Biological Agents and Terrorism: A Worldwide Threat

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How to Take This Course

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

1. **REVIEW THE OBJECTIVES**

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

2. **STUDY EACH SECTION IN ORDER**

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

3. **COMPLETE THE COURSE EXAM**

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

4. **GRADE THE TEST**

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

5. **FILL OUT THE EVALUATION FORM**

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

Introduction

Bioterrorism is a real and serious threat. Although governments and military entities have used biological weapons for centuries, the global threat of terrorism has increased significantly in recent decades. Americans have had a tragic wake-up call regarding terrorism: Domestic terrorism such as the letter bombs sent by the Unabomber, David Kaczinski or the bombing of the federal building in Oklahoma City, by Timothy McVie and Terry Nichols; as well as foreign threats such as the Al-Qaeda attack on September 11, 2001 with the simultaneous flying of aircraft into buildings in New York City, Washington DC and the crash of a plane in rural Pennsylvania.

Biological weapons used in a terrorist attack initially can be difficult to identify, as the domestic terrorism episodes of exposure to Anthrax in October and November of 2001 clearly demonstrated. This episode renewed concern for the tremendous effects that such exposures can have on our nation's people and healthcare system, as well as on law enforcement and national security.

Unlike conventional weapons of mass destruction, explosives, an atomic bomb or chemical releases, the unique effects of biological agents can go undetected for days. Only when individuals present themselves to healthcare providers in emergency rooms and ambulatory clinics with symptoms would any evidence of the attack appear, and even then the initial symptoms might not be recognized and accurately diagnosed. Furthermore, those presenting themselves with symptoms could be at great distances from the original site of exposure by the time symptoms occurred. Or, as evidenced by the 2001 Anthrax attacks, systems such as the US Postal Service can be used in order to disseminate the biological agent over wide geographic areas where it can come in contact with targeted individuals, workers and the general public.

In order to enhance our preparedness for and response to a bioterrorist attack, according to the Department of Health and Human Services (2001), the United States needs an improved network of infectious disease surveillance, including improved communications, upgraded laboratory facilities, advanced diagnostic techniques and expanded training of healthcare personnel. Since September 11th and the Anthrax attacks that occurred soon thereafter, the US healthcare system has been preparing itself by improving knowledge and skill in the management of biological, chemical and radiological threats.

The registered nurse performing triage often will be the first healthcare professional a symptomatic victim will encounter when arriving in the emergency room or ambulatory clinic. Therefore, early detection and response by this first-line responder is imperative. As potential first-line responders, all registered nurses must know what to do in such situations because our decisions can have dire consequences on the greater healthcare system and on the public's health.

The purpose of this course is to provide registered professional nurses with a basic understanding of the clinical presentation, transmission, diagnosis, pharmacological treatment, and post-exposure prophylaxis of some of the more common biological agents such as *Bacillus anthracis* (Anthrax), *Variola virus* (Smallpox), *Yersinia pestis* (Plague), *Clostridium botulinum* (Botulism), *Francisella tularensis* (Tularemia) and the viruses that cause the Viral Hemorrhagic Fevers. In addition, an overview is provided of the recommended notification procedures for local and state public health departments in the event of a bioterrorist incident.

Course Objectives

At the completion of this course, the student will be able to:

- Discuss the threat of bioterrorism.
- Identify Category A agents that may be used as a biological terror weapon.
- Describe the symptoms of these agents, as well as treatment options.
- Explain the procedures necessary to assure safety for healthcare providers.
- Identify steps that nurses can take to manage the threat of bioterrorism.
- State the reporting procedures in possible instances of bioterrorism.

About the Authors

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Overview of Bioterrorism

The use of biological weapons in warfare has been recorded throughout history. The Assyrians, in the 6th century B.C., contaminated enemy wells with poisonous herbs during the siege of Krissa. Smallpox was weaponized when the English provided Native Americans, loyal to the French, with contaminated blankets during the French and Indian War in the mid 18th Century. But governmental use during wartime is not the only use of biological weapons. In 1978, the Bulgarian secret service used an umbrella to inject rice toxin to assassinate a Bulgarian exile (USAMRIID, 2001). In 2001, the United States experienced bioterrorism attacks when B. Anthracis spores, which produce Anthrax disease, were sent through the US postal system.

According to the Department of the Army, there are at least ten countries around the world that have offensive biological weapons programs (US Army Medical Research Institute of Infectious Diseases [USAMRIID], 2001). There has been concern that the smallpox virus now stored in only two laboratories, the CDC in Atlanta and the Institute for Viral Precautions in Moscow, may be available in other countries. Preparedness for and response to an attack involving biological agents are complicated by:

- The large number of potential agents.
- The sometimes long incubation periods and consequent delayed onset of disease.
- The potential for secondary transmission.

In addition to naturally occurring pathogens, agents used by bioterrorists may be genetically engineered to resist current therapies and evade vaccine-induced immunity. Pathogens that have been identified as potential biological warfare agents include those that cause smallpox, anthrax, plague, botulism, tularemia, and viral hemorrhagic fevers.

Given the US's recent experience with bioterrorism, most specifically with anthrax, the knowledge and information that is gained is evolving with each new case of disease. The information provided here is the current state of knowledge. However, the reader is cautioned to recognize that our understanding of bioterrorism and each specific agent is evolving and greater knowledge is gained with additional experience.

