wide spectrum of cutaneous presentations:



SMALLPOX FACT SHEET – *Information for Clinicians*

Adverse Reactions Following Smallpox Vaccination

Smallpox vaccination (vaccinia) is generally a safe and effective means of preventing smallpox. However, in a number of individuals, smallpox vaccination can result in untoward effects and adverse reactions. Most are totally benign, but may be alarming in appearance. Some are serious, but treatable. A few, which rarely occur, are serious, life threatening and can be fatal. Severe adverse reactions are more common in persons receiving primary vaccination compared to those being revaccinated.

Local Reactions

- Primary vaccination can produce swelling and tenderness of regional lymph nodes beginning 3 to 10 days after vaccination and in some cases persisting up to 2 to 4 weeks after the skin lesion has healed.
- Other normal local reactions can include
    - local satellite lesions (which appear similar to the primary lesion),
    - considerable local edema,
    - what may be confused with bacterial cellulitis, but is simply intense inflammation accompanying the vaccination (viral cellulitis).
- In a recent study of adult primary vaccinees, 36% were sufficiently ill to miss work, school, or recreational activities or to have trouble sleeping.

Systemic Reactions

- In a recent study, 17% of adult primary vaccinees experienced fever of at least 100°F within two weeks of vaccination; 7% had a fever of 101°F or more, and 1.4% experienced a fever of 102°F or more. Beyond two weeks, fever was recorded in 0.3% of vaccinees.
- Other expected systemic reactions include malaise, soreness at the vaccination site, myalgia, local lymphadenopathy, and intense erythema ringing the vaccination site.
- A variety of erythematous or urticarial rashes occur approximately 10 days after primary vaccination in one person per 3700 vaccinated.
    - Vaccinees who develop these rashes are usually afebrile and the rash resolves spontaneously within 2 to 4 days.
    - Rarely, a more serious rash, called bullous erythema multiforme (or Stevens-Johnson syndrome) occurs.
- In a recent study of adult primary vaccinees, 36% were sufficiently ill to miss work, school, or recreational activities or had trouble sleeping.

Inadvertent Inoculation

Successful vaccination produces a lesion at the vaccination site. Beginning about four days after vaccination, the florid site contains high titers of vaccinia virus. This surface is easily transferred to the hands and to fomites, especially since itching is a common part of the local reaction.

- Accidental implantation occurs due to transfer of vaccinia virus from the primary site to other parts of the body, or to other individuals.
- This is the most frequent complication of smallpox vaccination (529 per million primary vaccinees), accounting for approximately half of all complications of primary vaccination and revaccination.*
- Lesions of inadvertent inoculation can occur anywhere on the body, but the most common sites are the face, eyelid, nose, mouth, genitalia, and rectum. Lesions in 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.
- Most lesions heal without specific treatment.

Generalized Vaccinia

- Generalized vaccinia consists of vesicles or pustules appearing on normal skin distant from the vaccination site.
- In the past, it was estimated to occur in 242 per million primary vaccinees.*
- It is believed to result from a vaccinia viremia with skin manifestations.
- Most rashes labeled as generalized vaccinia produce only minor illness with little residual damage.
- The rash is generally self-limited and usually requires only supportive therapy. However, patients with underlying immunosuppressed illnesses may have a toxic course and require Vaccinia Immune Globulin (VIG).

Eczema Vaccinatum

- Eczema vaccinatum is a localized or systemic spread of vaccinia virus.
- In the past, it was estimated to occur in 10-39 per million primary vaccinees.*
- Transfer of vaccinia virus can occur from autoinoculation or from contact with a vaccinee whose lesion is in the florid stages.
- Individuals with eczema or atopic dermatitis are at increased risk. Eczema vaccinatum can occur regardless of whether the eczema/atopic dermatitis is active at the time of vaccination.
- Virus implanted in disrupted skin (may be at multiple sites) spreads from cell to cell producing extensive lesions dependent on extent of abnormal skin.
- Treatment should include hospitalization and urgent treatment with VIG. Mortality has been prevented in patients treated promptly and adequately.
- Severe cases and fatalities have been observed after contact of recently vaccinated persons with persons who have active eczema/atopic dermatitis or a history of eczema/atopic dermatitis.

Vaccinia Keratitis

- Vaccinia keratitis results in lesions of the cornea due to accidental implantation of vaccinia virus, and is potentially threatening to eyesight.
- Symptoms appear ten days after transfer of vaccinia virus.
- Left untreated, considerable corneal scarring may result as lesion heals resulting in significant impairment of vision.
- Topical antiviral agents are the treatment of choice; therapy should be determined in immediate consultation with an experienced ophthalmologist.

Progressive Vaccinia

- Progressive vaccinia, also known as vaccinia necrosum, is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions (e.g., lesions at places other than the vaccination site).
- In the past, it was estimated that progressive vaccinia occurred in approximately 1 to 2 per million primary vaccinations, and was almost always fatal before the introduction of VIG and antiviral agents.*
- Rare in the past, it may be a greater threat today, given the larger proportion of susceptible persons in the population and the greater number with immunocompromise. Nearly all instances have been in people with defined cell-mediated immune defect (T-cell deficiency).
- Prompt hospitalization and aggressive use of VIG are required.
- Massive doses of VIG are necessary to control viremia. Up to 10 ml per kg of intramuscular VIG has been used.
- There is no proven antiviral therapy. Preliminary studies with cidofovir show some antiviral effect in vitro; studies in animals are pending.

- Immediate consultation with the CDC is recommended to determine if any experimental antiviral drugs are available.

Post-Vaccinial Encephalitis

- Encephalitis or meningoencephalitis following vaccination has been reported in about 3 to 12 per million primary vaccinees; how many such cases are coincidental in time and how many are related to the vaccination itself is impossible to know.*
- Because many different infectious agents and non-infectious processes can be responsible, it is often impossible to establish the etiology. Most cases are believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system.
- In general, this is a severe disease with high mortality and morbidity. Approximately 15-25% percent of affected vaccinees with this complication die, and 25% develop permanent neurological sequelae.
- There is no specific therapy. Supportive care, anticonvulsants and hospitalization in intensive care may be required in individual cases.
- VIG is **not** effective and is **not** recommended.

Fetal Vaccinia

- Fetal vaccinia is a rare complication of smallpox vaccination.
- Fewer than 50 cases of fetal vaccinia infection have been reported, usually after primary vaccination of the mother in early pregnancy.
- Fetal vaccinia usually results in stillbirth or death of the infant soon after delivery. Smallpox vaccine is not known to cause congenital malformations.

Death

- Death resulting from smallpox vaccination is rare, in the past approximately 1 to 2 primary vaccinees died per million vaccinated.*
- Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

Possible Causal Association Between Smallpox Vaccination and Myopericarditis

- Data from recent smallpox vaccinations have been found to be consistent with a causal association between vaccination and myopericarditis, although this is not proven. Persons receiving smallpox vaccine should be informed that myopericarditis is a potential complication of smallpox vaccination and that they should seek medical attention if they develop chest pain, shortness of breath, or other symptoms of cardiac disease after vaccination.

** Adverse event rates presented here are primarily from data collected in the 1960s. Rates in the United States today may be higher because there may be more persons at risk from 1) immune suppression from cancer, cancer therapy, organ transplantation, and other illnesses, such as HIV/AIDS, and 2) eczema or atopic dermatitis. Rates may be lower for persons previously vaccinated.*

This fact sheet is a brief overview of reactions following smallpox vaccination. Additional details for clinicians regarding diagnosis and management of patients with adverse reactions are available at the CDC smallpox website. Visual images of expected and adverse reactions can be viewed at www.bt.cdc.gov/training/smallpoxvaccine/reactions.

For more information, visit www.cdc.gov/smallpox, or call the CDC public response hotline at (888) 246-2675 (English), (888) 246-2857 (Español), or (866) 874-2646 (TTY)
March 28, 2003

SMALLPOX

Clinical Evaluation Tools for Smallpox Vaccine Adverse Reactions

Overview

The CDC and its partners in the Clinical Immunization Safety Assessment (CISA) network have developed Clinical Evaluation Tools to help health care providers manage patients with potential adverse reactions from smallpox vaccination in the absence of circulating smallpox virus (pre-event setting). These Clinical Evaluation Tools are based on studies conducted before routine childhood US smallpox vaccination was discontinued in 1972 and on expert opinion; they are not entirely evidence-based. The Tools may not apply to all patients with smallpox vaccine adverse reactions and are not intended to substitute for evaluation by a trained clinician. These tools are designed for use during face-to-face patient encounters and are not designed to be telephone triage tools, although they may useful as a companion to other telephone triage materials. Please direct feedback on these Tools to spoxtool@cdc.gov.

Clinical Evaluation Tools

- Dermatologic Reactions/ Localized to Vaccination Site - **UPDATED! (Mar 12, 2003)**
- Dermatologic Reactions/ Nontoxic Appearance, Distant from Vaccination Site (or in a Close Contact) - **UPDATED! (Mar 12, 2003)**
- Dermatologic Reactions/ Toxic Appearance, Distant from Vaccination Site (or in a Close Contact) - **UPDATED! (Mar 12, 2003)**
- Ophthalmologic Reactions/ Inadvertent Inoculation, Vaccinee (or in a Close Contact) - **NEW! (Mar 12, 2003)**
- Ophthalmologic Reactions/ Eye Splash or Other Potential Exposure to Vaccinia Virus, Vaccinee (or in a Close Contact) - **UPDATED! (Mar 25, 2003)**

How do I use the Clinical Evaluation Tools for Smallpox Vaccine Adverse Reactions?

The Clinical Evaluation Tools for Smallpox Vaccine Adverse Reactions are intended to be used by trained clinicians.

1. Choose the appropriate Clinical Evaluation Tool using the title as a guide.
2. Determine
   - the type of potential smallpox vaccine adverse reaction.
   - if the patient has a toxic or nontoxic appearance if applicable to the Tool (use both tools if toxicity is difficult to determine).
   - if the patient is a smallpox vaccine recipient (vaccinee) or a close contact of a smallpox vaccine recipient.
3. Work through the boxes in the Clinical Evaluation Tool to determine if your patient fits one or more of the descriptions.
4. Consider the differential diagnosis. The Clinical Evaluation Tools list clinical conditions not related to the smallpox vaccine that should be considered; this list is not exhaustive.
5. After narrowing the diagnostic considerations, read about the conditions in more detail (see question on more information about smallpox vaccine adverse reactions).
6. Review the diagnostic, treatment, and reporting information provided in the Clinical Evaluation Tool and contact your state/local health department and CDC as indicated.

What do the colors mean in the Clinical Evaluation Tools?

To assist clinicians triage and manage patients some of the Clinical Evaluation Tools are color coded. The morbidity and mortality risk legend is as follows:

Green - Low Risk
Clinical presentation / diagnosis that is normal, mild, or self-limiting. Low risk of progression to a more severe condition. Provide routine / symptomatic care and observe patient as indicated.

Yellow - Moderate Risk
Clinical presentation / diagnosis that may require medical intervention, shares similar features to a more severe condition or has potential to progress to a severe condition. Observe patient closely and manage as clinically indicated.

Red - High Risk
Clinical presentation / diagnosis which carries a high risk of morbidity and may be life threatening. Initiate urgent clinical care and provide appropriate interventions. These patients usually require medical intervention and hospitalization.

What is the difference between a "toxic" and "nontoxic" appearance?

The terms "toxic" and "nontoxic" are clinical descriptors. They are determined based on the appearance of the patient to an experienced clinician. Toxicity does not refer to whether or not the etiology of the patient's condition is infectious nor does it refer solely to the presence of systemic symptoms, such as fever. Although determining toxicity is subjective, certain signs and symptoms may be associated with toxicity. For example, toxic patients may have:

- abnormal vitals signs (including high fever, tachycardia, and decreased blood pressure)
- signs of poor perfusion (shock)
- alterations in mental status
- inability to maintain hydration without intravenous fluids

Where do I call to receive clinical consultation for a potential smallpox vaccine adverse reaction with or without a request for release of Vaccinia Immune Globulin (VIG) (first line agent) or Cidofovir (second line agent)?

1. Civilian health care providers who need clinical consultation with or without release of Vaccinia Immune Globulin (VIG) (first line agent) or Cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/local health department or the CDC Clinician Information Line at (877) 554-4625.
2. Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257.
3. Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.
4. Members of the general public with questions about smallpox vaccination should call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit www.cdc.gov/smallpox.
5. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Dermatologic Reactions/ Localized to Vaccination Site (3-12-2003 Version)

www.bt.cdc.gov/agent/smallpox/vaccination/clineval

Legend
Morbidity and Mortality Risk based on clinical presentation.

- Low
- Moderate
- High

Vaccine Recipient? NO → **Close Contact of Vaccine Recipient?** YES → **Go to Dermatologic Reactions/ Nontoxic Appearance, Distant from Vaccination Site (or in a Contact) Clinical Evaluation Tool.**

YES

Normal Vaccination Reaction

Typical reaction timeline

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

Timeline may be accelerated in persons with history of prior smallpox 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.
Equivocal reaction. Any reaction or response other than a "major reaction."

Common signs/symptoms after vaccination
- Pruritus
- Soreness at vaccination site
- Intense erythema ringing the vaccination site
- Small papules or vesicles around vaccination lesion (satellite lesions)
- Headache
- Local lymphadenopathy
- Malaise
- Myalgia
- Fever

Provide supportive care. Use antihistamines and NSAIDs PRN; avoid topical/ systemic steroids.

Erythematous Vaccination Reaction of Concern

Erythema present along lines of adhesive tape and no or mild systemic symptoms?

YES → **Tape sensitivity**
Try different tape. Change bandage frequently, rotate bandage, or take a judicious bandage "holiday" remembering to use other means (e.g. long sleeves) to prevent contact transmission. Use antihistamines PRN; avoid topical/ systemic steroids.

NO → Erythema with induration, warmth, and pain. May also have regional lymphadenopathy and fever.

Range of normal reactions, including Robust take (>3 inches or ~7.5 cm of redness with swelling, warmth and pain at vaccination site):
- Symptoms expected to peak at 8-10 days post vaccination.
- Symptoms typically improve within 24-72 hours of peak inflammation.

Provide supportive care. Use antihistamines and NSAIDs PRN; avoid topical/ systemic steroids. Observe & rest affected limb. Observe vigilantly until improvement noted.

Consider **Bacterial infection** if:
- Honey-crusted lesions (impetigo) or fluctuance is present at vaccination site.
- Symptom onset is within one week of vaccination or >15 days post vaccination.
- Symptoms are not improving within 72 hours after onset.
- Other concerning clinical features are present.

Streptococcal or staphylococcal infection is the most likely etiology, however other bacterial sources are possible. Obtain cultures of skin/ blood, other lab tests (including gram stain) and administer empiric antibiotics as indicated. Use infection control precautions; lesions may contain vaccinia virus.

Severe Vaccination Reaction

Rapid progressive painless extension of central vaccination lesion or progression without apparent healing after 15 days. Lesion often necrotic. Initially little or no inflammation. May present with few or no systemic symptoms.

Early Progressive vaccinia (Vaccinia necrosum, Vaccinia gangrenosum)
Go to Clinical Evaluation Tool for Dermatologic Reactions/Toxic Appearance, Distant from Vaccination Site (or in Contact). See Consultation and Reporting Information.

Differential diagnosis for localized smallpox vaccine adverse reactions
Consider conditions not related to smallpox vaccine such as:
- Acute contact dermatitis
- Furuncle/ carbuncle
- Pyoderma/ ecthyma
- Herpes simplex virus (HSV)
- Anthrax
- Atypical mycobacteria
- Molluscum contagiosum and other pox viruses
- Pyoderma gangrenosum
- Brown recluse spider bite

Laboratory testing
Consider use of licensed diagnostic tests to rule out etiologies not related to vaccina virus contained in smallpox vaccine.

Consultation and Reporting Information

Civilian health care providers who need clinical consultation with or without release of vaccinia immune globulin (VIG) (first line agent) or cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/ local health department or the CDC Clinician Information Line at (877) 554-4625. Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257.

Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.

Please call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit http://www.bt.cdc.gov/agent/smallpox/index.asp for general public information about smallpox vaccination. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Dermatologic Reactions/Nontoxic Appearance, Distant from Vaccination Site (or in a Close Contact)
www.bt.cdc.gov/agent/smallpox/vaccination/clineval **(03-12-2003 Version)**

Legend
Morbidity and Mortality Risk based on clinical preseool 2n.
- Low
- Moderate
- High

Vaccine Recipient or Close Contact? Yes → History of known risk factors for smallpox vaccine adverse reactions? Yes →

Consult with state/local health department and CDC to obtain clinical guidance and to report inadvertent exposure to vaccinia virus contained in smallpox vaccine. Management of the adverse reactions discussed in this Tool may be different when risk factor(s) are present. See Consultation and Reporting Information.

Vaccine recipients or close contacts with risk factor(s) should be reported, whether or not an adverse event develops.

Risk Factor	Adverse Reaction (Potential/ Reported Historically)
Atopic Dermatitis/Eczema	Eczema Vaccinatum
Acute Exfoliative Dermatitis	Inadvertent Inoculation
Immunocompromised including HIV+/AIDS	Progressive Vaccinia
Immunocompromised including HIV+/AIDS	Generalized Vaccinia (Severe form)
Allergy to vaccine component	Allergic Reaction
Pregnancy	Fetal Vaccinia and potential unknown risks to fetus

History of known risk factors for smallpox vaccine adverse reactions? No →

Urticarial, maculopapular, or acneform eruption; no vesicles, no signs of anaphylaxis. Usually appears 10 days after vaccination.

Urticaria or nonspecific rash
Provide routine care and observe patient. The rash usually resolves in 2-4 days. Use antihistamines PRN; avoid topical/ systemic steroids.

Dull red flat, urticarial or vesiculobullous lesions (target-like / bulls-eye) without systemic symptoms. Usually appears 10 days after vaccination.

Erythema multiforme minor
Provide routine care and observe patient. Use antihistamines PRN; avoid topical/ systemic steroids.

Watch for

Erythema multiforme major (Stevens-Johnson Syndrome)
Go to Clinical Evaluation Tool for Dermatologic Reactions/Toxic Appearance, Distant from Vaccination Site (or in a Close Contact) and see Consultation and Reporting Information.

Papules, vesicles or pustules suspicious for vaccinial lesions in localized areas distant from vaccination site or in a close contact.

Inadvertent inoculation or a regional form of Generalized vaccinia

Lesions in or near the eye?
- No → Severe, extensive or painful lesions?
  - No → **Provide routine care. Use infection control precautions.**
  - Yes → Consider requesting release of VIG (first line agent) or Cidofovir (second line agent). Provide supportive care. Use infection control precautions. → **See Consultation and Reporting Information.**
- Yes → **Go to Clinical Evaluation Tool for Ophthalmologic Reactions.**

Generalized papular, vesicular or pustular eruption with varying degrees of erythema usually within 6-9 days of vaccination. Evolves through normal vaccination stages. Lesions typically are in same stage of development. Absent or mild systemic symptoms.

Generalized vaccinia

Is there reason to suspect immune disorder?
- No → **Generalized Vaccinia**
  Provide supportive care. Use antihistamines and NSAIDs PRN; avoid topical/ systemic steroids. Use infection control precautions.
- Yes → **Generalized vaccinia (severe form)**
  Go to Clinical Evaluation Tool for Dermatologic Reactions/Toxic Appearance, Distant from Vaccination Site (or in a Close Contact) and see Consultation and Reporting Information.

Rapid, progressive, and painless extension of central vaccination lesion or progression without apparent healing after 15 days. Lesion often necrotic. Initially little or no inflammation, +/- distant metastatic lesions to skin, bones, and viscera. May present with few or no systemic symptoms.

Progressive vaccinia (Vaccinia necrosum, Vaccinia gangrenosum). Go to Clinical Evaluation Tool for Dermatologic Reactions/ Toxic Appearance, Distant from Vaccination Site (or in Contact) and see Consultation and Reporting Information.

Consultation and Reporting Information

Civilian health care providers who need clinical consultation with or without release of Vaccinia Immune Globulin (VIG) (first line agent) or Cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/ local health department or the CDC Clinician Information Line at (877) 554-4625.

Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257.

Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.

Please call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit http://www.bt.cdc.gov/agent/smallpox/index.asp for general public information about smallpox vaccination. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

Laboratory testing
Consider use of licensed diagnostic tests to rule out etiologies not related to vaccina virus contained in smallpox vaccine.

Differential diagnosis for smallpox vaccine adverse reactions distant from vaccination site (or in a Contact)

Consider conditions not related to smallpox vaccine such as:
- Varicella
- Disseminated herpes zoster
- Disseminated herpes simplex (HSV)
- Disseminated molluscum contagiosum
- Viral exanthem (e.g. enteroviral)
- Drug reaction
- Norwegian scabies
- Allergic contact dermatitis (e.g. poison ivy, poison oak)
- Pityriasis lichenoides
- Gianotti-Crosti syndrome (papular acrodermatitis of childhood)

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Dermatologic Reactions/Toxic Appearance, Distant from Vaccination Site (or in a Close Contact)
www.bt.cdc.gov/agent/smallpox/vaccination/clineval (03-12-2003 Version)

Legend
Morbidity and Mortality Risk based on clinical presentation.
- Low
- Moderate
- High

Vaccine Recipient or Close Contact? Yes → History of known risk factors for smallpox vaccine adverse reactions? Yes → Consult with state/ local health department and CDC to obtain clinical guidance and to report inadvertent exposure to vaccinia virus contained in smallpox vaccine. Management of the adverse reactions discussed in this tool may be different when risk factor(s) are present. See Consultation and Reporting Information.

Vaccine recipients or close contacts with risk factor(s) should be reported, whether or not an adverse event develops.

Risk Factor	Adverse Reaction (Potential/ Reported Historically)
Atopic Dermatitis/Eczema	Eczema Vaccinatum
Acute Exfoliative Dermatitis	Inadvertent Inoculation
Immunocompromised including HIV+/AIDS	Progressive Vaccinia
Immunocompromised including HIV+/AIDS	Generalized Vaccinia (Severe form)
Allergy to vaccine component	Allergic Reaction
Pregnancy	Fetal Vaccinia and potential unknown risks to fetus

No →

Widespread, extensive bullae and erosions with involvement of two or more mucosal surfaces. Systemic symptoms present.

Erythema multiforme major (Stevens-Johnson Syndrome)
- NOT recommended VIG (first line agent) or Cidofovir (second line agent).
- Hospitalize and provide supportive care.
- Role of steroids unclear; consult with dermatologist as indicated.

See Consultation and Reporting Information

Large contiguous patches of skin with vesicles and pustules (may be umbilicated and coalescing) that are suspicious for vaccinial lesions. Predilection for sites typical for eczema/ atopic dermatitis eruptions. Lesions often erupt over intact skin and are usually seen in vaccine recipients or contacts (especially young children) with history of atopic dermatitis/ eczema, irrespective of disease activity or severity. Systemic toxicity with worsening disease may occur.

Eczema vaccinatum
- Request release of VIG (first line agent) or Cidofovir (second line agent).
- Contact state health department for guidance.
- Hospitalize and provide supportive care with attention to hemodynamic support, secondary infections and meticulous skin care (severe cases may require burn unit).
- Use infection control precautions.

See Consultation and Reporting Information.

Generalized papular, vesicular or pustular eruption with varying degrees of erythema (typical lesion size > 5 mm). Lesions typically appear within 6-9 days of vaccination, evolve through normal vaccination stages and are in the same stage of development. Severe systemic symptoms present.

Generalized vaccinia (severe form)
- Request release of VIG (first line agent) or Cidofovir (second line agent).
- Contact state health department for guidance.
- Hospitalize and provide supportive care.
- Conduct immunologic work-up.
- Use infection control precautions.

See Consultation and Reporting Information.

Rapid, progressive, and painless extension of central vaccination lesion or progression without apparent healing after 15 days. Lesion often necrotic. Initially little to no inflammation, +/- distant metastatic lesions to skin, bones, and viscera.

Progressive vaccinia (Vaccinia necrosum, Vaccinia gangrenosum).
- Request release of VIG (first line agent) or Cidofovir (second line agent).
- Contact state health department for guidance.
- Hospitalize and provide supportive care with attention to secondary infections.
- Conduct immunologic work-up.
- Use infection control precautions.

See Consultation and Reporting Information.

Consultation and Reporting Information

Civilian health care providers who need clinical consultation with or without release of Vaccinia Immune Globulin (VIG) (first line agent) or Cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/ local health department or the CDC Clinician Information Line at (877) 554-4625. Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257.

Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.

Please call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit http://www.bt.cdc.gov/agent/smallpox/index.asp for general public information about smallpox vaccination. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

Laboratory testing

Consider use of licensed diagnostic tests to rule out etiologies not related to vaccina virus contained in smallpox vaccine.

Differential diagnosis for smallpox vaccine adverse reactions distant from vaccination site (or in a close contact)

Consider conditions not related to smallpox vaccine such as:
- Varicella
- Disseminated herpes zoster
- Disseminated herpes simplex virus (HSV)
- Meningococcemia
- Kawasaki syndrome
- Sweet's syndrome (Acute febrile neutrophilic dermatosis)
- Leukocytoclastic vasculitis (e.g. Henoch-Schonlein purpura)

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Ophthalmologic Reactions/Inadvertent Innoculation in a Vaccinee (or in a Close Contact)

www.bt.cdc.gov/agent/smallpox/vaccination/clineval **(03-12-2003 Version)**

Legend
Morbidity and Mortality Risk based on clinical presentation.

- Low
- Moderate
- High

Vaccine Recipient or Close Contact? → Yes → History of known risk factors for smallpox vaccine adverse reactions?

Yes → **Consult with state/local health department and CDC to obtain clinical guidance and to report inadvertent exposure to vaccinia virus contained in smallpox vaccine. Management of the adverse reactions discussed in this Tool may be different when risk factor(s) are present. See Consultation and Reporting Information.**

Vaccine recipients or close contacts with risk factor(s) should be reported, whether or not an adverse event develops.

Risk Factor	Adverse Reaction (Potential/ Reported Historically)
Atopic Dermatitis/Eczema (including severe atopic blepharitis	Eczema Vaccinatum
Acute Exfoliative Dermatitis	Inadvertent Inoculation
Immunocompromised including/HIV+	Progressive Vaccinia/Generalized Vaccinia (Severe form)
Pregnancy	Fetal Vaccinia and potential unknown risks to fetus
Topical Ocular Steroid Use	Autoinoculation to the eye

No → New onset red eye and/or lesions suspicious for vaccinia (papules, vesicles, pustules or ulcerations) in or near the eye up to 10 days after the period beginning with initial vaccination through final resolution and scarification of lesions at vaccination site.

Exposure resulted from inadvertent splash in laboratory setting?

No → **Patient history and physical exam of eye:** Use infection control precautions.
Consider differential diagnosis (see differential diagnosis box). Conduct ophthalmic evaluation to include:
- o Presence and severity of corneal and lid involvement
- o Visual acuity testing
- o Presence or absence of lesions/Location of lesions
- o Presence and severity conjunctival inflammation ("red eye")

Magnified exam of eye surface (slit lamp exam if available) and fluorescein exam for corneal epithelial defects
Obtain photos of involved eye if possible (or have ophthalmology consultant obtain) **[8]**

Yes → **Request VIG consultation (See Consultation and Reporting Information). Laboratory vaccinia strains may be of higher concentration and greater virulence.**

Continue with exam

PROBABLE **inadvertent inoculation** in or near the eye.

POSSIBLE **inadvertent inoculation** in or near the eye.

White non-inflamed eye associated with suspicious lid **[2]** or **periocular [1]** lesions only. No visible lesions in eye.

Red inflamed eye (**conjunctivitis [3]**) with suspicious lesions in or near the eye. Urgent ophthalmology consultation and consider beginning antivirals right away.

Red inflamed eye (**conjunctivitis [3]**) only - no visible lesion in or near the eye.

Lesions on or near lid margin (**blepharitis [2]**)?

No → **Isolated periocular lesions**: Close observation. Consider ophthalmology consultation to assist in management.

Yes → **Mild Blepharitis**: Recommend topical antiviral **prophylaxis [5]** especially if lesions are present on lid margin. Recommend ophthalmology consultation to assist in management.
Moderate/Severe Blepharitis: Begin topical antiviral **prophylaxis [5]**. Ophthalmology consultation in 12-24 hours (or sooner depending on severity) to evaluate and assist in management. Consider VIG consultation.

Corneal [4] lesions?

No → **Conjunctival [3], lid [2] or periocular [1] lesions.**
Mild: Begin prophylaxis [5], urgent ophthalmology consultation. Consider VIG consultation.
Severe: Begin prophylaxis [5], emergent ophthalmology consultation. Recommend VIG consultation.

Yes → **Associated conjunctival [3] or lid [2] lesions?**

No → **Keratitis only: Begin topical antiviral treatment [6]. Emergent ophthalmology consultation to evaluate and assist with management. VIG not indicated. See additional information at footnote [7]**

Yes → **Blepharitis and/or conjunctivitis associated with keratitis: Emergent ophthalmology consultation.**
Mild: Begin topical antiviral treatment [6].
Observe for progressive disease
Severe: Begin topical antiviral treatment [6]. Consider VIG (one dose).

Consider differential diagnosis for new onset red eye with high index of suspicion for vaccinia infection. Close observation for development of suspicious lesions.
Recommend ophthalmology consultation as indicated to evaluate for possible vaccinia versus other unrelated causes. Further treatment as indicated by ophthalmic exam

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Ophthalmologic Reactions/Inadvertent Innoculation in a Vaccinee (or in a Close Contact)

www.bt.cdc.gov/agent/smallpox/vaccination/clineval **(03-12-2003 Version)**

Footnotes:

1. **Periocular involvement:** (generally above the brow or below the inferior orbital rim)
   Papules, vesicles or pustules not involving the ocular adnexa, lids, lid margins or canthi.
2. **Blepharitis:** (lid involvement)
   Mild - few pustules, mild edema, no fever.
   Severe - pustules, edema, hyperemia, lymphadenopathy (preauricular and/or submandibular), cellulitis, fever.
3. **Conjunctivitis:** (involvement of membrane that lines inner surface of the eyelid and exposed surface of the eyeball; excluding the cornea)
   Mild - mild hyperemia and/or edema, no membranes or focal lesions.
   Severe - marked hyperemia, edema, membranes, focal lesions, lymphadenopathy (preauricular and/or submandibular), fever.
4. **Keratitis:** (corneal involvement)
   Mild - grey epitheliitis, no epithelial defect, no stromal haze or infiltrate (no cloudy cornea).
   Moderate - epithelial defect.
   Severe - ulcer, stromal haze or infiltrate (cloudy cornea).
5. **Prophylaxis:** To prevent extension of vaccinia infection to conjunctiva and cornea: Topical trifluridine - 5 times/day (every four hours while awake) for up to 14 days or until all periocular and/or lid lesions have healed and scabs have fallen off. If no improvement or symptoms worsen after 24-48 hours consider increasing to 9 times/day (see footnote [6]). Hyperemia is an expected consequence of therapy, especially after 14 days of use. Recommend ophthalmology consultation to assist in management anytime trifluridine is used.
6. **Treatment:** To minimize progression and begin resolution of vaccinia infection in cornea and conjunctiva: Topical trifluridine - 9 times/day (every two hours while awake) for up to 14 days or until all lesions have healed. Hyperemia is an expected consequence of therapy, especially after 14 days of use. Recommend ophthalmology consultation to assist in management anytime trifluridine is used.
   Available topical antiviral agents: Trifluridine (Viroptic®) and vidarabine (Vira-A®). Trifluridine and vidarabine are not approved by FDA for treatment of vaccinia disease, although the product labels for trifluridine and vidarabine state that the drugs have *in vitro* and *in vivo* activity against vaccinia virus. Vidarabine is no longer being manufactured, but supplies might be available in certain areas.
7. **Keratitis only:** VIG should not be withheld if a co-morbid condition exists (EV or PV). Consider topical ophthalmic antibacterial prophylaxis in the presence of keratitis. After corneal epithelium has healed consider use of topical steroids (steroids should only be used under supervision of an ophthalmologist).
8. **Photographs:** Recommend obtaining digital photos of involved eye and periocular region. Consult with ophthalmology as needed for photos (Digital photos preferred but 35mm photos or scanned images are welcome).

Differential Diagnosis for smallpox vaccine adverse reactions*

Consider non-smallpox vaccine related conditions, such as:
- Viral conjunctivitis (usually adenovirus)
- Bacterial conjunctivitis
- Allergic conjunctivitis
- Allergic contact dermatitis (e.g. poison ivy, poison oak)
- Contact lens-related infection
- Hordeolum (stye) or chalazion
- Subconjunctival hemorrhage
- Herpes simplex virus (HSV)
- Herpes zoster virus (varicella or shingles)
- Molluscum contagiosum
- Bacterial keratitis
- Preseptal or orbital cellulitis
- Drug reaction
- Insect bite
- Norwegian scabies
- Chemical/toxic exposure

* List should not be regarded as comprehensive.

This clinical tool is intended to guide primary care clinicians (such as ER physician, internist, pediatrician, family practice, optometrist, physician assistant or nurse practitioner) in preliminary evaluation/ treatment. Referral to ophthalmology for suspected cases as indicated is recommended.

Consultation and Reporting Information

Civilian health care providers who need clinical consultation with or without release of vaccinia immune globulin (VIG) (first line agent) or cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/ local health department or the CDC Clinician Information Line at (877) 554-4625. Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257. Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.

Please call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit http://www.bt.cdc.gov/agent/smallpox/index.asp for general public information about smallpox vaccination. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

Legend
Morbidity and Mortality Risk based on clinical presentation.

- Low
- Moderate
- High

Clinical Evaluation Tool for Smallpox Vaccine Adverse Reactions
Ophthalmologic Reactions / Eye Splash or Other Potential Exposure to Vaccinia Virus
www.bt.cdc.gov/agent/smallpox/vaccination/clineval (03-25-2003 Version)

History of potential inadvertent exposure to vaccinia virus in or near the eye(s).
No lesions or inflammation present.

History of known risk factors for smallpox vaccine adverse reactions?

Yes →

Consult with state/local health department and CDC to obtain clinical guidance and to report inadvertent exposure to vaccinia virus contained in smallpox vaccine. Management of the adverse reactions discussed in this Tool may be different when risk factor(s) are present. See Consultation and Reporting Information.

Vaccine recipients or close contacts with risk factor(s) should be reported, whether or not an adverse event develops.

Risk Factor	Adverse Reaction (Potential/ Reported Historically)
Atopic Dermatitis/Eczema (including severe atopic blepharitis	Eczema Vaccinatum
Acute Exfoliative Dermatitis	Inadvertent Inoculation
Immunocompromised including/HIV+	Progressive Vaccinia/Generalized Vaccinia (Severe form)
Pregnancy	Fetal Vaccinia and potential unknown risks to fetus
Topical Ocular Steroid Use	Autoinoculation to the eye

No ↓

Report incident of possible inadvertent inoculation in or near eye from laboratory setting or direct splash from smallpox vaccine.

Less than 7-10 days since exposure?

No → **Close observation. No immediate treatment indicated. Obtain ophthalmology consultation if symptoms develop.**

Yes ↓

See Consultation and Reporting Information

Consider immediate gentle irrigation of affected eye with sterile water or saline if exposure occurred within a few hours of presentation. Avoid irrigation under high pressure to prevent iatrogenic corneal abrasions.

Possible inadvertent inoculation in or near eye from high-risk vaccinia strain in laboratory setting (e.g. splash to eye). Laboratory vaccinia strains may be of higher concentration and greater virulence.

Request VIG consultation (see Consultation and Reporting box to obtain). Begin topical antiviral prophylaxis [1]. Close observation. Obtain immediate baseline ophthalmology consultation to assist in evaluation, management and follow-up.

Possible inadvertent inoculation in or near eye from vaccinia in smallpox vaccine (e.g. splash to eye). Vaccinia in smallpox vaccine is in lower concentration and less virulent than lab strains.

VIG not indicated. Recommend topical antiviral prophylaxis up to 5 days **[1]**. Close observation. Obtain immediate baseline ophthalmology consultation to assist in evaluation, management and follow-up.

Possible inadvertent inoculation in or near eye from vaccinia lesion in vaccine recipient or close contact. (e.g., contact with vaccine site followed by rubbing in or near eye). Obtain history of exposure to assess potential risk.

Does clinician feel there is significant risk of inadvertent inoculation?

Yes → VIG not indicated. Consider topical antiviral prophylaxis **[1]**. Close observation. Obtain baseline ophthalmology consultation to assist in evaluation, management and follow-up.

No → **Close observation. No immediate treatment indicated. Obtain ophthalmology consultation if signs/symptoms develop.**

Footnote:
1. **Topical antiviral prophylaxis:** Trifluridine eye drops - 5 times/day up to 5 days. Discontinue if no evidence of vaccinial infection is present after 5 days. Trifluridine may cause some eye redness/irritation with use. Close follow-up by ophthalmology indicated while on trifluridine to evaluate treatment.

Consultation and Reporting Information

Civilian health care providers who need clinical consultation with or without release of vaccinia immune globulin (VIG) (first line agent) or cidofovir (second line agent) for potential smallpox vaccine adverse reactions should contact their state/ local health department or the CDC Clinician Information Line at (877) 554-4625. Military health care providers (or civilian providers treating a DoD healthcare beneficiary) requesting clinical consultation should call (866) 210-6469, and if requesting VIG release should call (888) USA-RIID or (301) 619-2257. Health care providers should report smallpox vaccine adverse events to their state/ local health department and to the Vaccine Adverse Event Reporting System (VAERS) at http://www.vaers.org/ or (800) 822-7967.

Please call (888) 246-2675 (Español (888) 246-2857, TTY (866) 874-2646) or visit http://www.bt.cdc.gov/agent/smallpox/index.asp for general public information about smallpox vaccination. Persons experiencing urgent or life-threatening medical events should seek immediate medical assistance.

SMALLPOX FACT SHEET . *Information for Clinicians and Public Health Professionals*

Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir

Smallpox vaccination (vaccinia) is a generally safe and effective means to prevent smallpox. However, in a number of individuals, smallpox vaccination can result in untoward effects and adverse reactions. The majority of adverse reactions caused by the smallpox vaccine are mild to moderate complications that resolve on their own. Serious reactions are rare, but can be fatal.

There are two medications that may help persons who have certain serious reactions to the smallpox vaccine; vaccinia immune globulin (VIG) and cidofovir. VIG has been extensively used in the past and felt (but not shown in controlled studies) to be effective. Cidofovir may be effective based on studies in animals. Treatment with these medications may require the vaccine recipient to be in the hospital. They are investigational and may cause a number of serious side effects themselves.

Vaccinia Immune Globulin (VIG)

- Vaccinia immune globulin (VIG) is a product used to treat certain serious adverse reactions caused by smallpox vaccine. There are about 2,700 treatment doses of VIG (enough for predicted reactions with more than 27 million people). Additional doses of VIG are being produced this year.
- 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.
- An effort is underway to produce new lots of VIG that will meet the standards for intravenous immune globulin. This IV-VIG will require new recommendations for both dosage and preferred method of administration. The new IV-VIG has a low level of aggregated protein, allowing it to be used by either the IM or IV route. Intravenous VIG will be most likely administered at a lower dose than the intramuscular preparation.

VIG Indications, Precautions and Contraindications

- Historically, VIG has been indicated for accidental implantation involving extensive lesions, eczema vaccinatum, generalized vaccinia, and progressive vaccinia.
- VIG is NOT recommended for mild instances of accidental implantation, mild or limited generalized vaccinia, erythema multiforme, or encephalitis post-vaccination.
- For more information on the adverse reactions mentioned above, go to www.cdc.gov/smallpox.

Concomitant Use of VIG with Vaccination

In some instances, VIG was given concomitantly with vaccination to .prevent. complications in a susceptible person. Not enough is known about the efficacy of this practice to recommend its use. Furthermore, there is currently an insufficient amount of VIG to use prophylactically when the benefits are uncertain.

Dosage

When it was used in the 1950s-1970s, 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 ml/kg was used. These large doses were split into smaller units, and injected at multiple sites spread out over time.

Frequency of Use

Data from a CDC survey indicates that VIG was administered at a rate of 47 uses per 1 million primary vaccinees and 2 uses per million revaccinees.

Cidofovir

- Another drug that may be used to treat certain serious smallpox vaccine reactions is cidofovir, an antiviral drug marketed as Vistide.
- Cidofovir is currently licensed for the treatment of CMV 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 Investigational New Drug (IND) protocol. Under the IND, cidofovir would only be used when VIG was not efficacious.
- Renal toxicity is a known adverse reaction of cidofovir.

Obtaining VIG and Cidofovir

Indications for VIG/cidofovir release

- Vaccinia Immune Globulin (VIG) and cidofovir are indicated for the treatment of certain serious smallpox vaccine adverse events, including progressive vaccinia, eczema vaccinatum, generalized vaccinia (severe form or if underlying illness), and inadvertent inoculation (if judged to be severe due to the number of lesions, toxicity of affected individual, or significant pain). VIG is recommended as the first line of therapy. Cidofovir may be considered as a secondary treatment, and will only be released by CDC after all inventories of VIG have been exhausted, after a patient fails to improve with VIG treatment, or as a last effort for a patient who is otherwise near death.
- VIG and cidofovir are available for civilians through the CDC under Investigational New Drug (IND) protocols for treatment of specific smallpox vaccine reactions. Based on the anticipated number of adverse events resulting from the planned vaccination program for healthcare workers, CDC.s supply of VIG should be adequate.
- Physicians at military facilities may request VIG by calling the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at 301-619-2257 or 888-USA-RIID and asking for the physician on call.

Process for obtaining VIG/cidofovir under Investigational New Drug Protocol (IND)

- Physicians should first contact their State Health Department when seeking consultation for civilian patients experiencing a severe or unexpected adverse event following smallpox vaccination or when requesting VIG or cidofovir. If further consultation is required, or VIG or cidofovir is recommended, the physician will be referred to the **CDC Clinical Information Line (CIL) at 1-877-554-4625**. The nurses staffing the CIL will take basic information and then expedite the call to the CDC Smallpox Vaccine Adverse Events Clinical Consultation Team. The CDC Clinical Consultation Team will provide in-depth consultation and will facilitate VIG or cidofovir release as appropriate.

- According to FDA regulations, VIG or cidofovir released from the CDC must be administered according to their investigational new drug protocols (IND). The IND mandates that the treating physician must become a co-investigator. The responsibilities of the co-investigator are primarily to complete follow-up forms describing the clinical status of the patient being treated with VIG and/or cidofovir, including the prompt report of any significant adverse reaction in the recipient. Detailed information on the requirements of the IND will be shipped with the products.
- Details on the process for requesting VIG from USAMRIID for vaccinated military personnel with adverse reactions may be obtained at http://www.smallpox.army.mil/resource/vig.asp?ste=milvax.