On June 3-4, 1999, the Centers for Disease Control and Prevention (CDC) hosted 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 to review and comment on the threat potential of various agents to civilian populations. Members of this group became the Working Group on Civilian Biodefense.

The following general areas were used as criteria for their review:

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.

This Working Group on Civilian Biodefense reviewed lists of biological warfare or potential biological threat agents and selected those they felt posed the greatest threat to civilian populations.

The Working Group categorized potential agents as either A, B, or C. Category A agents have been 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 (Rotz, et al., 2002).

Table 1. Agents and the Diseases They Cause (Rotz, et al., 2002)

Category A

Biological Agent	**Disease**
Variola Major	Smallpox
Bacillus anthracis	Anthrax
Yersinia pestis	Plague
Clostridium botulinum (botulinum toxins)	Botulism
Francisella tularensis	Tularemia
Filoviruses (*Ebola virus*); Arenaviruses (*Lassa virus)*	Viral Hemorrhagic Fevers

Category B

Coxietta burnetii	Q Fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Alphaviruses: Venezuelen Equine (VEE), Eastern Equine (EEE), and Western Equine Encephalomyelitis (WEE)	Enchephalitis
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* 0157:H7)	
Water Safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)	

Category C

Emerging Threat Agents (*Nipah virus, hantavirus*)

This course will address the Category A agents and the diseases they cause.

***Variola Virus*/Smallpox**

Since the terrorist attacks on 9/11/2001, the US has been preparing for the possibility of a smallpox terrorism event. In response to the potential use of biological agents against the civilian population, the federal government has been upgrading plans for preparedness, readiness, and national defenses against bioterrorist weapons. The Centers for Disease Control and Prevention (CDC) has been designated as the lead agency for the national public health response to biological terrorism. There is particular concern that smallpox virus may exist outside the two World Health Organization (WHO) designated repository laboratories, i.e. with groups that might use it as a bioweapon. A single case of smallpox is likely to represent a bioterrorism release and will require an immediate and coordinated public health, medical, and law enforcement response to control the outbreak and to protect the public from any additional release.

The CDC updated the *Smallpox Response Plan and Guidelines* (CDC, 2003d); it incorporates, and extends, many of the concepts and approaches that were successfully employed 30 to 40 years ago to control smallpox outbreaks. These overall concepts for outbreak containment contributed greatly to the eventual global eradication of smallpox. Although updated, many of the elements in the plan have been extensively and successfully utilized in prior decades. The plan outlines the public health strategies that would guide the public health response to a smallpox emergency and many of the federal, state, and local public health activities that must be undertaken in a smallpox outbreak. This plan will continue to be updated to reflect changes in capacities and resources for responding to a smallpox emergency. The Smallpox Response Plan and Guidelines can be accessed at http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp#guidef.

Among the interventions to respond to smallpox is wide-spread training of healthcare providers on the subject of preparedness for a smallpox terrorism event (see the NYSNA online course *Smallpox as a Biological Weapon of Terror: Pre-event Information* for more detailed information regarding smallpox than is provided in this overview of bioterrorism).

Smallpox was declared globally eradicated in 1980 by the World Health Assembly, the supreme decision making body of the World Health Organization. However, it remains a serious biological threat because of its potential ease of large-scale production and the substantial public health consequences of its use as a biological weapon. The last naturally acquired case of smallpox occurred in 1977 in Somalia. The last cases of smallpox, from laboratory exposure, occurred in 1978. In the United States, routine vaccination against smallpox ended in 1972 (CDC, 2001d).

Surveillance for a disease that does not currently exist anywhere in the world presents unique challenges. If smallpox disease were to reoccur in the United States or elsewhere, the most likely possible sources of reintroduction would be (CDC, 2003d):

- An unintentional infection in a laboratory (currently there are only two WHO- approved smallpox virus research and repository laboratories which include the CDC in Atlanta, Georgia and the Institute of Virus Preparations in Moscow, Russia although there is concern that stocks of smallpox virus may exist in other laboratories).
- A bioterrorist attack involving deliberate infection of a person.
- A bioterrorist attack involving intentional release of smallpox virus into the environment.

The virus is fragile and in the event of an aerosol release of smallpox, all viruses will be inactivated or dissipated within 1-2 days. Buildings exposed to an initial aerosol release of the virus do not need to be decontaminated. By the time the first cases are identified, typically 2 weeks after the release, the virus in the building will be gone. Infected patients, however, will be capable of spreading the virus and possibly contaminating surfaces while they are sick.

A suspected case of smallpox is a public health emergency. It will require identification, making a definitive diagnosis with rapid laboratory confirmation at CDC, and preventing further smallpox transmission. A suspected smallpox case should be reported immediately by telephone to state or local health officials and advice obtained regarding isolation and laboratory specimen collection. State or local health officials should notify the CDC immediately at: (770) 488-7100 or (877) 554-4625 if a suspected case of smallpox is identified (CDC, 2003d).

Currently, specific therapies with proven treatment effectiveness for clinical smallpox are unavailable. Medical care of more seriously ill smallpox patients would include supportive measures only. If the patient's condition allows, medical and public health authorities should consider isolation and observation outside a hospital setting to prevent healthcare associated smallpox transmission and over taxation of medical resources. Clinical consultation and a preliminary laboratory diagnosis can be completed within 8-24 hours.