Shipment of VIG/cidofovir

- VIG/cidofovir will be shipped by the National Pharmaceutical Stockpile (NPS). The CDC Smallpox Vaccine Adverse Events Clinical Consultation Team will coordinate the shipment of VIG/cidofovir with NPS. The cost of VIG and cidofovir and the cost of shipping will be covered by the U.S. Government. Arrival of shipments should be expected within 12 hours of the approval for release.

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MMWR

Recommendations and Reports

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Smallpox Vaccination and Adverse Reactions

Guidance for Clinicians

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Summary

The guidance in this report is for evaluation and treatment of patients with complications from smallpox vaccination in the preoutbreak setting. Information is also included related to reporting adverse events and seeking specialized consultation and therapies for these events. The frequencies of smallpox vaccine-associated adverse events were identified in studies of the 1960s. Because of the unknown prevalence of risk factors among today's population, precise predictions of adverse reaction rates after smallpox vaccination are unavailable. The majority of adverse events are minor, but the less-frequent serious adverse reactions require immediate evaluation for diagnosis and treatment. Agents for treatment of certain vaccine-associated severe adverse reactions are vaccinia immune globulin (VIG), the first-line therapy, and cidofovir, the second-line therapy. These agents will be available under Investigational New Drug (IND) protocols from CDC and the U. S. Department of Defense (DoD).

Smallpox vaccination in the preoutbreak setting is contraindicated for persons who have the following conditions or have a close contact with the following conditions: 1) a history of atopic dermatitis (commonly referred to as eczema), irrespective of disease severity or activity; 2) active acute, chronic, or exfoliative skin conditions that disrupt the epidermis; 3) pregnant women or women who desire to become pregnant in the 28 days after vaccination; and 4) persons who are immunocompromised as a result of human immunodeficiency virus or acquired immunodeficiency syndrome, autoimmune conditions, cancer, radiation treatment, immunosuppressive medications, or other immunodeficiencies. Additional contraindications that apply only to vaccination candidates but do not include their close contacts are persons with smallpox vaccine-component allergies, women who are breastfeeding, those taking topical ocular steroid medications,

those with moderate-to-severe intercurrent illness, and persons aged <18 years. In addition, history of Darier disease is a contraindication in a potential vaccinee and a contraindication if a household contact has active disease. In the event of a smallpox outbreak, outbreak-specific guidance will be disseminated by CDC regarding populations to be vaccinated and specific contraindications to vaccination.

Vaccinia can be transmitted from a vaccinee's unhealed vaccination site to other persons by close contact and can lead to the same adverse events as in the vaccinee. To avoid transmission of vaccinia virus (found in the smallpox vaccine) from vaccinees to their close contacts, vaccinees should wash their hands with warm soapy water or hand rubs containing ≥60% alcohol immediately after they touch their vaccination site or change their vaccination site bandages. Used bandages should be placed in sealed plastic bags and can be disposed of in household trash.

Smallpox vaccine adverse reactions are diagnosed on the basis of clinical examination and history, and certain reactions can be managed by observation and supportive care. Adverse reactions that are usually self-limited include fever, headache, fatigue, myalgia, chills, local skin reactions, nonspecific rashes, erythema multiforme, lymphadenopathy, and pain at the vaccination site. Other reactions are most often diagnosed through a complete history and physical and might require additional therapies (e.g., VIG, a first-line therapy and cidofovir, a second-line therapy). Adverse reactions that might require further evaluation or therapy include inadvertent inoculation, generalized vaccinia (GV), eczema vaccinatum (EV), progressive vaccinia (PV), postvaccinial central nervous system disease, and fetal vaccinia.

Inadvertent inoculation occurs when vaccinia virus is transferred from a vaccination site to a second location on the vaccinee or to a close contact. Usually, this condition is self-limited and no additional care is needed. Inoculations of the eye and eyelid require evaluation by an ophthalmologist and might require therapy with topical antiviral or antibacterial medications, VIG, or topical steroids.

GV is characterized by a disseminated maculopapular or vesicular rash, frequently on an erythematous base, which usually occurs 6--9 days after first-time vaccination. This condition is usually self-limited and benign, although treatment with VIG might be required when the patient is systemically ill or found to have an underlying immunocompromising condition. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection.

EV occurs among persons with a history of atopic dermatitis (eczema), irrespective of disease severity or activity, and is a localized or generalized papular, vesicular, or pustular rash, which can occur anywhere on the body, with a predilection for areas of previous atopic dermatitis lesions. Patients with EV are often systemically ill and usually require VIG. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection.

PV is a rare, severe, and often fatal complication among persons with immunodeficiencies, characterized by painless progressive necrosis at the vaccination site with or without metastases to distant sites (e.g., skin, bones, and other viscera). This disease carries a high mortality rate, and management of PV should include aggressive therapy with VIG, intensive monitoring, and tertiary-level supportive care. Anecdotal experience suggests that, despite treatment with VIG, persons with cell-mediated immune deficits have a poorer prognosis than those with humoral deficits. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection.

Central nervous system disease, which includes postvaccinial encephalopathy (PVE) and postvaccinial encephalomyelitis (or encephalitis) (PVEM), occur after smallpox vaccination. PVE is most common among infants aged <12 months. Clinical symptoms of central nervous system disease indicate cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma. PVE and PVEM are not believed to be a result of replicating vaccinia virus and are diagnoses of exclusion. Although no specific therapy exists for PVE or PVEM, supportive care, anticonvulsants, and intensive care might be required.

Fetal vaccinia, resulting from vaccinial transmission from mother to fetus, is a rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception. It is manifested by skin lesions and organ involvement, and often results in fetal or neonatal death. No known reliable intrauterine diagnostic test is available to confirm fetal infection. Given the rarity of congenital vaccinia among live-born infants, vaccination during pregnancy should not

ordinarily be a reason to consider termination of pregnancy. No known indication exists for routine, prophylactic use of VIG in an unintentionally vaccinated pregnant woman; however, VIG should not be withheld if a pregnant woman develops a condition where VIG is needed.

Other less-common adverse events after smallpox vaccination have been reported to occur in temporal association with smallpox vaccination, but causality has not been established. Prophylactic treatment with VIG is not recommended for persons or close contacts with contraindications to smallpox vaccination who are inadvertently inoculated or exposed. These persons should be followed closely for early recognition of adverse reactions that might develop, and clinicians are encouraged to enroll these persons in the CDC registry by calling the Clinician Information Line at 877-554-4625.

To request clinical consultation and IND therapies for vaccinia-related adverse reactions for civilians, contact your state health department or CDC's Clinician Information Line (877-554-4625). Clinical evaluation tools are available at http://www.bt.cdc.gov/agent/smallpox/vaccination/clineval. Clinical specimen-collection guidance is available at http://www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp. Physicians at military medical facilities can request VIG or cidofovir by calling the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at 301-619-2257 or 888-USA-RIID.

Introduction

Smallpox vaccine is made from live vaccinia virus and protects against the disease smallpox. It does not contain variola virus, the causative agent of smallpox (*1*). Because viral replication and shedding occurs at the vaccination site (beginning 2--5 days postvaccination), unintended transmission is possible from the time immediately after vaccination until the scab separates from the skin (approximately 2--3 weeks) (*2*). Although virus exists in the scab, it is bound in the fibrinous matrix, and the scab is not believed to be highly infectious. Viral shedding might be of shorter duration among revaccinees (*2,3*). During the smallpox eradication era, transmission usually required close interaction and occurred most often in the home (*4*) (see Transmission of Vaccinia Virus; see Preventing Contact Transmission).

Worldwide, different vaccinia strains have been used for production of smallpox vaccine, but all U.S. vaccine formulations contain the New York City Board of Health (NYCBOH) vaccinia strain. This strain has been reported to be less reactogenic (i.e., it causes fewer adverse events) than other strains (*1*). U.S. National Pharmaceutical Stockpile (NPS) stores of smallpox vaccine include two previously manufactured calf-lymph--derived vaccines, Dryvax® (Wyeth Laboratories Inc., Marietta, Pennsylvania), and Aventis Pasteur vaccine (Swiftwater, Pennsylvania); and two newly developed vaccines from Acambis/Baxter Pharmaceuticals (Cambridge, Massachusetts), ACAM1000, which is grown in human embryonic lung cell culture (MRC-5), and ACAM2000, which is grown in African green monkey cells (VERO cells) (CDC Drug Services, unpublished data, 2002). Prospective studies are under way to determine the reactogenicity of the newer cell culture vaccines. Dryvax is the vaccine used in the current U.S. smallpox vaccination effort. CDC is holding other vaccines in reserve (*5*).

Smallpox vaccination in the preoutbreak setting is contraindicated for persons who have the following conditions or have a close contact with the following conditions: 1) a history of atopic dermatitis (commonly referred to as eczema), irrespective of disease severity or activity; 2) active acute, chronic, or exfoliative skin conditions that disrupt the epidermis; 3) pregnant women or women who desire to become pregnant in the 28 days after vaccination; and 4) persons who are immunocompromised as a result of human immunodeficiency virus or acquired immunodeficiency syndrome, autoimmune conditions, cancer, radiation treatment, immunosuppressive medications, or other immunodeficiencies. Additional contraindications that apply only to vaccination candidates but do not include their close contacts are persons with smallpox vaccine-component allergies, women who are breastfeeding, those taking topical ocular steroid medications, those with moderate-to-severe intercurrent illness, and persons aged <18 years. In addition, history of Darier disease is a contraindication in a potential vaccinee and a contraindication if a household contact has active disease. In the event of a smallpox outbreak, outbreak-specific guidance will be disseminated by CDC regarding populations to be vaccinated and specific contraindications to vaccination.

Normal Vaccination Progression

Smallpox vaccine is administered by using the multiple-puncture technique with a bifurcated needle (*6*). The vaccinia virus replicates in the dermis of the skin; 3--5 days later, a papule forms at the vaccination site of immunocompetent vaccine-naïve persons (also referred to as first-time or primary vaccinees) (*1*). The papule becomes vesicular (approximately day 5--8), then pustular, and usually enlarges to reach maximum size in 8--10 days. The pustule dries from the center outward and forms a scab that separates 14--21 days after vaccination, usually leaving a pitted scar (Figures 1--3).

Formation by days 6--8 postvaccination of a papule, vesicle, ulcer, or crusted lesion, surrounded by an area of induration signifies a response to vaccination; this event is referred to as a major reaction or a take, and usually results in a scar. During the smallpox eradication era, persons with vaccination scars had much lower attack rates when exposed to smallpox cases than did nonvaccinated persons. Therefore, a take has been a surrogate correlate of immunity to smallpox. Although the level of antibody that protects against smallpox infection is unknown, >95% of first-time vaccinees (i.e., persons receiving their first dose of smallpox vaccine) have increased neutralizing or hemagglutination inhibition antibody titers (*7*).

Interpreting Vaccination Results

Vaccination-site reactions are classified into two categories: major reactions and equivocal reactions (*1*). A major reaction indicates a successful vaccine take and is characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer. All other responses are equivocal reactions and are nontakes. Equivocal reactions can be caused by suboptimal vaccination technique, use of subpotent vaccine, or residual vaccinial immunity among previously vaccinated persons. Persons with equivocal reactions cannot be presumed to be immune to smallpox, and revaccination is recommended (Figures 4 and 5).

The World Health Organization (WHO) has recommended that response to vaccination be evaluated on postvaccination day 6, 7, or 8 (*1*). These are the days of peak viral replication, and the period during which take should be assessed for both first-time vaccinees and revaccinees. If the response to vaccination is evaluated too early (e.g., <6 days postvaccination), certain equivocal responses will look reactive because of dermal hypersensitivity to vaccinial proteins. These reactions are sometimes referred to as immediate reactions but are not successful takes. If the response to vaccination is evaluated too late (e.g., >8 days postvaccination), the vaccination take might be missed among persons with prior immunity to vaccinia who might experience a more rapid progression of the vaccination site. Responses among revaccinees that resolve in <6 days are sometimes referred to as accelerated reactions and are not successful takes.

Expected Range of Vaccine Reactions

A range of expected reactions occurs after vaccination. These normal reactions do not require specific treatment and can include fatigue, headache, myalgia, regional lymphadenopathy, lymphangitis, pruritis, and edema at the vaccination site, as well as satellite lesions, which are benign, secondary vaccinial lesions proximal to the central vaccination lesions (*8*) (Wyeth Laboratories. Dryvax [package insert]. Marietta, PA: Wyeth Laboratories, 1994).

Historically, 21% of reactions associated with first-time vaccination caused the vaccinee to consult a physician (*9*). A recent vaccination trial was conducted among 680 adults, all of whom were first-time vaccinees (*10*). During the 14 days after vaccination, all reported having ≥1 of the following symptoms at some point: fatigue (50%), headache (40%), muscle aches and chills (20%), nausea (20%), and fever, defined as a temperature ≥37.7°C or 100°F (10%). Symptom duration was not reported. The majority of local symptoms were reported during the second week after vaccination and included pain at the vaccination site (86%), and regional lymphadenopathy (54%). Approximately one third of vaccinees were sufficiently ill to have trouble sleeping or to miss school, work, or recreational activities. Similar findings are reported by the CDC Smallpox Diary Card Database, a reporting system of postvaccination symptoms among 633 vaccinees who received smallpox vaccine during 2001--2002 (CDC, unpublished data, 2001--2002). In this series, postvaccination days 3--7 were the days when the majority of vaccinees (78%) reported their symptoms. In both series, symptoms were self-limited and

required only symptomatic care.

During the smallpox eradication era, fever after vaccination occurred frequently but was less common among adults than children (CDC, unpublished data). For adults, fever is more frequently noted among first-time vaccinees than revaccinees (NIH, unpublished data, 2003). In one vaccination series involving children, approximately 70% experienced >1 day of temperatures >100°F during the 4--14 days after primary vaccination (*7*), and 15%--20% of children experienced temperatures >102°F. After revaccination, 35% of children experienced temperatures >100°F, and 5% experienced temperatures of >102°F (*11*).

Satellite lesions occasionally occur at the perimeter of the vaccination site and should not be confused with the early discrete vesicles that might coalesce into a central pox-like lesion. Satellite lesions are a benign finding, do not require treatment, and should be cared for as vaccination sites. (Figure 6).

Large Vaccination Reactions and Robust Takes

Large vaccination reactions (i.e., >10 cm in diameter) at the site of inoculation occur in approximately 10% of first-time vaccinees and are expected variants of the typical evolution of the vaccination site (*10*). However, sometimes these large vaccination reactions have been reported as adverse events and misinterpreted as cellulitis, requiring antibiotic treatment. In the 1968 national surveillance of the United States for smallpox vaccine complications, 13 of 572 adverse event reports were for unusually large and painful robust takes (RTs) (*9,12*) (Figures 7 and 8).

Bacterial infection of the vaccination site is uncommon but affects children more often than adults, because children are more likely to touch and contaminate their vaccination sites. In a 1963 U.S. national survey, 433 complications were reported among 14 million smallpox vaccinees; of these, two were secondary bacterial infections of the vaccination site (*13*). One case resolved without sequelae, whereas the other resulted in a nonfatal case of acute streptococcal glomerulonephritis. Other reports describe the occurrence of bacterial infection at the vaccination site, but do not provide details regarding the causative organisms (*9,12*). Specimens for bacterial cultures can be obtained by using swabs or aspiration. Gram stains can detect normal skin flora and are useful only when unusual pathogens are present. If empiric antibacterial therapy is administered, therapy should be adjusted after the bacterial pathogen and its sensitivities to various antibacterial medications are known.

Identifying RTs

Differentiating an RT from bacterial cellulitis can be difficult. RTs occur 8--10 days postvaccination, improve within 72 hours of peak of symptoms, and do not progress clinically. Fluctuant enlarged lymph nodes are not expected and warrant further evaluation and treatment. In contrast, secondary bacterial infections typically occur within 5 days of vaccination or >30 days postvaccination, and unless treated, the infection will progress (*14--16*). The interval of onset to peak symptoms is the key factor in diagnosing RTs. Fever is not helpful in distinguishing RTs from bacterial cellulitis because it is an expected immunologic response to vaccinia vaccination.

When an RT is suspected, management includes vigilant observation, patient education, and supportive care that includes rest of the affected limb, use of oral nonaspirin analgesic medications, as well as oral antipruritic agents. Salves, creams, or ointments, including topical steroids or antibacterial medications, should not be applied to the vaccination site.

During 2001, CDC staff vaccinated 191 federal public health smallpox response team members; 9 vaccinees (5%) met the case definition for an RT, with an area of redness >7.5 cm with swelling, warmth, and pain at the vaccination site (CDC, unpublished data, 2002). Six vaccinees with RTs were treated for suspected bacterial cellulitis. Three affected vaccinees did not seek medical care and, therefore, did not receive antibiotic therapy. All affected vaccinees reported peak of symptoms 8--10 days after vaccination and improvement of symptoms within 24--72 hours whether they were treated with antibacterial medications. Cases did not cluster by age, sex, vaccination status, or vaccine lot number.

To estimate an estimated rate of RTs, CDC staff conducted a limited survey and determined rates of 2% (2 of 99 persons) and 16% (13 of 80) (CDC, unpublished data, 2001). The different rates between clinics might be caused by different methods of case ascertainment. However, both clinics reported that irrespective of antibiotic therapy, symptoms peaked on postvaccination day 8--10, and improved within 24--72 hours. Antibacterial medications did not shorten the duration or lessen the severity of symptoms.

Transmission of Vaccinia Virus

Vaccinia can be transmitted from a vaccinee's unhealed vaccination site to other persons by close contact and can lead to the same adverse events as in the vaccinee. Cases arising from contact transmission have resulted in either eczema vaccinatum (EV) or inadvertent inoculation, and these cases occurred approximately 5--19 days after suspected exposure to the index case (*17*). In addition, two cases have been reported of contact transmission, which resulted in fetal vaccinia (*18,19*) (see Fetal Vaccinia).

No data exist to indicate that vaccinia transmission occurs by aerosolization (*17*). Although one study reported successful recovery of the vaccinia virus from the oropharynx of children receiving other vaccine strains (*20*), droplet infection has not been epidemiologically implicated in transmission of vaccinia. In one unpublished study in the 1960s (J. Michael Lane, M.D., formerly Director, Smallpox Eradication Program, Communicable Disease Center, personal communication, 2002), researchers were unable to recover the NYCBOH vaccinia strain from the nasal swabs of healthy vaccinees. The low rate of contact vaccinia and the link to direct physical contact indicate that aerosol transmission does not occur. The overall transmission of contact vaccinia in the 1960s occurred in the range of 2--6/100,000 first-time vaccinations (*4*); infection-control precautions should be taken to reduce this likelihood (*21*).

Preventing Contact Transmission

Correct hand hygiene prevents the majority of inadvertent inoculations and contact transmissions after changing bandages or other contact with the vaccination site (*21*). The vaccination site can be left uncovered or covered with a porous bandage (e.g., gauze) (*6*).

Preventing Contact Transmission Among Health-Care Workers

To prevent nosocomial transmission of vaccinia virus, health-care workers when involved in direct patient care should keep their vaccination sites covered with gauze or a similar material to absorb exudates that contain vaccinia. This dressing should be covered with a semipermeable dressing to provide a barrier to vaccinia virus. Using a semipermeable dressing alone is not recommended because it might cause maceration of the vaccination site and prolong irritation and itching, which subsequently leads to increased touching, scratching, and contamination of hands. If maceration of the vaccination site occurs, the lesion should be left open to air to allow the vaccination site to dry during a period that includes no direct contact with patients or other persons. The vaccination site should be covered during direct patient care until the scab separates (*21*). Administrative leave should be considered for health-care workers who are unable to adhere to the recommended infection-control measures, which require that vaccination sites be covered during patient care duties (*21*).

Preventing Contact Transmission in Other Settings

Transmission of vaccinia is also possible in other settings when close personal contact with children or other persons occurs. In these situations, the vaccination site should be covered with gauze or a similar absorbent material, and long-sleeved clothing should be worn. Careful attention should be paid to handwashing (*21*), which should be done with soapy warm water or hand-rub solutions that are $\geq$60% alcohol-based. Historically, the home was the setting where the majority of contact transmission occurred (*4*), presumably because of intimate contact and relaxed infection-control measures.

Recognizing Vaccinia Virus Transmission

When evaluating a skin or other condition consistent with vaccinia, a history of smallpox vaccination and exposure to a household or close contact who has been vaccinated recently will often provide a source of the virus. A history of exposure to vaccinia might be difficult to obtain. A person might have had an inadvertent exposure and be unaware of being exposed to vaccinia virus, and rarely, persons have been deliberately inoculated by others as a way to vaccinate outside the approved vaccination programs (and possibly unwilling to acknowledge this exposure to vaccinia). In either case, clinicians should obtain a thorough medical history, including possible vaccinia exposure and risk factors for smallpox vaccine-related adverse reactions. Clinicians should counsel these patients regarding appropriate infection-control measures, care of their lesions, and when appropriate, the infectious risks incurred through deliberate inoculation of others. Follow-up of the patient and administration of appropriate treatment are critical if a vaccinia-related adverse reaction develops. In addition, these patients might be at increased risk for infection from bloodborne pathogens, and they should be counseled and treated appropriately.

Adverse Reactions*

Adverse reactions caused by smallpox vaccination range from mild and self-limited to severe and life-threatening (*9*,*12*,*13*,*22*,*23*). Certain smallpox vaccine reactions are similar to those caued by other vaccines (e.g., high fever, anaphylaxis, and erythema multiforme [EM]). Other adverse reactions specific to smallpox vaccination include inadvertent inoculation, ocular vaccinia, generalized vaccinia (GV), EV, progressive vaccinia (PV), postvaccinial encephalopathy (PVE) and encephalomyelitis (PVEM), and fetal vaccinia. Vaccinia-specific complications can occur among vaccinees or their contacts who have been inadvertently inoculated with vaccinia (*3*,*7*,*24*--*26*).