Symptoms of and Course of Smallpox Disease

The viral biologic agents, variola major and variola minor, cause smallpox. Variola minor, or alastrim, is a milder form of smallpox (Henderson, et al, 1999). The incubation period ranges from one to approximately three weeks following exposure, the range being from 7-17 days (Henderson, et al, 1999). Symptoms generally begin within a 2-3 day period in which the patient experiences high fever, malaise, and prostration with severe headache and backache. Severe abdominal pain and delirium are sometimes present.

A maculopapular rash then appears, first on the mucosa of the mouth and pharynx, face and forearms, spreading to the trunk and legs. Within one or two days, the rash becomes vesicular and later pustular. The pustules are characteristically round, tense and deeply embedded in the dermis; they feel like a firm round object embedded in the skin (ACIP, 2001). Crusts begin to form about the eighth or ninth day. When the scabs separate, pigment-free skin remains, and eventually pitted scars form (Johns Hopkins University, 2000). The scars result from the destruction of sebaceous glands that is followed by shrinking of granulation tissue and fibrosis. Scars are most evident on the face (Henderson, et al., 1999).

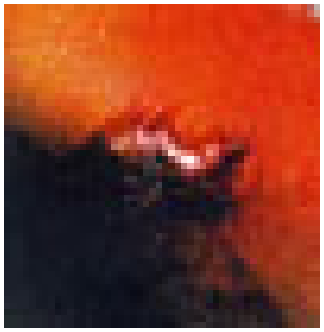
The lesions on the mouth and pharynx ulcerate quickly, releasing large amounts of virus into the saliva. Patients are most infectious during the first week, which corresponds with the high virus titers in the saliva (Henderson, et al., 1999). Patients are no longer infectious after all scabs have separated, approximately 3-4 weeks after the onset of the rash (ACIP, 2001).

Variola minor is more mildly characterized, has fewer symptoms, a sparser rash and has approximately a 1% mortality rate in unvaccinated victims. Those with residual immunity from a previous vaccination may also have a milder form of the disease. In those cases where partial immunity may be present, the rash can be atypical and sparse, and the progression of the lesions can be more rapid (Henderson, et al., 1999). Variola major, on the other hand, has a mortality rate of 3% in vaccinated victims and 30% in unvaccinated victims. Smallpox must be distinguished from chickenpox or contact dermatitis. Unlike varicella, variola lesions remain generally synchronous in their stages of development.

Exposure to Smallpox

The only known reservoir for the virus is humans; no known animal or insect reservoirs or vectors exist. The most frequent mode of transmission is person-to-person, spread through direct deposit of infective droplets onto the nasal, oral, or pharyngeal mucosal membranes, or the alveoli of the lungs from close, face-to-face contact with an infectious person. Indirect spread (i.e., not requiring face-to-face contact with an infectious person) through fine-particle aerosols or a fomite containing the virus is less common (ACIP, 2001). People with smallpox are most infectious during the first week of illness, because that is when the largest amount of virus is present in saliva. However, some risk of transmission lasts until all scabs have fallen off. Because smallpox

is highly communicable, any confirmed case requires immediate report to public health authorities.



Smallpox Vaccination

Smallpox vaccine is a highly effective immunizing agent. It is a live-virus vaccine composed of vaccinia virus, an orthopoxvirus that induces antibodies that also protect against smallpox. Vaccinia vaccine has enabled the global eradication of smallpox through a focused ring vaccination campaign, intensive surveillance, and contact-tracing (ACIP, 2001).

In the past two years, healthcare providers have been vaccinated on a volunteer basis, as part of the "Smallpox Response Teams" to improved preparedness in the event of a smallpox terrorism event. Vaccination is not currently recommended for the general public (CDC, 2002c).

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

The smallpox vaccine, currently available in the US is Dryvax®, produced by Wyeth Laboratories. It is a live-virus preparations of infectious vaccinia virus. Smallpox vaccine does not contain smallpox (variola) virus (CDC, 2003a).

The current vaccine was prepared in the early 1980s from calf lymph with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus. The vaccine is provided as a 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 (CDC, 2003a).

Smallpox vaccine is administered by using the multiple-puncture technique with a bifurcated needle, packaged with the vaccine and diluent. According to the product labeling, 2--3 punctures are recommended for primary vaccination and 15 punctures for revaccination. A trace of blood should appear at the vaccination site after 15--20 seconds; if no trace of blood is visible, an additional 3 insertions should be made by using the same bifurcated needle without reinserting the needle into the vaccine vial. If no evidence of vaccine take is apparent after 7 days, the person can be vaccinated again (Wharton, et al., 2003).

Although smallpox vaccine is considered a safe vaccine, post-vaccination adverse events can occur. These include: inadvertent inoculation, generalized vaccinia, eczema vaccinatum, progressive vaccinia and post-vaccinial encephalitis; death occurs in about one per million primary vaccinations and is usually a result of progressive vaccinia, post-vaccinial encephalitis or severe eczema vaccinatum. Those with a higher risk for developing post-vaccination complications include:

- 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 (CDC, 2003b);

- Anyone who has experienced a previous allergic reaction to the smallpox vaccine should not be vaccinated (CDC, 2003b);

- 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 (CDC, 2003b);
- Persons with eczema (including a history of eczema) or other forms of chronic dermatitis;

- Persons with altered immune states (HIV, AIDS, leukemia, lymphoma, immunosuppressive medications, etc.) (CDC, 2003c);

- Women who are breast feeding or who are pregnant (CDC, 2003c);

- Infants and children under the age of 12 months (CDC, 2003c);

- Persons with known cardiac disease such as previous myocardial infarction, angina, congestive heart failure, or cardiomyopathy (CDC, 2003c).