The information regarding adverse events presented in this report is primarily based on reports from the 1960s. Although the vaccine remains unchanged, supportive care and therapeutic care options have improved. The U.S. population has also changed and now has a higher proportion of persons with contraindications to smallpox vaccination and who are at increased risk for adverse reactions. This group includes persons with atopic dermatitis (commonly referred to as eczema), or persons who are immunocompromised as a result of cancer, radiation, autoimmune conditions, immunosuppressive therapies, or immune deficiencies (e.g., human immunodeficiency virus [HIV] or acquired immunodeficiency syndrome [AIDS]). Updated reports regarding the frequency of adverse reactions will be disseminated by CDC as data become available.

This guidance is for evaluation and treatment of patients with complications from smallpox vaccination administration during preoutbreak situations. In the event of a smallpox outbreak, considering smallpox disease will be necessary in the differential diagnosis of any recently vaccinated person who has an acute, generalized, vesicular, pustular rash illness. Until a determination is made regarding whether the rash is early smallpox disease or an adverse reaction to smallpox vaccine, these patients should be presumed to be highly infectious and placed in contact and respiratory isolation immediately. Appropriate local, state, and federal health and security officials should be contacted (*5*).

Treatments available for specific complications of smallpox vaccination include vaccinia immune globulin (VIG), cidofovir, and ophthalmic antivirals (see Ocular Vaccinial Infections and Therapy). None of these therapies have been tested in controlled clinical trials for efficacy against vaccinial infection. However, because worldwide historical experience with using VIG to treat vaccinia-related adverse events exists, it is the first-line therapy. It is available in intravenous (IV) and intramuscular (IM) preparations under Investigational New Drug (IND) protocols through CDC and the U.S. Department of Defense (DoD). Cidofovir is an antiviral medication licensed for treatment of cytomegalovirus (CMV) retinitis among patients with AIDS. Cidofovir has been demonstrated to be nephrotoxic among humans and carcinogenic among animals. Cidofovir has never been used to treat vaccinia infections among humans. In animal models, cidofovir apparently protects against subsequent orthopoxvirus growth, if administered within 24 hours after experimental inoculation (*27*). However, no studies have demonstrated it to have an effect on orthopoxvirus infection after infection has been fully established. It will be available under IND protocols from CDC and DoD and should be considered second-line therapy for vaccinia complications (see Treatments).

Frequencies of Adverse Reactions

Two primary sources are available regarding the frequency of adverse reactions from NYCBOH smallpox vaccine: the 1968 U.S. national survey (*12*) and the 1968 10-state survey (*9*) (Table 1). These two studies used different methodologies, but are complementary. In the national survey, information was gathered from seven nationwide sources. The majority of the information concerning adverse reactions came from the American Red Cross VIG-distribution system. Reactions that did not require use of VIG and those for which VIG use was not warranted were less likely to be reported through this system. The national survey statistics should be considered minimal estimates of the risks from smallpox vaccination. In the 10-state survey, clinicians were actively contacted and urged to report all adverse reactions, including those considered less severe. For this reason, the 10-state survey data probably present a better estimate of the number of persons having adverse reactions. The range of frequencies for these two studies provides an estimate for the frequencies of adverse reactions that might be expected today (*28*) (Table 1).

A review of vaccinia-related deaths (68) during a 9-year period (1959--1966 and 1968) revealed that deaths occurred among first-time vaccinees as a result of PVE (52%; 36 cases) and PV (28%; 19 cases) and among contacts as a result of EV (18%; 12 cases) (*23*).

The strain of vaccinia virus might correlate with the type and frequency of adverse reactions (*1,12*). All U.S. preparations of smallpox vaccine contain the NYCBOH strain, one of the less reactogenic strains (*1*). Therefore, the U.S. experience might not represent international experience, which reflects use of other vaccinia strains. Virulence of vaccinia strain is associated with risk for PVE and PVEM, as well as the likelihood of contact transmission (*1,4,17*).

Anticipated Adverse Reactions

Adverse reaction rates in the United States today might be higher than those previously reported because the proportion of persons at risk for adverse events is higher as a result of cancer, cancer therapy, radiation, immunomodulating medications, organ transplantation, and other illnesses (e.g., HIV/AIDS and eczema or atopic dermatitis). Adverse reactions might be better than previously expected because of advances in medical care. Rates for all adverse reactions are lower for persons previously vaccinated (*4*). During the smallpox eradication era, approximately two thirds of complications after smallpox vaccination might have been preventable and might have been avoided with better screening (*13,29*). However, screening will not eliminate risk, because the risk factors for certain adverse reactions have not been clearly defined and screening success is subject to recall bias and the participant's willingness to disclose personal information. Stringent medical screening of potential vaccinees for risk factors for adverse events, coupled with improved infection-control measures to prevent vaccinia transmission, will probably decrease preventable complications of vaccination.

Common Adverse Reactions

Local Skin Reactions

Local skin reactions can occur after smallpox vaccination. These include allergic reactions to bandage and tape adhesives, RTs, and less commonly, bacterial infections of the vaccination site (*4*). Reactions to adhesives usually result in sharply demarcated lines of erythema that correspond to the placement of adhesive tape (Figures 9 and 10). Patients have local pruritis but no systemic symptoms and are otherwise well. Frequent bandage changes, periodically leaving the vaccination site open to air, or a change to paper tape might alleviate symptoms. Care should be used to vary the positioning of tape or bandages. This condition is self-limited and resolves when bandages are no longer needed. Topical and oral steroid treatment for this reaction should be avoided because the site contains live vaccinia virus. Salves, creams, or ointments, including topical antibacterial medications, should not be applied to the vaccination site.

Nonspecific Rashes

Common nonspecific rashes associated with smallpox vaccination include fine reticular maculopapular rashes, lymphangitic streaking, generalized urticaria, and broad, flat, roseola-like erythematous macules and patches (Figure11). These rashes are believed to be caused by immune response to vaccination and do not contain vaccinia. Erythematous or

urticarial rashes can occur approximately 10 days (range: 4--17 days) after first-time vaccination. The vaccinee is usually afebrile, and the rash resolves spontaneously within 2--4 days (*8*). Nonspecific rashes are usually self-limited. These persons appear well and benefit from simple supportive care measures (e.g., oral anti-antihistamine agents).

Dermatologic Manifestations of Hypersensitivity Reactions

EM, sometimes referred to as roseola vaccinia or toxic urticaria, might appear as different types of lesions, including macules, papules, urticaria, and typical bull's-eye (targetoid or iris) lesions (*8*,*30*). Because the number of clinical descriptions of vaccinia-associated EM rashes is limited, the following details are extrapolated from common descriptions of EM occurring after herpes simplex or mycoplasma infections. The hallmark target lesion of EM associated with other infections usually appears with a central, dark papule or vesicle, surrounded by a pale zone and a halo of erythema, usually within 10 days after viral infection (*30*). The limited clinical descriptions of EM after smallpox vaccination indicate that it follows a similar course (*8*). The rash of EM might be extremely pruritic, lasting ≤4 weeks, and patients benefit from administration of oral antipruritics (*30*) (Figure 12).

Less commonly, hypersensitivity reactions can appear as a more serious condition, Stevens-Johnson syndrome (SJS). SJS can also arise from EM and typically includes systemic symptoms with involvement of ≥2 mucosal surfaces (*31*) or 10% of body surface area. This condition requires hospitalization and supportive care (*30*) (Figure 13).

The role of systemic steroids for treatment of SJS is controversial; therefore, the decision to administer systemic steroids to patients with postvaccinial SJS should be made after consultation with specialists in this area (e.g., dermatologists, immunologists, or infectious disease specialists), according to the prevailing standard of care. VIG is not used to treat nonspecific rashes, EM, or SJS, because these lesions are probably a manifestation of a hypersensitivity reaction and are not believed to contain vaccinia virus.

Vaccinia-Specific Adverse Reactions

The following guidance related to recognizing, evaluating, and treating smallpox vaccine-related adverse reactions (Table 2).

Inadvertent Inoculation

Inadvertent inoculation is a common but avoidable complication of smallpox vaccination (*9*,*22*). Inadvertent inoculation occurs when vaccinia virus is transferred from a vaccination site to a second location on the vaccinee or to a close contact. The most common sites involved are the face, eyelid, nose, mouth, lips, genitalia, and anus (Figure 14). Among immunocompetent persons, lesions follow the same course as the vaccination site.

Clinicians in the smallpox eradication era observed that when inadvertent inoculation of a vaccinee occurred close to the time of vaccination, the resulting secondary lesions matured at the same pace as the central lesion of the vaccination site. In contrast, lesions from inadvertent inoculation that occurred >5 days postvaccination appeared attenuated, which indicated that the developing immune response might limit the reaction (J. Michael Lane, M.D., formerly Director, Smallpox Eradication Program, Communicable Disease Center, personal communication, 2002) (*22*).

A primary prevention strategy to avoid inadvertent inoculation is to instruct vaccinees and their close contacts to avoid touching or scratching the vaccination site from the time of vaccination until the scab separates. In addition, vigilant handwashing with soap and warm water or hand rubs containing ≥60% alcohol, after touching an unhealed vaccination site or changing a vaccination dressing is critical. Lesions from an inadvertent inoculation contain live vaccinia virus, and the same contact precautions necessary for a vaccination site are necessary for these secondary lesions. Persons at highest risk for inadvertent inoculation are younger persons (e.g., children aged 1--4 years) and those with disruption of the epidermis.

Periocular and ocular implantation (hereafter referred to as ocular vaccinial disease) accounted for the majority of reported

inadvertent inoculations and were often noted within 7--10 days of vaccination among first-time vaccinees (*22*,*32*). Ocular vaccinial disease can occur in different forms, including blepharitis (inflammation of the eyelid), conjunctivitis, keratitis (inflammation of the cornea, including epithelial and stromal forms), iritis, or combinations thereof (*33*) (Figures 15--19). When evaluating a patient with the new onset of a red eye or periocular vesicles, vaccinia infection should be considered and history of recent vaccinia exposure (e.g., smallpox vaccination or close contact with a vaccine recipient) should be sought. The goal of therapy of ocular disease is to prevent complications, including corneal scarring associated with keratitis (Figures 17 and 18), and the patient should be comanaged with an ophthalmologist. In a limited study of vaccinia keratitis among rabbits, 1 dose of VIG did not alter the clinical course, but rabbits treated with 5 daily doses (2.5--5 times that recommended for humans) developed larger and more persistent corneal scars, compared with control animals (*34*). The 2001 Advisory Committee on Immunization Practices (ACIP) recommendation states that VIG is contraindicated in a patient with vaccinial keratitis (*6*). However, in November 2002, this recommendation was reevaluated and modified by the Public Health Service (see Ocular Vaccinial Infections and Therapy). VIG should not be withheld if a comorbid condition exists that requires administration of VIG (e.g., EV or PV) and should be considered for severe ocular disease, except isolated keratitis. In these situations, VIG should be administered if the risk of the comorbid condition is greater than the potential risk of VIG-associated complications of keratitis (see Ocular Vaccinial Infections and Therapy).

Uncomplicated inadvertent inoculation lesions are self-limited, resolving in approximately 3 weeks, and require no therapy. If extensive body surface area is involved, or severe ocular vaccinia infection (without keratitis) (Figure 19), or severe manifestation of inoculation has occurred, treatment with VIG can speed recovery and prevent spread of disease.

Ocular Vaccinial Infections and Therapy

Ocular vaccinial infections account for the majority of inadvertent inoculations. However, data upon which to base treatment recommendations are limited. Published reports of treatment of human infections are predominantly case series reports concerning clinical experience with older antiviral drugs (e.g., idoxuridine [IDU] or interferon) or VIG. These studies did not employ the prospective, randomized, double-blinded, controlled trials that are now standard; clinical details and follow-up information are often variable (*35*--*38*). None of the available topical ophthalmic antiviral agents have been studied among humans with ocular vaccinia disease, except in one case report, where vidarabine was apparently superior to IDU in treating blepharoconjunctivitis (*38*). Prophylaxis of the cornea with topical antiviral drugs is common ophthalmologic practice in treating ocular herpes simplex and varicella-zoster infections (*33*). Therapies that have been considered for treatment of ocular vaccinial infections include topical ophthalmic antiviral drugs (trifluridine [Viroptic,® King Pharmaceuticals, Inc., Bristol, Tennessee] and vidarabine [Vira-A,® King Pharmaceuticals, Inc., Bristol, Tennessee]) and parenteral VIG. Trifluridine and vidarabine are not approved by the Food and Drug Administration (FDA) for treatment of vaccinia disease, although the product labels for trifluridine and vidarabine state that the drugs have in vitro and in vivo activity against vaccinia virus. Vidarabine is no longer being manufactured, but supplies might be available in certain areas.

Among humans with GV and EV, VIG treatment decreases size and limits extension of vaccinial lesions within 24--48 hours. Consequently, VIG has been considered a means to prevent spread of facial vaccinia to the eye and spread of ocular vaccinia without corneal involvement. No evidence exists that VIG is effective in treating vaccinial infection of the cornea (i.e., vaccinial keratitis).

Case reports exist of human patients with vaccinial keratitis not treated with VIG who apparently experienced more severe sequelae (including corneal scarring and disciform edema) than described in case reports where VIG therapy was used (*35*,*39*--*41*), as well as a case report concerning use of VIGIM in treating vaccinial keratitis in which corneal scarring did not develop (*41*). Case reports indicated efficacy of VIGIM in treating vaccinial blepharoconjunctivitis and blepharitis (*32*,*40*,*42*). To discuss treatment options for ocular vaccinia, CDC convened a meeting of ophthalmology and infectious disease consultants in November 2002. On the basis of available data and input from these consultants, this report offers the following guidance for clinicians:

- Suspected ocular vaccinia infections should be managed in consultation with an ophthalmologist to ensure a

thorough and accurate eye evaluation, including a slit-lamp examination, and the specialized expertise needed to manage potentially vision-threatening disease.

- Although vaccine splashes to the eye occur rarely because of the viscosity of smallpox vaccine, these occurrences should be managed by immediate eye-washing with water (avoid pressure irrigation, which can cause corneal abrasion) and a baseline evaluation by an ophthalmologist. In this situation, off-label prophylactic use of topical ophthalmic trifluridine or vidarabine has been recommended by ophthalmologists (CDC, unpublished data, 2002). Further treatment might not be necessary.
- Off-label use of topical ophthalmic trifluridine or vidarabine has been recommended by certain ophthalmologists (CDC, unpublished data, 2002) and can be considered for treatment of vaccinia infection of the conjunctiva or cornea. Prophylactic therapy with these drugs might also be considered to prevent spread to the conjunctiva and cornea if vaccinia lesions are present on the eyelid, including if near the lid margin, or adjacent to the eye. The potential benefits of these drugs for prophylaxis should be balanced against the minimal but potential risk of drug toxicity and of introducing virus into the eye by frequent manipulation.
- Topical antivirals should be continued until all periocular or lid lesions have healed and the scabs have fallen off, except that topical trifluridine usually is not used for >14 days to avoid possible toxicity. When used for >14 days, trifluridine can lead to superficial punctate keratopathy, which resolves on discontinuation of the medication. Topical vidarabine might be preferable for use among children because it can be compounded into an ointment that allows less frequent dosing and stings less initially than trifluridine.
- VIG should be considered for use in severe ocular disease when keratitis is not present (e.g., severe blepharitis or blepharoconjunctivitis). Severe ocular disease is defined as marked hyperemia, edema, pustules, other focal lesions, lymphadenophy, cellulitis, and fever. If keratitis is present with these conditions, consideration of possible VIG use must be weighed against evidence in an animal model for increased risk for corneal scar formation if a substantial dose is administered during multiple days.
- VIG can be considered if the ocular disease is severe enough to pose a substantial risk of impaired vision as a long-term outcome (e.g., vision-threatening lid malformation). If VIG is administered specifically to treat ocular disease in the presence of keratitis, treatment usually should be limited to 1 dose, and the patient or guardian should be informed of the possible risks and benefits before its use.
- Using VIG as recommended to treat other severe vaccinia disease (e.g., EV) is indicated, even in the presence of keratitis. VIG is not recommended for treating isolated keratitis.
- Topical ophthalmic antibacterials should be considered for prophylaxis of bacterial infection in the presence of keratitis, including if a corneal ulcer is present or steroids are used. In severe cases of keratitis (e.g., with an ulcer and stromal haze or infiltrate) and in iritis, topical steroids should be considered after the corneal epithelium is healed to decrease immune reaction; mydriatics are also indicated.
- Topical steroids should not be used without ophthalmologic consultation and should not be used acutely without topical antiviral therapy. Patients with ocular vaccinia infection, including with keratitis or iritis, should receive careful follow-up evaluation by an ophthalmologist to detect and treat possible late onset complications (e.g., scarring and immune reactions).

Additional data from animal and human clinical studies are needed to improve the evidence base and to refine recommendations for ocular vaccinia disease. Physicians treating patients with ocular vaccinia infection are encouraged to enroll in studies designed to evaluate the safety and efficacy of VIG and available antiviral preparations for treatment of ocular complications.

GV

GV is characterized by a disseminated maculopapular or vesicular rash, frequently on an erythematous base, that usually occurs 6--9 days after first-time vaccination (*1*,*8*). The rash spans the spectrum of vaccinial lesions, from maculopapules to vesicles. Maculopapules can be mistaken for EM when they are accompanied by a substantial component of erythema (*9*) (J. Michael Lane, M.D., formerly Director, Smallpox Eradication Program, Communicable Disease Center, personal communication, 2002) (Figure 20). In other instances, the pearly vesicles of GV resemble the lesions of smallpox; however, GV does not follow the centrifugal distribution that is characteristic of smallpox (*1*) (Figure 21).

GV rash might be preceded by fever, but usually, patients do not appear ill (Figure 22). Lesions follow the same course as the vaccination site. Lesions can be present anywhere on the body, including the palms and soles and can be numerous or limited. GV can appear as a regional form that is characterized by extensive satellite vesiculation around the vaccination site, or as an eruption localized to a body part (e.g., arm or leg), with no evidence of inadvertent inoculation (*4*) (Figure 23). A mild form of GV also exists, which appears with only a limited number of scattered lesions.

The skin lesions of GV are believed to be spread by the hematogenous route (*1*) and might contain vaccinia virus. Therefore, contact precautions should be used when treating these patients. Patients should be instructed to keep lesions covered and avoid physical contact with others if their lesions are too numerous to cover with bandages or clothing. The differential diagnosis of GV includes EM, EV, inadvertent inoculation at multiple sites, and uncommonly, early stages of PV or other vesicular diseases (e.g., disseminated herpes or severe chickenpox).

GV is self-limited among immunocompetent hosts. These patients appear well and do not require VIG, but might benefit from simple supportive care measures (e.g., nonsteroidal anti-inflammatory agents [NSAIDS] and oral antipruritics). VIG might be beneficial in the rare case where an immunocompetent person appears systemically ill. GV is often more severe among persons with an underlying immunodeficiency, and these patients might benefit from early intervention with VIG.

EV

EV is a localized or generalized papular, vesicular, or pustular rash, which can occur anywhere on the body, with a predilection for areas of previous atopic dermatitis lesions. Persons with a history of atopic dermatitis are at highest risk for EV. Onset of the characteristic lesions can be noted either concurrently with or shortly after the development of the local vaccinial lesions (*1*). EV cases resulting from secondary transmission usually appeared with skin eruptions approximately 5--19 days after the suspected exposure (*1,17*) (Figures 24 and 25). EV lesions follow the same dermatological course as the vaccination site in a vaccinee, and confluent lesions can occur (Figure 26). The rash is often accompanied by fever and lymphadenopathy, and affected persons are systemically ill (*43*). EV tends to be more severe among first-time vaccinees or unvaccinated contacts (*12,44*) (Figure 27).

Atopic dermatitis, regardless of disease severity or activity, is a risk factor for experiencing EV among either vaccinees or their close contacts (*21,22,44--46*), but no data exist to predict the absolute risk for these persons. The majority of primary-care providers do not distinguish between eczema and atopic dermatitis when describing chronic exfoliative skin conditions, including among infants and young children (*47,48*). Animal studies demonstrate that an immunologic T-cell dysregulation predisposes persons affected with atopic dermatitis to disseminated progressive papular, vesicular, and pustular lesions, even in intact skin (*47*).

EV can be associated with systemic illness that includes fever and malaise. Management includes hemodynamic support (e. g., as for sepsis) and meticulous skin care (e.g., as for burn victims). Patients might require volume repletion and vigilant monitoring of electrolytes as a result of disruption of the dermal barrier. Patients with EV are at risk for secondary bacterial and fungal infections of the lesions, and antibacterials and antifungals are indicated as necessary.

One study determined that the mortality from EV was reduced from 30%--40% to 7% after the introduction of VIG (*41*). Therefore, establishing the diagnosis early not delaying treatment with VIG is imperative to reducing mortality. Patients are usually severely ill and can require multiple doses of VIG. Virus can be isolated from EV lesions, making these patients highly infectious. Infection-control precautions should be used to prevent secondary transmission and nosocomial infection (*17*).