While vaccination is contraindicated for those above, there are no absolute contraindications to post-exposure vaccination of a person who experiences bona fide exposure to variola. 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 (CDC, 2003c).

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

The level of immunity, if any, among persons who were vaccinated before 1972 is uncertain; therefore, these persons are assumed to be susceptible. For those who were vaccinated, it is not known how long immunity lasts. Most estimates suggest immunity from the vaccination lasts 3 to 5 years. This means that nearly the entire U.S. population, with the exception of those healthcare providers who were recently vaccinated, as well as current and former military personnel, has partial immunity at best. Immunity can be boosted effectively with a single revaccination. Prior infection with the disease grants lifelong immunity (CDC, 2001d).

A single, laboratory confirmed case will initiate implementation of the national CDC, state and local health departments' smallpox response plans. Other criteria for implementation of the response plan include (CDC, 2003d):

- A large outbreak of a clinically compatible illness pending etiologic confirmation;
- Reports of suspected or probable cases once an outbreak has been identified elsewhere in the country; and
- Confirmation of smallpox virus in an environmental sample, package, or device associated with human exposure.

Surveillance, outbreak investigation and control activities including contact identification, tracing, vaccination and surveillance will need to be prioritized once smallpox is confirmed in a local jurisdiction. Following the confirmation of a smallpox case, especially if it is the first case confirmed in the United States, an epidemiological investigation will need to occur in collaboration with law enforcement and state and federal authorities. If a smallpox case is confirmed anywhere

in the United States or in the world, enhanced surveillance for smallpox should be initiated and decisions on vaccination will be made in collaboration with state and federal authorities (CDC, 2003d).

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

The following are considered high risk groups and should be prioritized for vaccination in a smallpox outbreak (CDC, 2003d):

1. Face-to-face close contacts (≤ 6.5 feet or 2 meters) or household contacts to smallpox patients after the onset of the smallpox patient's fever. Although individuals with smallpox are not infectious until the onset of rash, vaccinating contacts from the time of the onset of fever helps provide a buffer and assures that contacts who may have been exposed at the early onset of rash, when the rash may have been faint and unrecognized, have been vaccinated.

2. Persons exposed to the initial release of the virus (if the release was discovered during the first generation of cases and vaccination may still provide benefit).

3. Household members, without contraindications to vaccination, of contacts to smallpox patients in order to protect household contacts should smallpox case contacts develop disease while under fever surveillance at home. Household members of contacts who have contraindications to vaccination should be housed separately from the other vaccinated household members until the vaccination site scab has separated (~ 2 weeks) to prevent inadvertent transmission of vaccinia virus. They should be housed separately from the contact until the incubation period for smallpox has passed and the contact is released from surveillance.

4. Persons involved in the direct medical care, public health evaluation (this includes personnel whose public health activities involve direct patient contact such as case interviewing), or transportation of confirmed or suspected smallpox patients.

5. Laboratory personnel involved in the collection and/or processing of clinical specimens from suspected or confirmed smallpox patients.

6. Other persons who have a high likelihood of exposure to infectious materials (e.g., personnel responsible for hospital laundry, waste disposal, and disinfection).

7. Personnel involved in contact tracing and vaccination, or quarantine/isolation or enforcement, or law-enforcement interviews of suspected smallpox patients.

8. Persons permitted to enter any facilities designated for the evaluation, treatment, or isolation of confirmed or suspected smallpox patients (only essential personnel should be allowed to enter such facilities). Only personnel without contraindications to vaccination should be chosen for activities that would require vaccination for their protection. Personnel with contraindications should not perform duties that would place them at risk for smallpox exposure and should otherwise only be vaccinated if an exposure has already occurred.

9. Persons present in a facility or conveyance with a smallpox case if fine-particle aerosol transmission was likely during the time the case was present (e.g. hemorrhagic smallpox case and/or case with active coughing). Evaluation of the

potential risk for aerosol transmission and initiation of vaccination for non-direct contacts will be done by CDC, state, and local public health personnel. The decision to offer vaccination to non-direct contacts of smallpox cases will be made jointly by federal and state health officials.

Once a smallpox outbreak is confirmed it is important to expand the number of vaccinated personnel to ensure sufficient staff to rapidly and safely control the outbreak. In addition, persons whose jobs place them at increased risk of being exposed to smallpox cases should also be offered vaccine. These persons would include healthcare workers, public health personnel, first responders, and law enforcement personnel as well as others indicated by the local situation.

Smallpox Treatment

There is no proven treatment for smallpox, but research to evaluate new antiviral agents is ongoing. 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.

The CDC's *Smallpox Response Plan and Guidelines* (2003d) provides detailed public health strategies that would guide the public health response to a smallpox emergency and many of the federal, state, and local public health activities that must be undertaken in a smallpox outbreak.

Bacillus anthracis/Anthrax

The bacterial etiologic agent of anthrax is *Bacillus anthracis*. It is an encapsulated, aerobic, gram-positive, spore-forming, rod-shaped (*bacillus*) bacterium (CDC, 2002a). The *B. anthracis* spore is an exceptionally resilient bacteria; it is resistant to sunlight, heat and disinfectants. In the past, humans have become infected with anthrax after handling the contaminated hides, flesh, or manufactured products of infected cattle, sheep, or horses. The disease most commonly occurs in herbivores, which are infected by ingesting spores from the soil. In 1945, during an outbreak of anthrax in Iran, 1 million sheep died (Inglesby, et al, 1999).

During October-November, 2001, twenty-two confirmed or suspected cases were identified in the 2001 outbreak of bioterrorism-related anthrax. Cases were reported from Florida, New York, New Jersey, the District of Columbia, and Connecticut (CDC, 2002b). Although clearly a tragic occurrence, this situation provided the US healthcare system with the opportunity to update knowledge on the identification and treatment of *B. anthracis* exposure.

Signs and Symptoms of Anthrax Disease

Human anthrax has several major clinical forms: cutaneous, inhalation, gastrointestinal and oropharyngeal. If left untreated, anthrax in all forms can lead to septicemia and death.

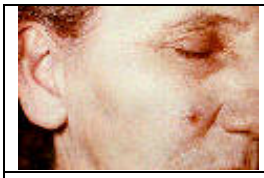
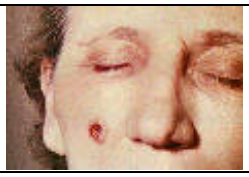
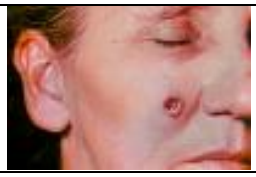
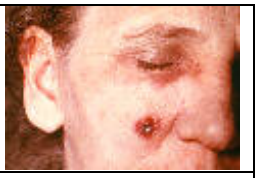
Cutaneous anthrax is the most common naturally occurring type of infection (>95%) and usually occurs when the bacterium from contaminated meat, wool, hides, or leather from infected animals enters a cut or abrasion on the skin. In the US, 224 cases of cutaneous anthrax were reported between 1944 and 1994. The largest reported international epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10,000 human cases of anthrax were reported, nearly all of them cutaneous anthrax (Inglesby, 1999). In the 2001 Anthrax terrorism attack in the US, there were 7 cases of confirmed cutaneous anthrax and 4 cases of suspected cutaneous anthrax (CDC, 2002b).

Skin trauma was not associated with the 2001 cutaneous anthrax cases in the US. Exposure to contaminated mail was the apparent source of infection in all patients. The incubation periods after exposure ranged from 1 to 10 days. The initial symptom was often a pruritic papule resembling an insect bite. The papules vesiculated, with some becoming hemorrhagic. The vesicles ruptured to form depressed ulcers, often with local edema, ultimately forming dry eschars. These stages occur regardless of antibiotic therapy. The differential diagnosis of cutaneous anthrax includes brown recluse spider bite, ecthyma, ulceroglandular tularemia, accidental vaccinia, and necrotic herpes simplex (CDC, 2002b).

The name "anthrax" comes from the Greek word for coal and refers to the characteristic eschar. Although the lesion is usually painless, patients also may have fever, malaise, headache, extensive edema, regional lymphadenopathy and other systemic signs (CDC, 2002b). About 20% of untreated cases of cutaneous anthrax will result in death. Deaths are rare if patients are given appropriate antimicrobial therapy (CDC, 2001a).

Gram stain and culture of the lesion are recommended; however, prior antibiotic treatment rapidly renders the infected site culture-negative for *B. anthracis*. Serologic testing and punch biopsy at the edge of the lesion, examined by silver staining and immunohistochemical testing, are useful in diagnosing cutaneous anthrax in patients who have received antibiotic therapy (CDC, 2002b).

Clinical recognition and diagnosis issues needing further consideration and research include rapid, reliable, and readily available detection methods (e.g., PCR and antigen detection); education and ready access to information for clinicians regarding anthrax clinical features and risk stratification; recognition of anthrax in children; and the role of serologic testing in the diagnosis and management of both inhalational and cutaneous anthrax (CDC, 2002b).

				
Day 4	**Day 5**	**Day 6**	**Day 8**	**Day 11**

Inhalational anthrax is the most lethal form of anthrax. Anthrax spores must be aerosolized in order to cause inhalational anthrax. In 1979, the accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union resulted in at least 79 cases of anthrax infection and 68 deaths (Inglesby, 1999). Anthrax aerosol is odorless and invisible and has the potential to travel large distances; both persons indoors and outdoors are at risk (Inglesby, 1999). According to the CDC (2001a) 4,000 - 5,000 spores must be present to cause an infection. Prior to 2001, the most recent case of inhalational anthrax was in 1976; a California fiber artist was exposed to *B. anthracis* from imported yarns (CDC, 2001a). During the anthrax terrorism attack in the US in 2001, there were 11 cases of confirmed inhalation anthrax (CDC, 2002b).