PV

PV (also referred to as vaccinia necrosum, vaccinia gangrenosa, prolonged vaccinia, and disseminated vaccinia), is a rare, severe, and often lethal complication that occurs among persons with immunodeficiencies (*43,49--51*). This diagnosis should be suspected if the initial vaccination lesion continues to progress without apparent healing ≥15 days after smallpox

vaccination (*8*). Anecdotal experience suggests that, despite treatment with VIG, persons with cell-mediated immune deficits have a poorer prognosis than those with humoral deficits (*1*).

PV is characterized by painless progressive necrosis at the vaccination site with or without metastases to distant sites (e.g., skin, bones, and other viscera) (*50*) (Figure 28). The vaccination lesion does not heal, presumably secondary to an immune derangement, and progresses to an ulcerative lesion, often with central necrosis (*9*) (Figure 29). Initially, limited or no inflammation appears at the site, and histopathology can reveal absence of inflammatory cells in the dermis (*52*). During the weeks that follow, patients might experience bacterial infection and signs of inflammation (J. Michael Lane, M.D., formerly Director, Smallpox Eradication Program, Communicable Disease Center, personal communication, 2002). In a 1963 study, the majority of 66 cases initially reported to be PV were reclassified after follow-up as severe primary (i.e., major) reactions (*22*). Cases of severe major reactions cleared within 1--2 weeks without VIG treatment (Figures 30 and 31).

With PV, vaccinia virus continues to spread locally and can metastasize to distant sites through viremia (Figure 32). Live vaccinia virus can be isolated from the skin lesions of these patients. Infection-control precautions, which include contact isolation, are required to avoid vaccinial infection of other persons and to limit risk for secondary infections.

The differential diagnosis of PV includes severe bacterial infection, severe chickenpox, other necrotic conditions (e.g., gangrene), and disseminated herpes simplex infections. Persons at highest risk for PV include those with congenital or acquired immunodeficiencies, HIV/AIDS, cancer, and those on immunosuppressive therapies for organ transplantation or autoimmune disease. The degree and type of immunocompromise probably correlates with the risk for PV, although the protective level of cellular count or humoral immunity is unknown.

Before the introduction of VIG and early antiviral medications, PV was universally fatal (*23*); but after VIG was used for PV treatment, the survival rate improved (*9,13*). Surgical debridement was used infrequently with variable success to treat the primary progressive necrotic lesions of PV (V. Fulginiti, M.D., Universities of Arizona and Colorado, personal communication, 2002). Management of PV should include aggressive therapy with VIG, intensive monitoring, and tertiary-level supportive care. Despite advances in medical care, PV probably will continue to be associated with a high mortality rate.

Postvaccinial Central Nervous System Disease

Central nervous system (CNS) disease after smallpox vaccination is most common among infants aged <12 months and is a diagnosis of exclusion (*12*). Clinical symptoms reflect cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma (*43*). CNS lesions occur in the cerebrum, medulla, and spinal cord. Lumbar puncture can reveal an increased opening cerebral spinal fluid (CSF) pressure, and examination of CSF might indicate monocytosis, lymphocytosis, and elevated CSF protein (*1,12,43*).

Both PVE and PVEM have been described (*1*). PVE typically affects infants aged <2 years and reflects cerebral damage as a result of vascular changes. Acute onset of symptoms occurs 6--10 days postvaccination and can include seizures, hemiplegia, aphasia, and transient amnesia. Associated histopathological changes include generalized cerebral edema, mild lymphocytic menigineal infiltration, widespread ganglion degenerative changes, and occasionally, perivascular hemorrhages. Patients can be left with cerebral impairment and hemiplegia (*1*).

PVEM (or encephalitis) affects persons aged ≥2 years and includes abrupt onset of fever, vomiting, headache, malaise, and anorexia approximately 11--15 days after vaccination. Symptoms can progress to loss of consciousness, amnesia, confusion, disorientation, restlessness, delirium, drowsiness, seizures, and coma with incontinence or urinary retention, obstinate constipation, and sometimes menigismus. CSF, although under increased pressure, reveals normal chemistries and cell count. Histopathological features include perivenous demyelination and microglial proliferation in demyelinated areas with lymphocytic infiltration but limited cerebral edema. These pathological features are similar to what is observed in other postinfectious encephalitides (*1,53*).

The strain of vaccinia virus used in smallpox vaccines might influence the frequency of PVE and PVEM (*1*). Reports based on European data indicate generally higher rates of PVE among persons vaccinated with non-NYCBOH strains (*53*). In the United States, where the principal strain used was the NYCBOH, the occurrence of PVE or PVEM was rare among first-time vaccinees (*1,9,12*).

Unrelated diseases that cause encephalomyelitis or encephalopathy might be temporally related to smallpox vaccination (*1*). U.S. rates might include these unrelated events, artificially increasing the rates of PVE/PVEM (*1,9*).

The pathophysiology of PVE/PVEM is not well understood, although an autoimmune process has been hypothesized (*53,54*). Vaccinia virus has been isolated from CSF and CNS tissue of affected persons (*12,53,55*). The significance of this finding is unknown in the absence of controlled trials that examine CSF of healthy vaccinees.

No clinical criteria, radiographic findings, or laboratory tests are specific for the diagnosis of PVE. PVE/PVEM are diagnoses of exclusion, and other infectious or toxic etiologies should be considered before making these diagnoses. In the past, recipients of the NYCBOH strain who experienced PVE or PVEM had a 15%--25% mortality rate, and 25% of survivors were left with varying neurological deficits (*12*).

No study has indicated that VIG can be an effective therapy for PVE or PVEM, and therefore, VIG is not recommended for treatment of PVE or PVEM. A prospective study of prophylactic use of VIG among Dutch army recruits demonstrated reduced incidence of PVE among persons vaccinated with a non-NYCBOH strain (*56*). This led to routine administration of VIG in first-time vaccinations of adults in the Netherlands (*57*). However, the incidence of PVE after smallpox vaccination with the NYCBOH strain is low (*9*); therefore, concomitant administration of VIG at time of vaccination has never been recommended with the NYCBOH strain.

No specific therapy exists for PVE or PVEM; however, supportive care, anticonvulsants, and intensive care might be required. Because the clinical symptoms of PVE or PVEM are not believed to be a result of replicating vaccinia virus, the role of antivirals is unclear.

Fetal Vaccinia

Fetal vaccinia, resulting from vaccinial transmission from mother to fetus, is a rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception; <50 cases have been reported in the literature (*58--60*). Fetal vaccinia is manifested by skin lesions and organ involvement, and often results in fetal or neonatal death (*61*). The skin lesions in the newborn infant are similar to those of GV or PV and can be confluent and extensive (Figures 33 and 34). The number of affected pregnancies maintained until term is limited. Affected pregnancies have been reported among women vaccinated in all three trimesters, among first-time vaccinees as well as in those being revaccinated, and among nonvaccinated contacts of vaccinees (*18,19*). Because fetal vaccinia is so rare, the frequency of, and risks for, fetal vaccinia cannot be reliably determined. Whether virus infects the fetus through blood or by direct contact with infected amniotic fluid is unknown. No known reliable intrauterine diagnostic test is available to confirm fetal infection.

Apart from the characteristic pattern of fetal vaccinia, smallpox vaccination of pregnant women has not been clearly associated with prematurity, low birth weight, and fetal loss. In addition, smallpox vaccine has not been demonstrated to cause congenital malformations (*62--64*).

VIG might be considered for a viable infant born with lesions, although no data exist for determining the appropriate dosage or estimating efficacy. If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccinia vaccination, she should be counseled regarding the basis of concern for the fetus. However, given the rarity of congenital vaccinia among live-born infants, vaccination during pregnancy should not ordinarily be a reason to consider termination of pregnancy. No indication exists for routine, prophylactic use of VIG for an unintentionally vaccinated pregnant woman; however, VIG should not be withheld if a pregnant woman experiences a condition where VIG is needed (e.g., EV). To expand understanding of the risk for fetal vaccinia and to document whether adverse pregnancy outcome

might be associated with vaccination, CDC is establishing a prospective smallpox vaccination pregnancy registry (see Requests for Clinical Consultation and IND Therapies and for Registries Enrollment).

Other Vaccine-Specific Adverse Events

Less frequently reported adverse events temporally associated with after smallpox vaccination include myocarditis, pericarditis (*65--70*), precipitation of erythema nodosum leprosum or neuritis among leprosy patients (*1*), and osteomyelitis (sometimes confirmed by recovery of vaccinia virus) (*1,71*). Reported skin changes at the vaccination scar have included malignant tumors (e.g., melanoma [*8*], discoid lupus [*72*], and localized myxedema as a symptom of Graves disease [*73*]). Reported neurologic complications after smallpox vaccination include transverse myelitis, seizures, paralysis, polyneuritis, and brachial neuritis (*53,74*).

Whether these conditions are caused by smallpox vaccination or represent coincidental occurrences after vaccination is unclear. Temporal association alone does not prove causation (*75*). Other unknown adverse events after smallpox vaccination might yet be described. Determining causality of reported postvaccination events associated with a specific vaccine is challenging and requires careful weighing of all the scientific evidence, evaluation of the quality and consistency of the data, and consideration of biologic plausibility of the association between the vaccination and the event (Box 1) (*76*). Clinicians should report unexpected and clinically relevant adverse events after vaccination to the Vaccine Adverse Event Reporting System (VAERS) and follow local, state, and territorial reporting requirements (see Smallpox Adverse Event Reporting).

Revaccination of Persons with History of Adverse Events

Before the eradication of smallpox, clinicians were often faced with the decision of whether to revaccinate persons who had documented serious adverse reactions. One study recommended that persons with a history of postvaccinial CNS disease (e. g., PVE/PVEM) or PV should not be revaccinated. Revaccination of children who had EV was not contraindicated, although it was recommended that they receive VIG concomitantly. Revaccination of children with a history of inadvertent inoculation or erythematous or urticarial rashes presented no known or theoretical risk (*8*).

Persons with a history of an adverse reaction to smallpox vaccination that leads to deferral should not knowingly be placed in a situation where they might be exposed to smallpox. No absolute contraindications exist regarding vaccination of persons with high-risk exposures to smallpox; persons at greatest risk for experiencing serious vaccination complications are also at greatest risk for death from smallpox. In this situation, the benefits of smallpox vaccination probably outweigh the risks for an adverse reaction from smallpox vaccine (*6*).

Prophylaxis for Persons at High Risk Inadvertently Exposed to Vaccinia Virus Either Through Vaccination or Contact Transmission

Historically, VIG was administered prophylactically to persons at increased risk for vaccine-related adverse events who required vaccination or who were inadvertently vaccinated (*8*). However, VIG administration is not without risk, and the efficacy of VIG as a prophylactic against vaccinial infection has not been studied in a controlled setting.

Until VIG is evaluated for such use, VIG is not recommended for prophylaxis when persons with contraindications to smallpox vaccination are inadvertently exposed to vaccinia and are otherwise well. Such persons should have careful clinical follow-up to ensure prompt diagnosis and treatment of an adverse event, if one occurs. Furthermore, in the absence of circulating smallpox virus, VIG is not recommended for concomitant use with smallpox vaccination among persons with contraindications. As recommended by ACIP, careful screening criteria should be used to exclude persons with contraindications from preoutbreak smallpox vaccination programs (*21*).

To better understand the risks for vaccinia exposure among persons with contraindications to smallpox vaccination, CDC plans to maintain a registry of inadvertent exposures among groups at high risk (e.g., vaccinee or contact with dermatologic

or pregnancy contradications). Clinicians are encouraged to report these cases to CDC so that prompt treatment can be initiated when necessary, and patients can be followed by using a standardized protocol. These data will be used to assess risk for experiencing an adverse event and the potential role for prophylactic therapy among these patients (see Requests for Clinical Consultation and IND Therapies and for Registries Enrollment).

Laboratory Diagnostics

Clinical evaluation and a careful patient history of recent smallpox vaccination or contact with a recent vaccinee are the mainstays of diagnosis of smallpox vaccine-related adverse events. In situations where clinical diagnosis is not straightforward, laboratory diagnostics for vaccinia might be helpful and might prevent inappropriate use of potentially toxic therapies. However, diagnostics for conditions easily confused with vaccinia infection (i.e., varicella, herpes zoster, herpes simplex, and enteroviruses), should be considered first, in particular for a nonvaccinee or someone believed to be a noncontact of a vaccinee.

Serologic testing for vaccinia is probably uninformative because it cannot be used to distinguish vaccinia immunity from vaccinia infection unless baseline antibody titers are available. Diagnostic tests for vaccinia include electron microscopy to identify presence of orthopoxvirus, and gene amplification (polymerase chain reaction [PCR]), and viral culture for vaccinia. Regarding vaccinia, these tests are available only for research purposes, but are undergoing multicenter validation studies that might enable FDA to approve the test reagents for diagnostic use. After that approval, testing will be made available through the Laboratory Response Network (LRN) (*77*), an extensive system of public health and private laboratories that can be accessed through consultation with state and local health departments. Consultation regarding appropriate use of specialized vaccinia laboratory testing will be available through CDC.

Laboratory Specimen Collection

A suspected case of an adverse event after smallpox vaccination should be promptly reported to the appropriate local, state, or territorial health department. When appropriate, public health officials might recommend that clinical specimens be collected for further evaluation of a possible case. Specimen collection guidelines are available at http://www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp.

Treatments

VIG, cidofovir, and topical ophthalmic antiviral drugs are among the therapies that can be used to treat adverse events after smallpox vaccination. Ophthalmic drugs are discussed elsewhere in this report (see Ocular Vaccinial Infections and Therapy).

VIG

VIG is a sterile solution of the immunoglobulin fraction of plasma, containing antibodies to vaccinia virus from persons who were vaccinated with smallpox vaccine. The available preparation of VIG is a previously licensed IM product (VIGIM) (produced by Baxter Healthcare Corporation in 1994) containing 0.01% thimerosal (a mercury derivative) as a preservative. Two new IV preparations (VIGIV) are in production and do not contain thimerosal. All preparations of VIG will be available as IND products through CDC and DoD.

VIG has demonstrated efficacy in the treatment of smallpox vaccine adverse reactions that are secondary to continued vaccinia virus replication after vaccination (*41*,*78*). Such adverse reactions include EV, PV, or vaccinia necrosum, and severe cases of GV. VIG has no proven effectiveness for postvaccinia central nervous system disease.

VIG is recommended for treating EV and PV. Because the majority of cases of GV are self-limited, VIG is recommended for treating GV only if the patient is seriously ill or has serious underlying disease that is a risk factor for a complication of vaccination (e.g., such immunocompromised conditions as HIV/AIDS). VIG can also be useful in treating ocular vaccinia

that results from inadvertent implantation. When ocular vaccinia with keratitis is present, consideration of VIG should include the possible increased risk for corneal scarring (see Ocular Vaccinia Infections and Therapy) (Box 2).

Side Effects

VIG administration has been associated with mild, moderate, and severe adverse reactions. Mild adverse reactions include local pain and tenderness, swelling, and erythema at the injection site after IM administration of immunoglobulins and can persist from hours to 1--2 days after administration.

Moderate adverse reactions include joint pain, diarrhea, dizziness, hyperkinesis, drowsiness, pruritis, rash, perspiration, and vasodilation. Back and abdominal pain, nausea, and vomiting can occur within the first 10 minutes of injection. Chills, fever, headache, myalgia, and fatigue can begin at the end of infusion and continue for hours. More severe reactions of this type might require pretreatment with corticosteroids or acetaminophen, if another dose of VIG is required.

Serious adverse events associated with administration of VIGIV are expected to be similar to those observed with other intravenous immune globulin (IVIG) products, and can include hypotension, anaphylaxis and anaphylactoid systemic reactions, renal dysfunction, and aseptic meningitis syndrome (AMS). When AMS occurs, it usually begins from within hours to 2 days after treatment and can occur more frequently in association with high dosage (2 g/kg body weight) therapy. It is characterized by severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Discontinuation of IVIG treatment has resulted in remission of AMS within days without sequelae.

Anaphylaxis and anaphylactoid systemic reactions have been reported after IM or IV injection of human immunoglobulin preparations. The symptoms of classic anaphylactic reactions include flushing, facial swelling, dyspnea, cyanosis, anxiety, nausea, vomiting, malaise, hypotension, loss of consciousness, and in certain cases, death. Symptoms appear from within seconds to hours after infusion. The treatment of such reactions is immediate discontinuation of immune globulin and administration of epinephrine, oxygen, antihistamines, IV steroids, and cardiorespiratory support.

When proteins prepared from human blood or plasma are administered, the potential for transmission of infectious agents cannot be totally excluded. This also applies to infectious agents that might not have been discovered or characterized when the current preparations of VIG were formulated. To reduce the risk of transmitting infectious agents, stringent controls are applied in the selection of blood and plasma donors, and prescribed standards are used at plasma-collection centers, testing laboratories, and fractionation facilities.

VIG Risks and Contraindications

Contraindications to VIG administration include an acute allergic reaction to thimerosal (for VIGIM) or a history of a severe reaction after administration of human immunoglobulin preparations. Persons with selective immunoglobulin A (IgA) deficiency might have antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA. In a rabbit model of vaccinia keratitis, substantial doses of VIG were associated with corneal scarring (*34*) (see Ocular Vaccinia Infections and Therapy).

Whether VIG can cause fetal harm when administered to a pregnant woman or if it affects reproductive capacity is unknown. Although clinical experience with other preparations containing immunoglobulins indicates that no fetal adverse events result from immunoglobulins, no studies have evaluated the adverse effects of VIG on the fetus. VIG should be administered to a pregnant woman only if clearly needed. Similarly, whether VIG is excreted in breast milk is unknown; therefore, caution should be exercised when VIG is administered to a nursing woman.

VIG is made from human plasma; therefore, a possible risk of transmission of viruses and a theoretical risk of transmission-adventitious agents that can cause Creutzfeldt-Jacob disease exist. The risk that these products contain infectious agents has been reduced by questioning plasma donors about risk factors for infection and by testing for the presence of certain viruses in the plasma. Furthermore, manufacturing processes have been validated for their ability to inactivate and remove viruses.

Administration

Detailed instructions regarding the administration of IM and IV VIG are included in the Investigator's Brochure portion of the IND materials that accompany the products. For treatment of vaccinial complications, the recommended dose of VIGIM (16.5% solution) is 0.6 mL/kg body weight (100 mg/kg body weight). VIGIM is to be administered intramuscularly, preferably in the buttock or the anterolateral aspect of the thigh. To reduce local pain and discomfort, dividing the dose into smaller volumes to be administered by multiple injections might be necessary (*79*).

Because the concentration of the new VIGIV products differs from that of the IM preparation, clinicians should refer to the manufacturer's package insert, or IND protocol, for correct dosages. The dose for IV administration of VIG might range from 100 mg/kg body weight to 500 mg/kg body weight, depending on the VIGIV formulation.

Cidofovir

Cidofovir (Vistide,® Gilead Sciences, Foster City, California), a nucleotide analogue of cytosine, has demonstrated antiviral activity against certain orthopoxviruses in cell-based in vitro and animal model studies (*80*--*82*). Its effectiveness in the treatment of vaccinia-related complications among humans is unknown. Cidofovir has been demonstrated to be nephrotoxic among humans and carcinogenic among animals, even at low doses (Gilead Sciences. Cidofovir [Package insert]. Foster City, CA: Gilead Sciences, Inc; 2000). It is administered with probenecid and hydration.

Cidofovir is approved by FDA for treating CMV retinitis among patients with AIDS. Its use for treating smallpox vaccination complications is recommended only under IND protocol sponsored by CDC. This IND is a research protocol to evaluate the clinical effect and outcomes of cidofovir as a secondary treatment of vaccinia-related complications that do not respond to VIG treatment. CDC will supply cidofovir at no cost for use under this IND protocol.

Cidofovir will be released for civilian use by CDC and for military use by DoD, if 1) a patient fails to respond to VIG treatment; 2) a patient is near death; or 3) all inventories of VIG have been exhausted. This proposed use of cidofovir is investigational and has not been studied among humans; therefore, the benefit of cidofovir therapy for vaccinia-related complications is uncertain. Insufficient information exists to determine the appropriate dosing and accompanying hydration and dosing of probenecid if antiviral therapy is needed to treat smallpox vaccine-related adverse events among the pediatric age group. Dosages for these patients should be determined in consultation with specialists at CDC and DoD. Additional information regarding dosing and administration of cidofovir is included in the Investigator's Brochure that accompanies the release of this product to the clinician when cidofovir is used under the IND protocol.

Side Effects

The major complication of cidofovir therapy is renal toxicity, which is sometimes irreversible, results in renal failure, and requires dialysis to prevent death. To reduce the renal toxicity of cidofovir, it must be administered with careful IV hydration and with probenecid, a renal tubular blocking agent. Cidofovir has also been associated with neutropenia, proteinuria, decreased intraocular pressure/ocular hypotony, anterior uveitis/iritis, and metabolic acidosis. Cidofovir-related carcinogenicity, teratogenicity, and hypospermia have been reported in animal studies. Mammary adenocarcinomas developed in rats exposed to 0.04 times the human exposure at the dose used in clinical practice on the basis of area-under-the-curve comparisons (Gilead Sciences, Inc. Cidofovir [Package insert]. Foster City, CA: Gilead Sciences, Inc; 2000).

Probenecid has been associated with headache, anorexia, nausea, vomiting, urinary frequency, hypersensitivity reactions, anemia, hemolytic anemia, nephritic syndrome, hepatic necrosis, gout, uric acid stones, and renal colic. Probenecid should be used with caution among children, pregnant women and persons with sulfa drug allergy (see manufacturer's package insert).