Of the 11 patients with inhalational anthrax, 9 (and possibly all 11) are believed to have been exposed to mail containing or contaminated with *B. anthracis* spores. Median age was 56 years (range 43-94 years). Average incubation from known exposure to symptoms was 4 days (range 4-6 days). Fever, chills, drenching sweats, profound fatigue, minimally productive cough, nausea or vomiting, and chest discomfort were symptoms reported by most patients. Rhinorrhea and productive cough were uncommon. Chest X-ray at initial examination showed mediastinal widening, paratracheal fullness, hilar fullness, and pleural effusions or infiltrates or both, but in some patients these initial findings were subtle. Pleural effusions were a complication in all 11 patients; among all 8 patients who had not received antibiotics, *B. anthracis* grew in blood cultures drawn at initial examination. Six (55%) of 11 patients have survived with aggressive supportive care and multidrug antibiotic regimens including a fluoroquinolone (CDC, 2002b). With multidrug antibiotic regimens and supportive care, survival of patients (60%) was markedly higher (<15%) than previously reported.
Prior the 2001 Anthrax events, it was thought that the incubation period of inhalational anthrax was in a range from 1 to 7 days, possibly ranging up to 60 days. Severe respiratory distress follows and septicemia, shock and death occur within 24-36 hours after the onset of respiratory distress. Approximately half of cases, prior to 2001, are accompanied by meningitis.

The differential diagnosis of inhalational anthrax versus influenza-like illness is challenging. Respiratory viruses, including influenza, are common causes of influenza-like illness and tend to circulate in winter. These viruses are readily communicable, in contrast to anthrax, which is not spread from person to person. A history of influenza vaccination is not helpful in evaluating the likelihood of anthrax. Influenza-like illnesses have many causes besides influenza viruses, and influenza vaccine is not 100% effective. Unlike patients with inhalational anthrax, adults with influenza or other viral respiratory illnesses do not usually have shortness of breath and vomiting but often have sore throat or rhinorrhea. Rapid identification tests for influenza are available but vary widely in sensitivity (CDC, 2002b).

Table 2. Differences in symptoms between Flu and Anthrax (FDA, 2001)

Flu Symptoms	Inhalation Anthrax	Cutaneous Anthrax	Intestinal Anthrax
Fever, muscle aches, headache, lack of energy, a dry cough, sore throat, and possibly a runny nose. These symptoms usually last for several	Initial symptoms are much like a common cold, and may mimic flu-like symptoms. However, several hours to several days later they progress to	Skin infection begins as a raised itchy bump that resembles an insect bite, but within one to two days develops into a sore, and then into a	Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea.

days for most people; however, they can last for as long as two weeks.	severe breathing problems and shock.	painless ulcer with a black (dead) center. Lymph glands in the adjacent area may swell.	

The classic chest X-ray findings--widened mediastinum or pleural effusions--may be subtle or absent on initial medical evaluation. In addition, these radiographic findings are not unique to anthrax: histoplasmosis, sarcoidosis, tuberculosis, and lymphoma, for example, are included in the differential diagnosis. A chest computed tomography scan is helpful in detecting hemorrhagic mediastinal lymph nodes and edema, peribronchial thickening, and pleural effusions, findings seen in patients with inhalational anthrax. Hyperdense mediastinal and hilar adenopathy plus mediastinal edema suggest anthrax. The hemorrhagic pleural effusions of inhalational anthrax typically increase during hospitalization (CDC, 2002b).

Blood cultures and *B. anthracis*-specific polymerase chain reaction (PCR) of blood and pleural fluid are important in the diagnosis of inhalational anthrax. Serologic testing has also been valuable. An enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulin (Ig) G response to *B. anthracis* protective antigen (PA) is highly sensitive (detects 98.6% of true positives) but is only approximately 80% specific. To improve specificity, a PA-competitive inhibition ELISA is used as a second, confirmatory step. Preliminary studies indicate that specific IgG anti-PA antibody can be detected as early as 10 days, but peak IgG may not be seen until 40 days after onset of symptoms (CDC, 2002b).

Immunohistochemical examination of pleural fluid or transbronchial biopsy specimens, using antibodies to *B. anthracis* cell wall and capsule, also has an important role in the diagnosis of inhalational anthrax, especially in patients who have received prior antibiotics. Immunohistochemical examination can detect intact bacilli or *B. anthracis* antigens. PCR, serologic tests, and immunohistochemical tests are currently available at CDC or at certain laboratories in the Laboratory Response Network (LRN) (CDC, 2002b)..

Gastrointestinal anthrax is uncommon; however, outbreaks reported in Africa and Asia (Inglesby, 1999) usually follow the consumption of raw or undercooked contaminated meat. It has an incubation period of 1-7 days and is associated with severe abdominal distress, lower bowel inflammation, nausea, loss of appetite, vomiting and fever followed by abdominal pain, vomiting blood, and bloody diarrhea (CDC, 2001a), followed by fever and signs of septicemia.

Oral-pharyngeal anthrax involves the pharynx and is usually characterized by lesions at the base of the tongue, sore throat, dysphagia, fever and regional lymphadenopathy. In 1982 there were 24 cases of oral-pharyngeal anthrax in rural Thailand, following the consumption of contaminated buffalo meat.

Detection of Anthrax in the Environment

The clinical presentation gives rise to the suspicion of anthrax, however, it is confirmed through laboratory testing. Hand-held assays (sometimes referred to as "Smart Tickets") are sold commercially for the rapid detection of *B. anthracis*. These assays are intended only for the screening of environmental samples. First responder and law enforcement communities are using these as instant screening devices and should forward any positive samples to authorities for more sensitive and specialized confirmatory testing. The results of these assays should not be used to make decisions about patient management or prophylaxis. The utility and validity of these assays are unknown.

The CDC does not recommend the use of these assays at this time due to limited scientific data. The analytical sensitivity of these assays is limited by the technology. Data provided by manufacturers indicate that a minimum of 10,000 spores is required to generate a positive signal. This number of spores would suggest a heavy contamination of the sample. Therefore, a

negative result does not rule out a lower level of contamination. Data collected from field use also indicates specificity problems with some of these assays. Some positive results have been obtained with spores of the non-anthrax Bacillus bacteria that may be found in the environment.

Anthrax Vaccination

A protective vaccine was developed in the United States during the 1950s and 1960s for human use and was licensed by the FDA in 1970. It is a cell-free filtrate, produced from a strain of anthrax that does not cause disease. The vaccine contains no whole bacteria, dead or alive. Since 1970, it has been safely and routinely administered to at-risk wool mill workers, veterinarians, laboratory workers, livestock handlers and military personnel (AVIP, DOD, 2001).

Vaccination is recommended only for those at high risk, such as workers in research laboratories that handle anthrax bacteria routinely. The antibiotics used in post exposure prophylaxis are very effective in preventing anthrax disease from occurring after an exposure.

The Advisory Committee on Immunization Practices (ACIP) has recommend anthrax vaccination for the following groups:

- Persons who work directly with the organism in the laboratory.
- Persons who work with imported animal hides or furs in areas where standards are insufficient to prevent exposure to anthrax spores.
- Persons who handle potentially infected animal products in high-incidence areas. While incidence is low in the United States, veterinarians who travel to work in other countries where incidence is higher should consider being vaccinated.
- Military personnel deployed to areas with high risk for exposure to the organism.

The vaccine helps the immune system to prevent the anthrax bacteria from growing and producing toxins that lead to disease and death. The best protection from anthrax exposure is achieved following the full course of six injections, maintained with booster doses. In a study of experimental monkeys, injection with the anthrax vaccine at 0 and 2 weeks offered complete protection against aerosol anthrax challenge at 8 and 38 weeks and 88% effectiveness at 100 weeks (USDOD, AVIP, 2001).

According to the United States Department of Defense, Anthrax Vaccine Immunization Program (USDOD, AVIP), the original study of anthrax vaccine showed 92.5% fewer anthrax infections (combining both cutaneous and inhaled cases of anthrax) among vaccinated people, compared to unvaccinated people. No cases of inhaled (inhalation) anthrax occurred among vaccine recipients. Five cases of anthrax occurred among unvaccinated or incompletely vaccinated people. This difference involved too few people to be statistically conclusive, although the trend is obvious.

Hypothetically, the antibodies that result from any vaccine can be overwhelmed if one is exposed to extremely large doses of any pathogen. Even if vaccinated, one may not be completely safe if one is close to the point of release of the biologic agent. Antibiotics for such people offer additional protection. Vaccination is only one part of the health force protection efforts, which also include protective gear and detection equipment. For continued protection, annual booster doses are required.

According to the USDOD, AVIP (2001), possible side effects; and percentage of people vaccinated, include:

- Mild local reactions in about 30% of men and 60% of women. (Less than 1" of redness, swelling, and/or tenderness at the site of injection - not unlike other vaccine shots)

- Moderate local reaction (1" to 5" with redness, minor swelling, and tenderness at the injection site) occurs in 1% to 5% of those immunized.

- Large local reactions (redness greater than 5", swelling at the site of injection and forearm), in about 1% of those immunized.

Beyond the injection site, from 5% up to 35% of people will notice muscle aches, joint aches, headaches, rash, chills, fever, nausea, loss of appetite, malaise, or related symptoms. These symptoms usually go away after a few days. Over-the-counter medications to treat these symptoms, before or after the anthrax vaccine may help reduce bothersome symptoms.

Serious events, such as those requiring hospitalization, are rare. They happen about once per 200,000 doses. Severe allergic reactions can occur after any vaccination, less than once per 100,000 doses.

There have been no patterns of long-term side effects, persistent side effects, or delayed side effects.

Like all other vaccines in the US, the anthrax vaccine has not been formally studied for effects on the reproductive system. Therefore, vaccinations should be deferred during pregnancy unless clearly indicated. Women will be questioned about the possibility of pregnancy. If a vaccine is inadvertently given to a pregnant woman, no adverse pregnancy outcome or fetal harm is expected because of the vaccine's inactive state (USDOD, AVIP, 2001).

Treatment of Anthrax

Inhalational anthrax historically, has almost always been fatal when treatment is initiated after patients become significantly symptomatic. The *B. anthracis* associated with the 2001 outbreak were sensitive to the quinolones, rifampin, tetracycline, vancomycin, imipenem, meropenem, chloramphenicol, clindamycin, and the aminoglycosides. The isolates have intermediate-range susceptibility to the macrolides but are resistant to extended-spectrum cephalosporins, including third-generation agents (e.g., ceftriaxone), and to trimethoprim-sulfamethoxazole (CDC, 2002b).

Doxycycline, another first-line agent, should not be used if meningitis is suspected because of its lack of adequate central nervous system penetration. Bacteremic patients are often initially treated with a multidrug regimen to which an offending organism is presumed sensitive; this treatment also allows empiric coverage for other pathogens. Thus, the recommendation for initial treatment of inhalational anthrax is a multidrug regimen of either ciprofloxacin or doxycycline along with one or more agents to which the organism is typically sensitive. After susceptibility testing and clinical improvement, the regimen may be altered (CDC, 2002b).