Administration

Details for administration of cidofovir are included with the medication and IND materials that are shipped by CDC. The proposed dose of cidofovir for treatment of vaccinia complications is 5 mg/kg body weight administered intravenously, one time, during a 60-minute period. A second dose 1 week later should be considered if no response occurs to the first dose. Dose adjustment might be needed to compensate for decreased excretion caused by renal dysfunction if a second dose is needed. Administration procedures include assessment of renal function and use of saline hydration, and probenecid, before and after cidofovir, according to the regimen specified in the IND protocol (and in the package insert for treatment of CMV retinitis). Patients who receive cidofovir should be followed closely, both for drug toxicities and for the outcome of their serious adverse reaction. IND protocols require viral cultures to monitor for emerging viral resistance to cidofovir. The protocol materials will be supplied to facilitate monitoring and information collection. Long-term follow-up is required under the IND protocol to monitor for carcinogenicity, renal insufficiency, and teratogenicity.

Requests for Clinical Consultation and IND Therapies and for Registries Enrollment

In October 2002, ACIP recommended that enhanced terrorism preparedness should include vaccination of smallpox public health response and health-care teams (*21*). Implementation of this vaccination program was determined to be the responsibility of the states and territories in conjunction with local predesignated hospitals. Before participation in the vaccination program, states and territories should establish a comprehensive program to manage vaccinees and their contacts who experience an adverse event after smallpox vaccination. Hospitals that participate should assign physicians with expertise in infectious diseases, neurology, dermatology, allergy/immunology, and ophthalmology to assess and manage adverse events among vaccinees and their contacts. Vaccinees and their affected contacts should have access to evaluation and medical care for a suspected adverse event 24 hours/day and 7 days/week. CDC will provide consultation to state and territorial public health officials, their surrogate providers, and other requesting physicians regarding recognition, evaluation, diagnosis, and treatment of adverse events after smallpox vaccination through an information line for clinicians that will be staffed 24 hours/day, 7 days/week. In addition, CDC will provide consultation for evaluation and care of persons with contraindications to smallpox vaccination that have an inadvertent exposure to vaccinia virus (e.g., vaccination of a pregnant woman or a person with atopic dermatitis). These persons also will be enrolled in a vaccination registry for prospective follow-up.

Referring providers should complete a thorough vaccination history and physical examination on all patients with a suspected adverse event before accessing CDC's Clinician Information Line. In addition, high-resolution digital photographs of dermatological manifestations of adverse events can aid in the recognition of specific dermatological manifestations of adverse events and should be obtained with the patient's permission and forwarded whenever possible. Providers seeking assistance should first contact their state health department before accessing the CDC consultation service or requesting VIG or cidofovir (Box 3).

To aid providers in discerning the presence or severity of vaccine-related complications, CDC has developed draft clinical evaluation tools to assist with expected adverse events. These clinical evaluation tools are available at http://www.bt.cdc.gov/agent/smallpox/vaccination/clineval; this website will be updated as additional information becomes available. Feedback regarding the utility of these clinical evaluation tools is requested and can be submitted by e-mail to spoxtool@cdc.gov. In addition, CDC and other U.S. Department of Health and Human Services agencies will collect data related to the frequency of smallpox vaccine adverse events and the clinical outcome of affected persons. These data will provide an update concerning the medical risks associated with smallpox vaccination and the efficacy and safety of INDs used in the treatment of adverse events.

Smallpox Vaccine Adverse Event Reporting

Providers are strongly encouraged to report serious adverse events to VAERS after the administration of the smallpox vaccine (Box 4). VAERS is a passive reporting system for safety monitoring of all vaccines licensed in the United States, and is jointly managed by CDC and FDA. CDC and FDA will monitor smallpox vaccine-related adverse event reports daily, and will provide enhanced surveillance of adverse events after administration of the smallpox vaccine. However, adverse events that are judged to be serious or unexpected and which require CDC consultation or IND therapies (VIG or

cidofovir) should not be solely reported to VAERS. These cases should instead be immediately reported by phone to the appropriate state health department officials and CDC, who will assist the reporting provider with completion of a VAERS form. All other smallpox vaccine adverse events that are serious, but do not require CDC consultation or administration of IND therapies, should be reported directly to VAERS within 48 hours of recognition. All other adverse events should be directly reported to VAERS within 1 week (Box 4).

Additional Information

CDC, in collaboration with the U.S. Department of Health and Human Services, has developed a website, which is available at http://www.bt.cdc.gov/training/smallpoxvaccine/reactions. Information and photographs related to smallpox vaccination, normal vaccination reactions, adverse events after vaccination, and treatments for adverse reactions can be located at this website.

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List of Abbreviations Used in This Report

ACIP	Advisory Committee on Immunization Practices
AMS	aseptic meningitis syndrome
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebral spinal fluid
DoD	U.S. Department of Defense
EM	erythema multiforme
EV	eczema vaccinatum
FDA	Food and Drug Administration
GV	generalized vaccinia
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
IDU	idoxuridine
IgA	immunoglobulin A
IM	intramuscular
IND	Investigational New Drug
IV	intravenous
IVIG	intravenous immune globulin
LRN	Laboratory Response Network
NIAID	National Institute of Allergy and Infectious Diseases
NSAIDS	nonsteroidal anti-inflammatory agents
NPS	National Pharmaceutical Stockpile

NYCBOH	New York City Board of Health
PCR	polymerase chain reaction
PV	progressive vaccinia
PVE	postvaccinial encephalopathy
PVEM	postvaccinial encephalomyelitis
RTs	robust takes
SJS	Stevens-Johnson syndrome
VAERS	Vaccine Adverse Event Reporting System
VIG	vaccinia immune globulin
VIGIM	intramuscular vaccinia immune globulin
VIGIV	intravenous vaccinia immune globulin
WHO	World Health Organziation

* An adverse reaction is an untoward effect that occurs after a vaccination and is extraneous to the vaccine's primary purpose of producing immunity. Adverse reactions have been demonstrated to be caused by the vaccination. Adverse reactions also are referred to as vaccine side effects or complications. In contrast, adverse events are untoward effects observed or reported after vaccinations, but a causal relation between the two have yet to be established. Therefore, adverse events include both 1) adverse reactions and 2) other events associated with vaccinations only by coincidence (i.e., they would have occurred also in the absence of vaccination). This report focuses on adverse reactions known to be caused by smallpox vaccine on the basis of extensive prior experience. Additional previously unknown adverse events might be reported with reintroduction of smallpox vaccinations; however, whether they are causally related will require additional evaluation.

Table 1

TABLE 1. Smallpox vaccine adverse event rates (number per million vaccinees) — United States, 1968

	National survey		10-state survey	
	All primary (i.e., first-time) vaccinees	Vaccinees aged ≥1 yr	All primary (i.e., first-time) vaccinees	Vaccinees aged ≥1 yr
Serious, but not life-threatening reactions				
Inadvertent inoculation	25.4	27.1	529.2	532.0
Generalized vaccinia	23.4	17.7	241.5	222.8
Erythema multiforme	NA*	NA	164.6	131.3
Total number of serious, but not life-threatening reactions	**48.8**		**935.3**	
Life-threatening reactions				
Postvaccinal encephalitis/encephalomyelitis	2.9	2.4	12.3	8.6
Progressive vaccinia (vaccinia necrosum)	0.9	1.0	1.5	1.7
Eczema vaccinatum	10.4	10.6	38.5	41.5
Total number of life-threatening reactions	**14.2**		**52.3**	
Deaths	**1.1**	**0.6**	**1.5**	**NR†**

*Not available.
†None reported.
Source: CDC. Smallpox adverse event rates, 1968. Atlanta, GA: US Department of Health and Human Services, CDC, 2002. Available at http://www.bt.cdc.gov/agent/smallpox/vaccine-safety/adverse-events-chart.asp.

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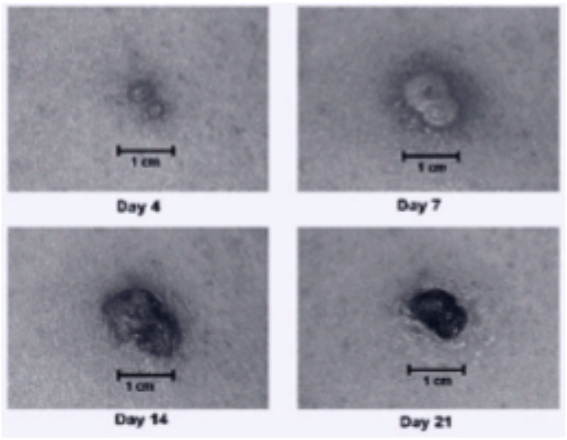
Figure 1

FIGURE 1. Expected smallpox vaccination-site reaction (i.e., a take) in a first-time vaccinee, demonstrating the progression from papule (day 4) to pustule (days 7–14), to scab (day 21)



Source: CDC.

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Box 1

BOX 1. Evaluating side effects after vaccination: temporal versus causal associations*

An adverse event can be causally attributed to vaccine more readily if

- the exact chronology of vaccination and adverse event is known;
- the adverse event corresponds to those previously associated with a particular vaccine;
- the event conforms to a specific clinical syndrome whose association with vaccination has strong biologic plausibility (e.g., anaphylaxis);
- a laboratory result confirms the association (e.g., isolation of vaccine-strain varicella vaccine from skin lesions of a patient with rash);
- the event recurs on readministration of the vaccine (positive rechallenge); or
- a controlled clinical trial or epidemiologic study demonstrates greater risk for a specific adverse event among vaccinated versus unvaccinated (control) groups.

* **Source:** Iskander JK, Miller ER, Pless RP, Chen RT. Vaccine safety post-marketing surveillance: the Vaccine Adverse Event Reporting System. US Department of Health and Human Services, CDC, National Immunization Program. Available at http://www.cdc.gov/nip/vncsaft/VAERS/CME-post-mktg-san.pdf.

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Table 2

TABLE 2. Summary of vaccinia-related adverse events*

Adverse event	Description	Risk factor or predisposition	Treatment
Eczema vaccinatum (EV)	• High fever • Generalized lymphadenopathy with extensive vesicular and pustular eruption • Onset: concurrently or shortly after local vaccinial lesion in vaccinee, or in contacts, 5–19 days after suspected exposure • Risk for secondary bacterial or fungal infections • Virus recovered from lesions • High morality rate with poor prognosis	• History of eczema or atopic dermatitis irrespective of disease activity or severity • Less frequently, persons without a history of dermatological conditions	• Prompt evaluation and diagnosis • Infection-control precautions • Might require multiple doses of vaccinia immune globulin (VIG) (cidofovir, second-line therapy) • Hemodynamic support • Volume and electrolyte repletion • Observe for secondary skin infections
Progressive vaccinia (PV)	• Nonhealing vaccination site • Painless progressive (central) necrosis at the vaccination site • Occasional metastatic lesions in skin, bones, and viscera • No inflammation initially • Absence of inflammatory cells on histopathological examination • Inflammation weeks later • Bacterial infection might develop • Differential diagnosis: severe bacterial infection, severe chickenpox, disseminated herpes simplex, and other necrotic conditions • Prognosis: poor, despite therapy	• Humoral and cellular immunocompromise (e.g., malignancy, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), severe combined immunodeficiency syndrome (SCIDS), or hypogammaglobulinemia) • Protective level of T-cell count or humoral immunity unknown	• Prompt evaluation and diagnosis • Infection-control precautions • Might require multiple doses of VIG (cidofovir second-line therapy) • Surgical debridement of progressive necrotic lesions not proven useful
Postvaccinial encephalitis (PVE) or encephalomyelitis (PVEM)	• Diagnosis of exclusion • Appears similar to postinfectious encephalomyelitis or toxic encephalopathy caused by other agents • Abrupt onset of symptoms: fever, headache, malaise, lethargy, vomiting, meningeal signs, seizures, paralysis, drowsiness, altered mental status, or coma • Age <2 years (encephalopathy): cerebral vascular changes occurring 6–10 days postvaccination • Age ≥2 years (encephalomyelitis): demyelinating changes occurring 11–15 days postvaccination • Cerebral spinal fluid (CSF): normal or nonspecific; monocytosis, lymphocytosis, or elevated protein • Prognosis: mortality, 25%; neurological sequelae, 25%; complete recovery, 50%	• Age <1 year	• Intensive supportive care • Anticonvulsants as needed • VIG not recommended • Antiviral role unclear • Use of modern imaging studies has not been evaluated
Fetal vaccinia (FV)	• Incidence: rare (<50 reported cases) • Route of transmission: unknown • Outcomes: premature birth, fetal loss, high mortality • Not associated with congenital anomalies	• Cases in all trimesters of pregnancy • Greatest risk, third trimester	• Efficacy of VIG unknown • Antivirals not recommended
Generalized vaccinia (GV)	• Maculopapular or vesicular rash • Onset: 6–9 days postvaccination • Nontoxic, with or without fever • Differential diagnosis: erythema multiforme (EM), varicella, inadvertent inoculation, progressive vaccinia (PV), and smallpox	• Hematogenous spread • Lesions contain vaccinia • More serious among immunocompromised persons	• Usually self-limited in immunocompetent person • Infection-control precautions • VIG usually not indicated • Anti-inflammatory medications • Antipruritic medications • Antivirals usually not indicated

* See text for details.

TABLE 2. (*Continued*) Summary of vaccinia-related adverse events*

Adverse event	Description	Risk factor or predisposition	Treatment
Inadvertent inoculation	• Most common complication • Physical transfer of vaccinia virus from a vaccination site to second site on the vaccinee or to a close contact of vaccinee	• Manipulation of vaccination site • Children aged <4 years • Conditions that disrupt the epidermis (e.g., burns, severe acne, or psoriasis)	• Usually self-limited • Resolution in 3 weeks • Infection-control precautions • VIG if extensive body surface involved or severe ocular disease (cidofovir, second-line therapy)
Ocular vaccinia Inadvertent periocular or ocular implantation with vaccinia virus Can range from mild to severe	Keratitis • Marginal infiltration or ulceration with or without stromal haze/infiltration Conjunctivitis • Hyperemia, edema, membranes, focal lesions, fever, lymphadenopathy Blepharitis • Lid pustules on or near the lid margin, edema, hyperemia, lymphadenopathy, cellulitis, fever	• Manipulation of vaccination site, followed by eye rubbing • More likely with conditions that cause eye itching and scratching (conjunctivitis, corneal abrasion/ulceration)	• Ophthalmologic consultation • Certain ophthalmologists consider off-label topical antiviral medications • Topical prophylactic antibacterial medications for keratitis • VIG for severe blepharitis and blepharoconjunctivitis (without keratitis) • VIG not indicated for isolated keratitis • VIG considered for keratitis with vision-threatening conditions • VIG indicated for keratitis with life-threatening conditions that require VIG
Erythema multiforme (EM) and Stevens-Johnson Syndrome (SJS)	• Typical bull's eye (target) lesions • Hypersensitivity reaction • Pruritis • Onset: 10 days postvaccination • Can progress to SJS	• No known risk factors	• Antipruritic medications • VIG not indicated • Hospitalization and supportive care for SJS • Steroid use for SJS is controversial
Pyogenic infections of vaccination site	• Uncommon • Onset: 5 days postvaccination • Fever not specific for bacterial infection • Fluctuance at vaccination site	• More frequent in children (touching vaccination site)	• Gram stain • Bacterial culture • Antibacterial medications, if clinically indicated • No topical medications
Robust take (RT)	• >7.5 cm with swelling, warmth, and pain at vaccination site • Fluctuant lymph nodes not expected • Peak symptoms: 8–10 days postvaccination • Nonprogressive • Improvement in 24–72 hours	• Might be more likely among first-time vaccinees	• Observation most important • Antibacterial medications not indicated • Rest affected limb • Antipruritic medications • Anti-inflammatory medications • No salves or ointments
Tape adhesive reactions	• Sharply demarcated raised lines of erythema that correspond to adhesive placement • Local pruritis • No systemic illness	• Sensitivity to adhesives	• No salves, ointments, or topical/oral steroids • Frequent bandage changes • Periodic bandage removal

* See text for details.

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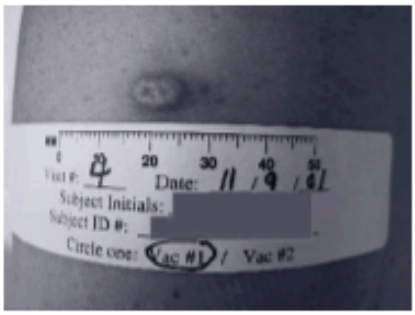
Figure 2

FIGURE 2. Normal smallpox vaccination reaction (day 7 postvaccination)



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Box 2

BOX 2. Summary of recommendations for using vaccinia immune globulin for treatment of smallpox vaccine-related adverse events

Recommended

- Inadvertent inoculation (severe as a result of number of lesions, toxicity of affected person or substantial pain)
- Eczema vaccinatum
- Generalized vaccinia (severe form or if underlying illness)
- Progressive vaccinia

Not recommended

- Inadvertent inoculation (not severe)
- Generalized vaccinia (mild or limited — the majority of instances)
- Nonspecific rashes, erythema multiforme, or Stevens-Johnson syndrome
- Postvaccinial encephalitis or postvaccinial encephalomyelitis

Considered

- Severe ocular complications (except isolated keratitis)

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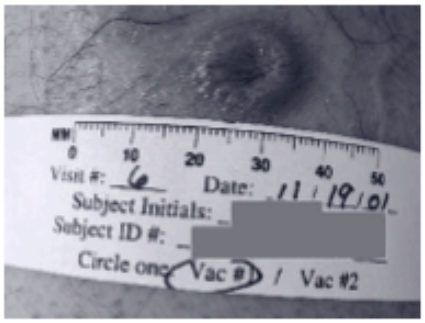
Figure 3

FIGURE 3. Normal smallpox vaccination reaction (day 12), indicating heaped up border with pustule drying from center outward



Source: Reproduced with permission of Stephen P. Heyse, M.D., National Institutes of Health.
Note: Vaccination reactions among vaccinia-naïve volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Units at Saint Louis University, University of Maryland, and University of Rochester, and the Respiratory Pathogens Unit at Baylor College of Medicine in 2001.

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Box 3

BOX 3. Contact information for requesting vaccinia immune globulin or cidofovir

Physicians at civilian medical facilities may request vaccinia immune globulin (VIG) or cidofovir by calling CDC's Smallpox Vaccinee Adverse Events Clinician Information Line at 877-554-4625. Physicians at military medical facilities may request VIG or cidofovir by calling the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at 301-619-2257 or 888-USA-RIID.

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Box 4

BOX 4. Reporting smallpox vaccine-related adverse events to the Vaccine Adverse Event Reporting System (VAERS)

Secure Internet-based VAERS reporting is available at https://secure.vaers.org/VaersDataEntryintro.htm. Printable VAERS forms are located online at http://www.vaers.org/pdf/vaers_form.pdf. Completed forms can be faxed to 877-721-0366 (toll free) or mailed to P.O. Box 1100, Rockville, MD 20894-1100. Additional assistance with completing forms is available at 800-822-7967 or by e-mail at info@vaers.org.

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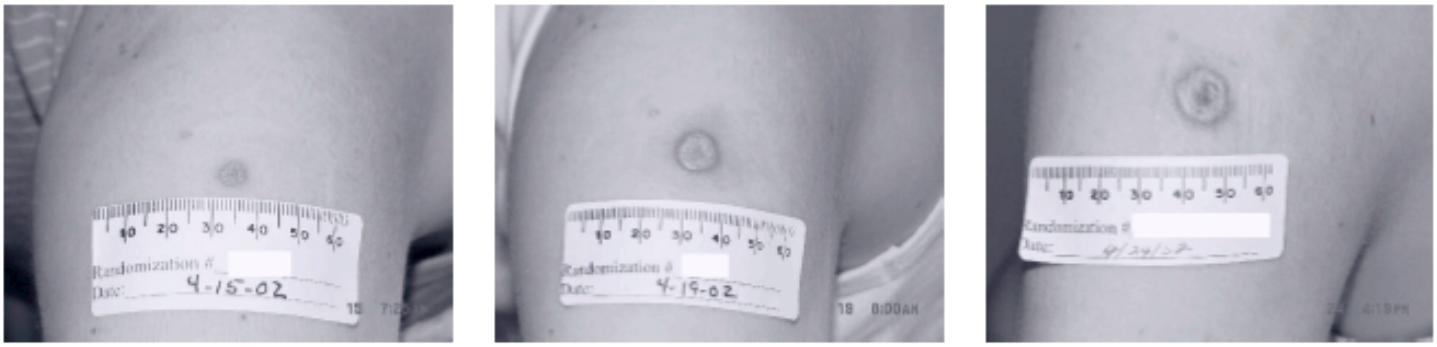
Figure 4

FIGURE 4. Example of a major reaction (i.e., a take) in a first-time smallpox vaccinee at 6 (left), 10 (middle), and 15 (right) days postvaccination



Source: Reproduced with permission of Stephen P. Heyse, M.D., National Institutes of Health.
Note: Vaccination reactions in vaccinia-naïve and previously vaccinated volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Unit at Saint Louis University in 2002.

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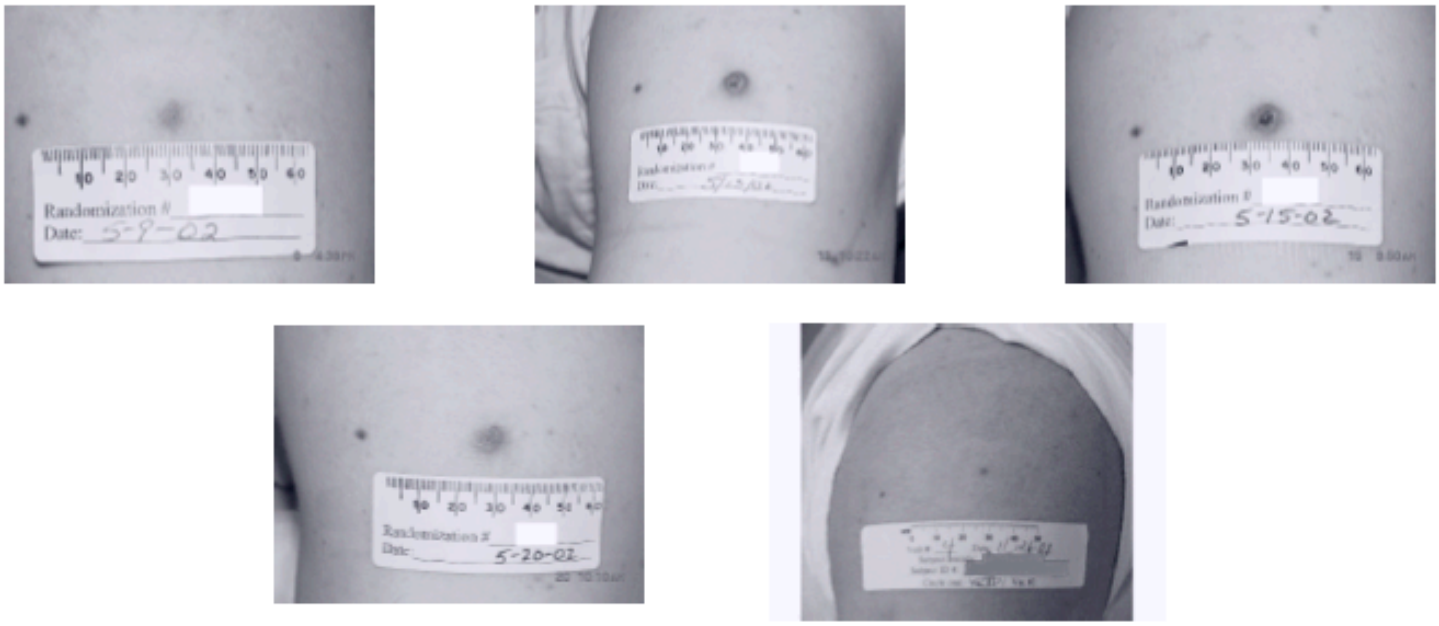
Figure 5

FIGURE 5. Example of a major reaction in a smallpox revaccinee at 4 (top left), 8 (top middle), 10 (top right), and 15 (bottom left) days postvaccination, in contrast with an equivocal reaction (nontake) in a first-time vaccinee (bottom right)



Source: Reproduced with permission of Stephen P. Heyse, M.D., National Institutes of Health.
Note: Vaccination reactions in vaccinia-naïve and previously vaccinated volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Unit at Saint Louis University in 2002.

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Figure 6

FIGURE 6. Examples of satellite lesions: (left) satellite lesions in a vaccination-naïve patient at day 7 postvaccination; (right) additional satellite lesions

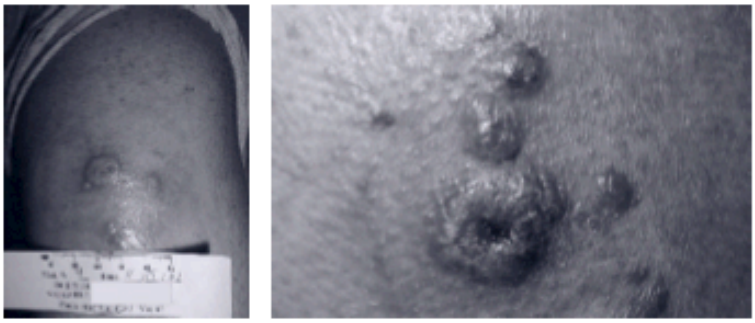

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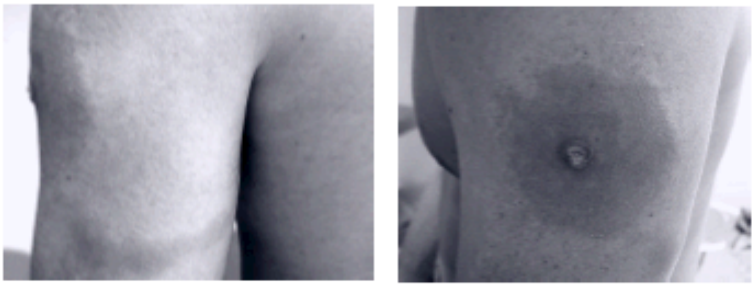
Figure 7

FIGURE 7. (Left) Robust take with lymphangitis; extensive erythema and induration with a linear streak posteriorly on day 9. (Right) Same patient—full view indicating vaccination site



Sources: (Left) Reproduced with permission of the Massachusetts Medical Society, ©2002; (right) National Institutes of Health.

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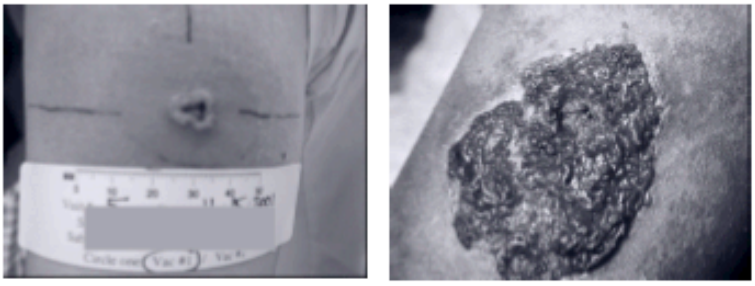
Figure 8

FIGURE 8. (Left) Robust take; note the extensive area of erythema. (Right) In contrast, note the impetignous changes associated with the uncommon bacterial infection of the vaccination site



Sources: (Left) National Institutes of Health; (right) V. Fulginiti, M.D.; digital enhancement: ©Logical Images.
Note: Vaccination reactions among vaccinia-naïve volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Units at Saint Louis University, University of Maryland, and University of Rochester, and the Respiratory Pathogens Unit at Baylor College of Medicine in 2001.

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Figure 9

FIGURE 9. Erythema as a result of irritation from adhesive dressing on postvaccination day 7, two different vaccinia-naïve volunteers; (left) volunteer 1; (right) volunteer 2

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Note: Vaccination reactions among vaccinia-naïve volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Units at Saint Louis University, University of Maryland, and University of Rochester, and the Respiratory Pathogens Unit at Baylor College of Medicine in 2001.

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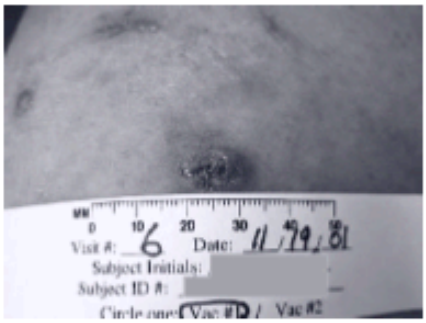
Figure 10

FIGURE 10. Vesicle at the edge of an adhesive dressing; viral culture did not detect the presence of vaccinia virus, and the lesions did progress to a pustular stage; these lesions appear to be a secondary reaction to the dressing



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Note: Vaccination reactions among vaccinia-naïve volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Units at Saint Louis University, University of Maryland, University of Rochester, and the Respiratory Pathogens Unit at Baylor College of Medicine in 2001.

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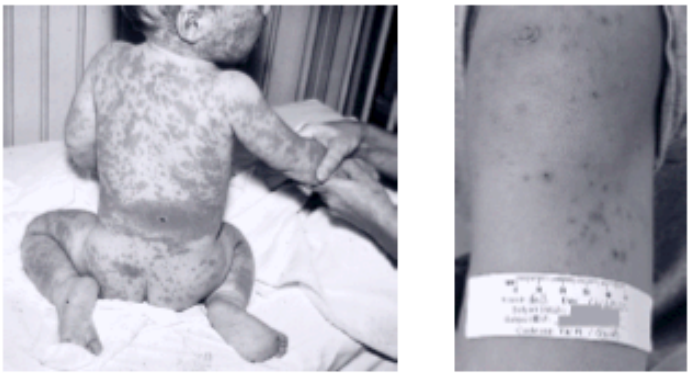
Figure 11

FIGURE 11. Examples of nonspecific rashes; (left) an infant aged 14 months with a vaccination site on the small of his back; he has extensive erythematous patches over his entire body, except for relative sparing of the soles of the feet. (Right) Nonspecific maculopapular rash in a first-time vaccinee



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Note: (Right) Vaccination reactions among vaccinia-naïve volunteers in a clinical study of diluted Dryvax® smallpox vaccine; volunteers were enrolled at the NIAID-supported Vaccine Treatment and Evaluation Units at Saint Louis University, University of Maryland, and University of Rochester, and the Respiratory Pathogens Unit at Baylor College of Medicine in 2001.

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Figure 12

FIGURE 12. Hallmark bull's eye lesion of erythema multiforme above the ankle on day 8 postvaccination

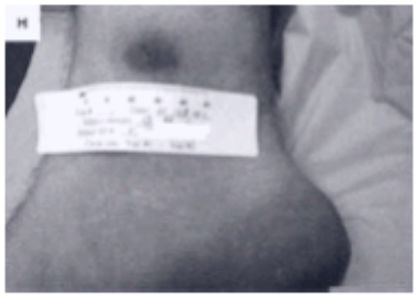

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Figure 13

FIGURE 13. Stevens-Johnson Syndrome approximately 2 weeks after vaccination of an infant aged 8 months; lesions are raised, circinate, and widespread

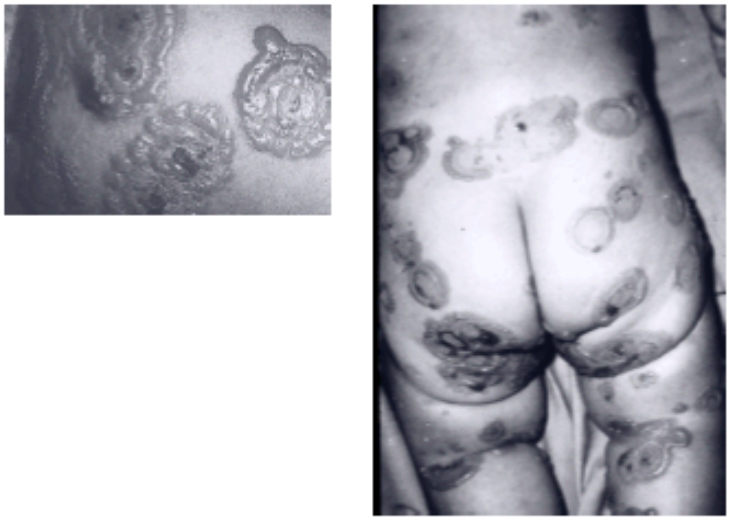

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Figure 14

FIGURE 14. (Left) Child aged 6 years with multiple inadvertent inoculation sites on face, which later healed without scarring. (Right) Child aged 5 years with inadvertent inoculation to bilateral lower eyelid; typical vaccinia lesions are visible

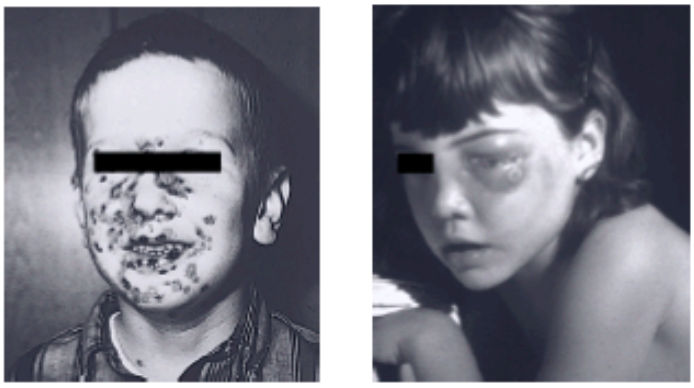

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Figure 15

FIGURE 15. (Top left) Palpebral autoinocuation in contact of a vaccinee. This and the next three figures demonstrate the progression and residue of severe palpebral vaccinia. This male, aged 2 years, acquired vaccinia from his mother who was vaccinated 12 days before his ocular vaccinia became apparent. He was hospitalized for 9 days and treated with vaccinia immune globulin (photograph was taken 4 days after onset of his vaccinia). (Top right) Demonstrates considerable resolution and beginning scarring of the eyelids (photograph was taken 8 days after onset). (Bottom left) Note the loss of eyelashes and the rolled-up lid margins (photograph was taken 2 weeks after onset). (Bottom right) Same child's normal contralateral eye with sharp lid margins and normal eyelashes

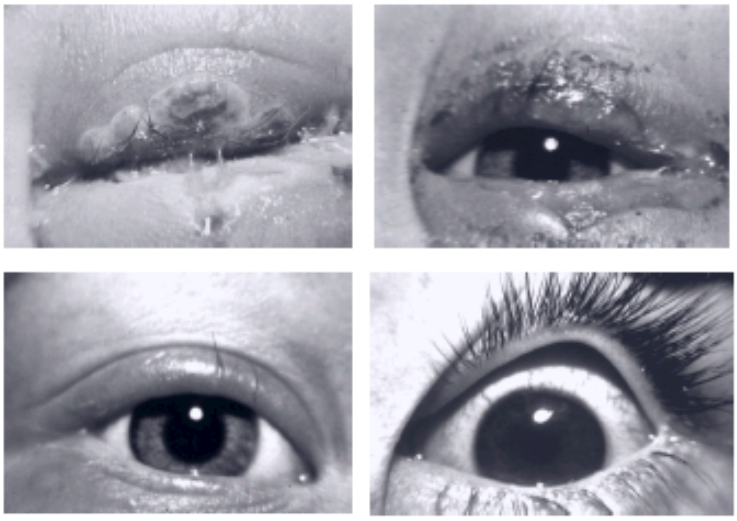

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Figure 16

FIGURE 16. (Left) Acute blepharoconjunctivitis in a male aged 22 years; (right) healing blepharoconjunctivitis 14 days later

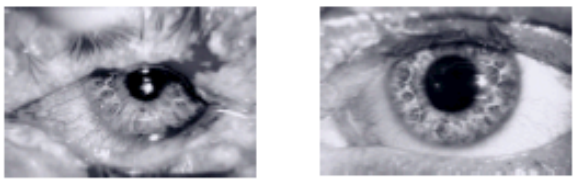

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Figure 17

FIGURE 17. Acute vaccinial corneal ulcer (keratitis)

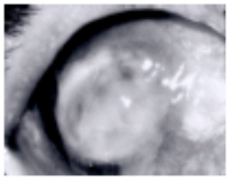

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Figure 18

FIGURE 18. Residual vaccinial corneal scarring and low-grade immune keratitis (inflammation of the cornea)

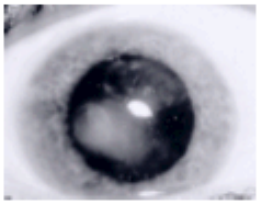

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Figure 19

FIGURE 19. (Left) Severe vaccinial blepharoconjunctivitis; (right) same eye indicating healing vaccinial blepharoconjunctivitis on day 10

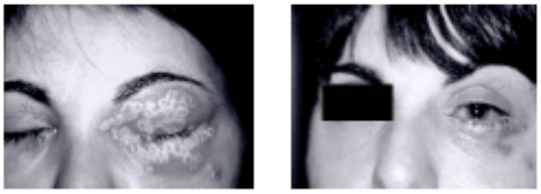

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Figure 20

FIGURE 20. Generalized vaccinia with a substantial erythematous base in an infant; note the vaccination site at the left axilla and the apparently well child

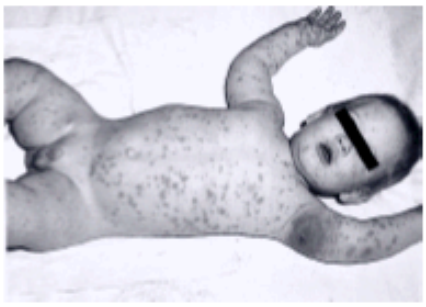

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Figure 21

FIGURE 21. The lesions of generalized vaccinia can be difficult to distinguish from variola (smallpox) infection; generalized vaccinia does not follow the centrifugal distribution that is characteristic of smallpox lesions

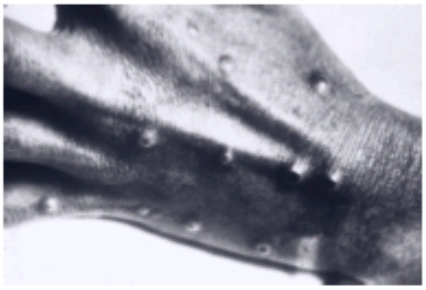

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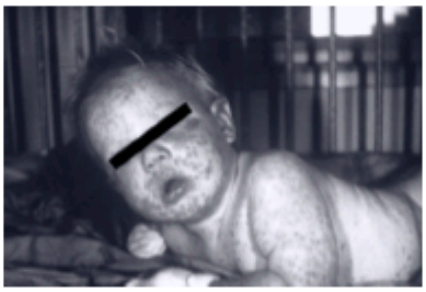
Figure 22

FIGURE 22. Generalized vaccinia in an apparently normal child; the child recovered without sequelae



Source: CDC (photo used previously courtesy of John M. Leedom, M.D.)

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Figure 23

FIGURE 23. Regional generalized vaccinia characterized by an extensive halo of vesiculation around the vaccination site. This differs from satellite lesions because of the number and extent of vesiculation

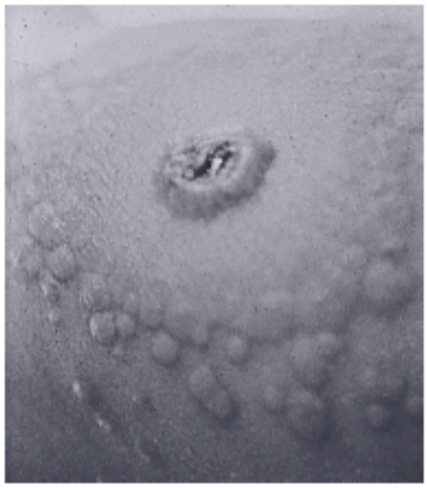

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Figure 24

FIGURE 24. (Top left) A woman aged 22 years with eczema vaccinia acquired from a close contact. She became critically ill, with nearly total involvement of her body, and required thiosemicarbazones, as well as substantial doses of vaccinia immune globulin; (right) side view; (bottom left) residual scarring after resolution of systemic illness

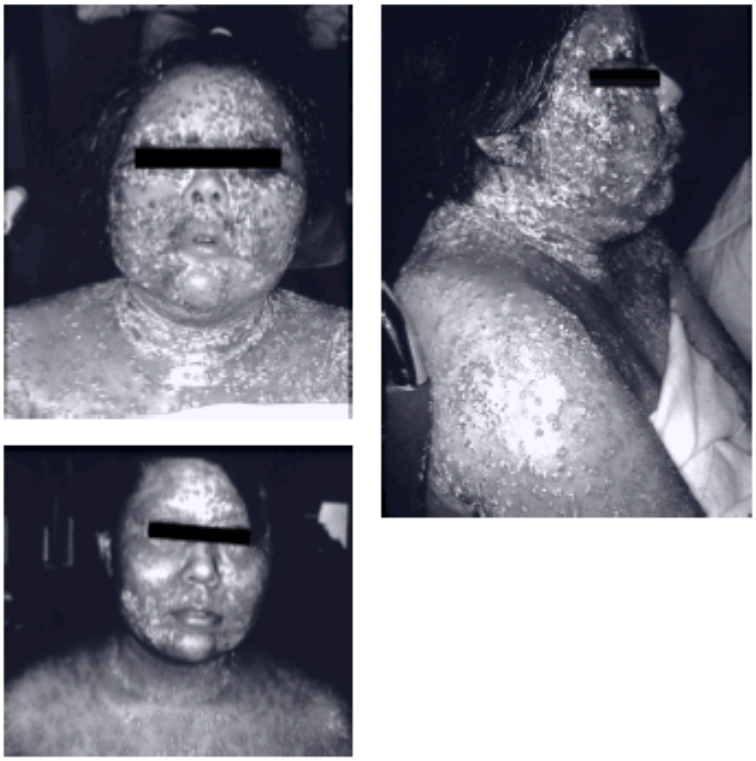

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Figure 25

FIGURE 25. (Left) Face of a previously unvaccinated woman, aged 27 years, with moderately severe eczema vaccinatum 8 days after vaccination. The lesions with confluence and umbilication are typical of vaccinia. (Middle) Three days later, immediately after initiation of treatment with vaccinia immune globulin (VIG). She has marked edema of the face, exudation, crusting, and confluence of the lesions. (Right) Fourteen days after vaccination and 3 days after treatment with VIG, with marked resolution of her lesions and limited pitting and scarring

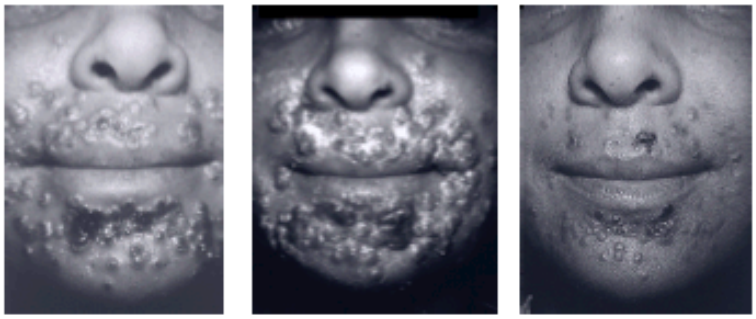

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Figure 26

FIGURE 26. Lesions of eczema vaccinatum in a girl, aged 3 years, who acquired vaccinia from a recently vaccinated close contact. She was extremely ill and hospitalized for 2 weeks. The lesions indicated typical umbilication and developed similarly to the lesions of normal primary vaccination. Despite vigorous therapy with vaccinia immune globulin and careful fluid and electrolyte balance, she had extensive residual scarring after recovering

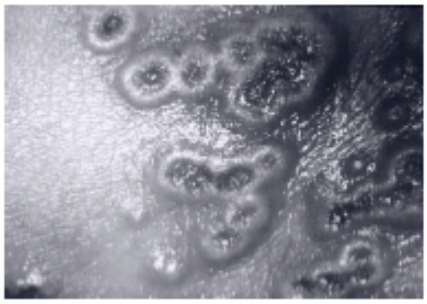

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Figure 27

FIGURE 27. Severe eczema vaccinatum in a male, aged 13 months, who acquired vaccinia from a recently vaccinated contact. He died despite treatment with vaccinia immune globulin, steroids, transfusions, and antibiotics

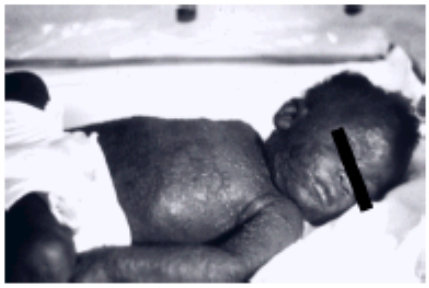

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Figure 28

FIGURE 28. Male with progressive vaccinia; note the extensive involvement with minimal inflammation

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Figure 29

FIGURE 29. Mild and nonfatal atypical case of vaccinia necrosum in a male, aged 64 years, who had a reduction of immunoglobulin G, A, and M, with a lymphoma. In addition to the large, necrotic vaccination site, he had a metastatic lesion on his wrist. His lesions healed after a 2-month course and extensive therapy with vaccinia immune globulin

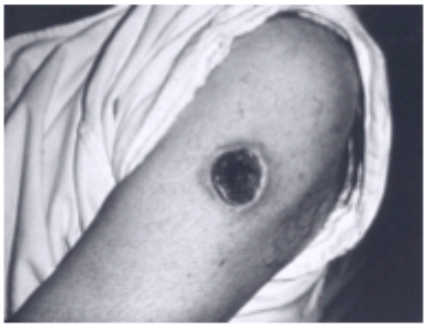

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Figure 30

FIGURE 30. Enlarged vaccination site that should not be mistaken for progressive vaccinia (child with large ulcer at the vaccination site, 9 days after vaccination). The lesion is larger than the majority of cases of progressive vaccinia at 9 days. It is distinguished by the well-demarcated, heaped up inflamed border, and extensive surrounding areas of redness and tenderness, and should not be confused with indolent painless early progressive vaccinia

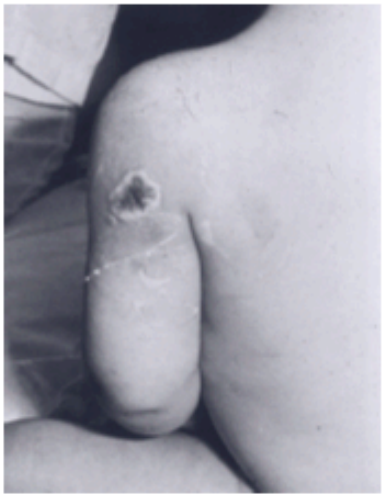

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Figure 31

FIGURE 31. Ulceration of vaccination site, not to be mistaken for progressive vaccinia (unusually severe ulcer after first-time vaccination). This lesion is well-circumscribed and does not have vaccinial vesicles at its margin. Of importance is that this patient did not have an underlying immunologic disease

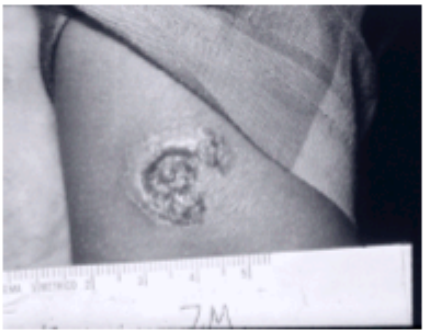

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Figure 32

FIGURE 32. Progressive vaccinia in a woman, aged 62 years, with chronic lymphocytic leukemia. Note the distant lesions on her face, neck, and chest and the progression of the vaccination site

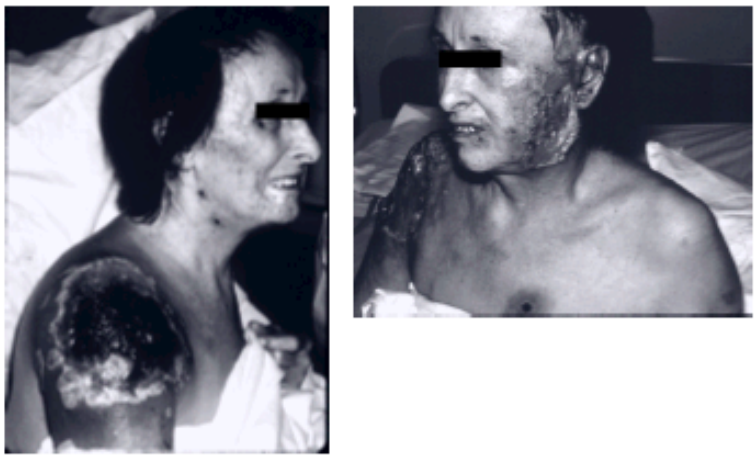

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Figure 33

FIGURE 33. Fetal vaccinia in a premature infant, 28 week's gestation. Mother received vaccination at 23 week's gestation. The infant died at age 8 days, and vaccinia was isolated from the placenta

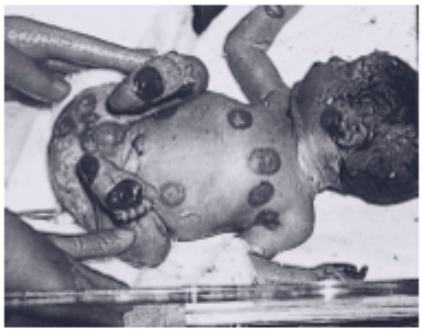

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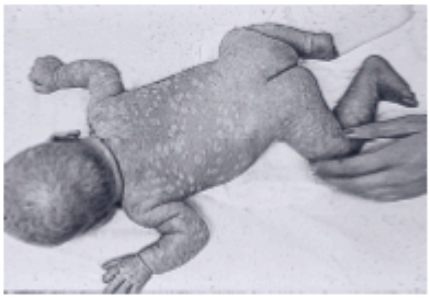
Figure 34

FIGURE 34. Fetal vaccinia scars in an otherwise healthy infant who was born at approximately 32 week's gestation. The child did well, and reports indicated normal development. Mother was vaccinated at 2 month's gestation



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Guide F – Environmental Control of Smallpox Virus

Guide F. Environmental Control of Smallpox Virus

A. Purpose:

This document provides general guidance on environmental infection control and decontamination for use in any setting where care is given to smallpox patients. This information will be beneficial to:

- Healthcare workers,
- Housekeeping and laundry personnel,
- Mortuary personnel and morticians,
- Public health officials,
- Emergency responders in handling cases of smallpox, and
- Persons who manage the treatment and disposal of regulated medical waste.

B. Introduction:

Variola virus is a member of the genus *Orthopoxvirus* within the family *Poxviridae.* Poxviruses are large, brick-shaped, enveloped viruses with a double-stranded DNA genome. Of the four orthopoxviruses known to infect humans, variola virus (major and minor) produces the most significant clinical disease (smallpox).

C. Transmission and Engineering Controls:

Smallpox is transmitted routinely person-to-person (a form of direct contact) via inhalation of variola virus present in droplets generated from the respiratory tract of infected, symptomatic patients. Since disease transmission is via direct contact, infection control and prevention measures are based primarily on contact and droplet precautions.[1] Historically, secondary transmission of infection has been limited to susceptible contacts in the immediate vicinity of patients. Patients become infectious at onset of their rash. Lesions develop primarily on the skin soon after onset and eventually form scabs that can slough off. Viable viruses can be present in these scabs, and the protein material of the scab can protect the viruses from desiccation. Poxviruses shed during the course of infection therefore tend to be more resistant to the effects of drying compared to other enveloped viruses (e.g., influenza viruses, rubella virus). Poxviruses (e.g., vaccinia virus, variola virus) are tightly bound with the fibrin matrices of the scab, however, and this limits the efficiency of virus transfer from environment to persons via reaerosolization.[2] There are limited reports of airborne spread of variola virus in healthcare facilities and laboratories[3, 4] and reaerosolized transmission from fabric or bedding fomites.[5, 6] The mechanisms of virus spread as described in these reports, however, may represent potentially important exceptions to the usual mode of transmission. Additional factors present in these situations (e.g., enhanced efficiency of viral shedding from oral and pharyngeal lesions, poorly engineered facility ventilation) may have contributed to and facilitated viral dispersion in ways that might not be consistently duplicated in contemporary healthcare facilities.[3]

A properly engineered heating, ventilation, and air-condition (HVAC) system can minimize the possibility of airborne spread of variola virus in facilities providing care for smallpox patients. Placing smallpox patients in airborne infection isolation (AII) rooms (i.e., rooms under negative air pressure relative to the corridor or other adjacent space) can help to limit distribution of virus in the air.[7] Existing AII rooms in healthcare facilities need not be modified beyond the current engineering specifications.[8] A more in-depth discussion of variola virus transmission can be found in Guide A—Smallpox Surveillance and Case Reporting; Contact Identification, Tracing, Vaccination, and Surveillance; and Epidemiologic Investigation

Variola virus could hypothetically be used as a weapon either through airborne dispersion or through intentionally infecting one or more persons and encouraging them to circulate among groups of people, thereby exposing these contacts to variola virus infection. If introduced into the air, it is likely that the virus would be inactivated within 24 hours, and certainly would not be present in the environment by the time any cases might occur 7-17 days later. The expected outcome resulting from this form of release would most likely be large numbers of cases with clustered onsets. Establishing epidemiologic association among these cases could be problematic, depending on the site and extent of virus dispersion. If introduced through intentionally infected persons, the origin of the virus (i.e., the index case) and the extent of the outbreak could likely be tracked using standard epidemiologic and laboratory methods.

D. Occupational Issues:

The following activities should be limited preferably to persons with active immunity to smallpox:

- Patient-care activities,
- Laundry ,
- Decontamination procedures, and
- Mortuary procedures.

Refer to Guide B—Vaccination Guidelines for State and Local Health Agencies part 1, part 2, and part 3 for information on vaccination strategies for workers who provide these services and for those not involved with these functions. Personal respiratory protection (i.e., N95 respirators) may be indicated for those workers who provide direct care to smallpox patients. Whenever possible, disposable versions of PPE should be used as appropriate and discarded after use as per routine medical waste disposal practices.[9] All personnel should adhere to hand hygiene practices as per current recommendations.[10] Refer to Guide C part one—Infection Control Measures for Healthcare and Community Settings for information about the appropriate types of PPE and indications for their use.

E. Decontamination and Disinfection:

In general, large enveloped viruses have less intrinsic resistance to inactivation by either physical or chemical methods of disinfection compared to nonenveloped viruses

and many types of bacteria or fungi. The envelope surrounding the core particle of a large virus (e.g., variola virus) contains lipids, and this biochemical property renders this and other enveloped viruses particularly sensitive to chemical disinfection (Figure 1).

Figure 1. Relative Resistance of Microorganisms to Chemical Disinfection*

(*Most Resistant*)

Bacterial endospores
⇓
Mycobacteria
⇓
Non-lipid and small viruses
(e.g., Norwalk virus, polio virus)
⇓
Fungi
⇓
Vegetative bacteria
⇓
Lipid or medium sized viruses
(e.g., herpes simplex virus [HSV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], varicella-zoster virus [VZV], vaccinia virus, variola virus)

(Least Resistant)

* Note: Modified from reference #11

There are no disinfectant products registered by the U.S. Environmental Protection Agency (EPA) specifically for the inactivation of variola virus on surfaces, nor have any products been evaluated for this purpose using this specific virus in potency testing. It has been established, however, that viruses with biophysical and biochemical properties similar to those of variola virus (i.e., vaccinia virus) are readily inactivated by a variety of active ingredients found in EPA-registered chemical germicides that provide low- or intermediate-level disinfection during general use (Table 1).[12, 13] If a manufacturer has submitted data to EPA showing that the product inactivates vaccinia virus, and the EPA has accepted those data and approved such a claim (as it has for a number of products), then the product's label would bear specific use directions for killing vaccinia virus on environmental surfaces. The empiric presumption is that such products would be expected to have sufficient potency to inactivate variola virus on nonporous surfaces.

Table 1. Chemical Inactivation of Vaccinia Virus on Surfaces: Inactivation After 10 Minutes Contact Time at Room Temperature[a]

Chemical Disinfectant	Minimum Concentration to Achieve Inactivation
Chemicals Used on Environmental Surfaces for Low- or Intermediate-Level Disinfection	
Ethyl alcohol	40%
Isopropyl alcohol	30%
Benzalkonium chloride	100 ppm[b]
Sodium hypochlorite	200 ppm
Ortho-phenylphenol	0.12%
Iodophor	75 ppm

a. Modified from references #12, 13, and 14
b. ppm: Parts per million
c. Use of this chemical in health care is limited.

Concentrations of the chemicals listed in Table 1 are lower than those commonly used in healthcare applications. It is therefore expected that manufacturer-recommended use-concentrations of EPA-registered germicides will be adequate for routine disinfection of cleaned environmental surfaces for management of smallpox care areas. The nature and extent of surface contamination will dictate the level of disinfection (i.e., low-level or intermediate-level) needed to make the surface safe to handle or use. It is also expected that high-level disinfectants or liquid chemical sterilants cleared by the U.S. Food and Drug Administration (FDA) for the purpose of achieving high-level disinfection of semi-critical instruments and devices will be effective at inactivating vaccinia virus and variola viruses. All sterilization methods currently cleared by FDA for medical instruments and devices will also inactivate these viruses. Use of high-level disinfectants or liquid chemical sterilants on large environmental surfaces (e.g., table tops, floors, walls) is not indicated under any circumstances.

F. Environmental Infection Control of Smallpox:

When developing a strategy for the environmental control of variola virus, the following elements should be included:

1. Control measures to reduce viral contamination on fabrics, clothing, and bedding,
2. Cleaning and disinfection of reusable equipment,
3. Cleaning and appropriate reprocessing of medical instruments,
4. Cleaning and decontamination of large environmental surfaces,
5. Regulated medical waste containment, treatment, and disposal, and
6. Indications (if any) for decontamination of air space in rooms or vehicles.

1. Laundry: Textiles and Bedding:

Textiles and fabrics (e.g., protective clothing, bed linens, clothing) from patients and their immediate contacts should be handled with minimum agitation to avoid contamination of air, surfaces, and persons.[15] This prevents the dispersion of potentially contaminated sloughed-off scabs and skin squames into the air. Textiles and clothing should be bagged or contained at the point of use in accordance with Occupational Safety and Health Administration (OSHA) regulations.[9] These items should not be sorted prior to laundering. Most, if not all forms of containment used for routine healthcare laundry are acceptable for containing textiles and fabrics generated in care areas for smallpox patients. Wet textiles should be bagged first and then placed in a leak-proof container. Reusable fabric laundry bags commonly used for laundry transport can be laundered along with the clothing and other fabrics. The use of a water-soluble bag is another option for minimizing direct contact and manipulation of these fabrics and clothing prior to washing. If laundry is transported to an off-site facility, the procedures that are currently used for transporting and safe handling of contaminated textiles off-site will be adequate for these situations. Laundry should be labeled in such a way that laundry staff should be prompted to wear appropriate PPE and handle potentially contaminated laundry with a minimum of agitation.[9]

The laundry area in a healthcare facility that receives potentially contaminated textiles and clothing should be set at negative air pressure as per normal operating standards, and be physically separate from the area where clean laundry is dried, folded, and packed for transport and distribution.[8]

Textiles and fabrics from care areas for smallpox patients can be laundered using routine protocols for healthcare facilities (i.e., hot water [71ºC or 160°F] washing with detergent and bleach and hot air drying).[7, 11] No special laundering protocols are needed, nor is it necessary to launder materials from smallpox care areas separately from laundry generated elsewhere in the facility. If contaminated clothing and bed linens are to be washed at home, use the hot water cycle at the highest temperature possible with detergent followed by hot air drying. The use of chlorine bleach during hot-water washing can provide additional measure for safety. The use of cold water washing has not been evaluated with respect to inactivation of variola virus. If no other wash cycles other than cold water are available, use detergents and laundry additives that are specifically formulated for cold-water washing and dry using a hot air cycle for the dryer.[7]

2. Reusable Medical Equipment:

The surfaces of reusable medical equipment should be cleaned and then subjected to either low- or intermediate-level disinfection with an EPA-registered chemical germicide in accordance with label instructions. Current protocols and procedures for cleaning and disinfection need not be changed.[7, 11]

3. Medical Instruments:

Disposable medical instruments and patient-care devices should be placed in containment for safe handling and discarded as per state regulations for the routine handling of medical waste. All reusable medical instruments should be cleaned after use as per standard protocols. These instruments should then be either sterilized or subjected to high-level disinfection depending on their intended use as per the Spaulding classification.[11] There is no need to presoak the instruments unless the instruments cannot be cleaned and reprocessed immediately after use. In this situation, water or saline with or without detergents are adequate soaking agents.

4. Environmental Surfaces:

Environmental surfaces that are touched frequently by hand can be cleaned and subjected to low- to intermediate-level disinfection with EPA-registered chemical germicides according to label instructions.[7] Large housekeeping surfaces such as floors and tabletops can be cleaned using an EPA-registered detergent disinfectant according to manufacturer's instructions.[7] There is no evidence for transmission of variola virus from nonporous surfaces. Therefore, there is no indication to use extraordinary procedures to clean and disinfect the interior surfaces of ambulances or other spaces occupied by smallpox patients. Routine approaches for cleaning and disinfection are adequate in these areas.

Current procedures and schedules can be used for management of floors and furniture.[7] Use a vacuum cleaner equipped with a high efficiency particulate air (HEPA) filter for cleaning carpeted floors or upholstered furniture. Disinfection of the vacuum cleaner is not required when a HEPA filter is properly installed and remains intact during use. Full vacuum cleaner bags can be placed in another closable container and discarded as a routine solid waste.[7] If carpets and upholstered furniture require cleaning to remove visible soil, commercially available products for this purpose are acceptable for use as per usual.

5. Regulated Medical Waste:

Regulated medical waste should be placed in containment, subjected to a decontamination treatment, and discarded in accordance with medical waste regulations of the state or other appropriate jurisdiction. This includes the use of offsite medical waste treatment services. However, if healthcare facilities have the capability of treating/decontaminating medical waste onsite, this capacity should be the first option for medical waste management.[7] All currently approved methods of medical waste decontamination can be expected to inactivate pox viruses.

State health departments or other authorities having jurisdiction should partner with state environmental agencies to develop appropriate policies and/or regulations to ensure the safe disposal of treated regulated medical wastes. These agencies should provide

assurance to landfill operators that these treated wastes will not pose significant risk of smallpox exposure to either the landfill workers or to the general public. There is no scientific basis for refusing landfill disposal of these treated wastes.

Many, if not all states, consider anatomical and pathological wastes as regulated medical wastes, but the remains of a decedent are usually excluded from this category. Incineration is one option for effectively treating anatomical and pathological wastes prior to disposal; other treatment options may be allowed for this waste category as per state regulations or the regulations of the authority having jurisdiction. Remains can be safely managed in mortuary settings using the current practices of barrier protection, Standard precautions, and other appropriate safety procedures during embalming or otherwise preparing the body for cremation (e.g., safe handling and disposal of embalming chemicals, proper ventilation, environmental surface clean-up and disinfection).

The public health authority may choose to exercise the powers regarding the safe disposal of human remains as outlined in Section 504 of the Model State Emergency Health Powers Act if it is determined that a state of public health emergency exists.[16]

6. Indications for Decontamination of Air Space in Rooms or Vehicles:

There is no evidence to support air space decontamination of rooms, facilities, or vehicles (e.g., fumigation). Therefore, fumigation is not indicated for environmental control of variola virus. In controlled laboratory dispersion studies using aerosolized vaccinia virus, infectious virions were rapidly inactivated in the environment, such that only 10% viable particles were detectable 24 hrs after the release.[17] Factors affecting the rate of viral inactivation in this study included:

- Temperature,
- Humidity, and
- Exposure to ultraviolet irradiation (i.e. a release outdoors).[17]

An additional laboratory study of variola virus aerosols under controlled conditions has shown that increasing levels of humidity have little effect on viral inactivation (biological decay) compared to other viruses.[18] In this study, only 10%–30% of viable variola viruses were recovered from controlled aerosols after 1 hour.

However, by the time cases appear in the community following an aerosol release, the presumption is that no viable virus would be remaining in the environment from that release. Additionally, modern HVAC systems and current engineering specifications for those systems provide for air cleaning via air changes per hour (ACH).[7] As stated previously, it is also unlikely that variola virus embedded in the fibrin material from scabs will be easily released from this material and dispersed into the air. If the virus were able to persist in an infectious form in the environment, then additional cases having no contact with infected persons would have been identified. This observation was noted in studies conducted during the smallpox eradication era.[19]

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