Current recommendations, however, include intravenous ciprofloxacin (400 mg IV q 12 hours) or doxycycline (200 mg IV load followed by 100 mg IV q 12 hours) at the earliest signs of disease. Antibiotic treatment should continue for 60 days (see Table 3).

Table 3. Inhalation Anthrax Treatment Protocol*.† for Cases Associated With the Bioterrorism Attacks of September-November 2001.

Category	Initial Therapy (Intravenous)	Duration
Adults	Ciprofloxacin 400 mg every 12 hours* or Doxycycline 100 mg every 12 hrs.†† and One or two additional antimicrobials¶	IV treatment initially **. Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg po BID or Doxycycline 100 mg po BID Continued for 60 days (IV and po combined)§§
Children	Ciprofloxacin 10 - 15 mg/kg every 12 hrs¶¶*** or Doxycycline. †††,†† >8 yrs and > 45kg: 100 mg every 12 hrs >8yrs and < or = 45kg: 2.2 mg/kg every 12 hrs < or = 8 yrs: 2.2 mg/kg every 12 hrs and One or two additional antimicrobials¶	IV treatment initially**. Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10 - 15 mg/kg po every 12 hrs*** or Doxycycline: ††† >8 yrs and > 45 kg: 100 mg po BID >8 yrs and < or = 45 kg: 22mg/kg po BID < or = 8 yrs: 2.2 mg/kg po BID Continue for 60 days (IV and po combined) §§
Pregant Women§§§	Same for nonpregnant adults (the high death rate from infection outweighs the risk posed by the antimicrobial agent)	IV treatment intially. Switch to oral antimicrobial therapy when clinically appropriate.† oral therapy regimens same for nonpregnant adults.
Immunocompromised Persons	Same for nonimmunocompromised persons and children.	Same for nonimmunocomprised persons and children.

*For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.
†Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.
§Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.
¶Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenern, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamasses in Bacillus Anthracis, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.
**Initial therapy may be altered based on clinical course of the patient; one or two antimicrobial agents (e.g., ciprofloxacin or doxycycline) may be adequate as the patient improves.
††If meningitis is suspected, doxycyline may be less optimal because of poor central nervous system penetration.

§§Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.
¶¶If intravenous ciprovloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentration are attained 1-2 hours after oral dosing but may not be achieved if vomiting or ileus are present.
***In children, ciprofloxacin dosage should not exceed 1 g/day.
†††The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections. (e.g., Rocky Mountain spotted fever).
§§§Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dos related; therefore, doxycycline might be used for a short time (7-14 days, before 6 months of gestation.

Two months after the 2001 outbreak, 6 of 11 patients with inhalational anthrax had survived. Keys to successful management appear to be early institution of antibiotics and aggressive supportive care. Chest tube drainage of the recurrent pleural effusions, which are typically hemorrhagic, often leads to dramatic clinical improvement. Because these effusions tend to reaccumulate rapidly, insertion of a chest tube or tubes has been beneficial (CDC, 2002b).

In cases of **cutaneous anthrax**, if signs of systemic disease, pervasive edema or lesions of the head and neck are present, treatment with the same IV antibiotics used to treat inhalation anthrax is recommended. In cases of cutaneous anthrax without systemic involvement, it is typically treated for 7-10 days. The drugs of choice for treatment of cutaneous disease are also ciprofloxacin or doxycycline. A penicillin such as amoxicillin or amoxacillin/clavulanic acid may be used to complete the course if susceptibility testing is supportive (CDC, 2002b). However, since the bioterrorist attacks of September – November 2001, the CDC recommends oral antibiotic treatment for 60 days due to the risk of simultaneous aerosol exposure (see Table 4.).

Treatment for **gastrointestinal anthrax** is the same as treatment recommended for inhalation anthrax.

TABLE 4. Cutaneous Anthrax Treatment Protocol* for Cases Associated With This Bioterrorism Attack

Category	Initial Therapy (oral)†	Duration
Adults	Ciprofloxacin 500 mg BID or Doxycycline 100 mg BID	60 days§
Children*	Ciprofloxacin 10-15 mg/kg every 12 hrs (not to exceed 1 g/day) or Doxycyline:¶ >8 yrs and > 45 kg: 100 mg every 12 hrs <8 yrs and ? 45 kg: 2.2 mg/kg every 12 hrs >/= 8 yrs: 2.2 mg/kg every 12 hrs	60 days§
Pregnant Women*'**	Ciprofloxacin 500 mg BID or Doxycycline 100 mg BID	60 days§
Immunocomprimised Persons*	Same for nonimmunocompromised persons and children.	60 days§

*Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended. (Table 4)
†Ciprofloxacin or Doxycycline should be considered first-line therapy. Amoxicillin 500 mg po TID for adults or 80 mg/kg/day divided every 8 hours for children is an option for completion of

therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.
§Previous guidelines have suggested treating cutaneous anthrax for 7-10 days, but 60 days is recommended in the setting of this attack, given the likelihood of exposure to aerosolized B. Anthracis.
¶The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections. (e.g., Rocky Mountain Spotted Fever).
**Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

Standard precautions should be utilized in the treatment of anthrax disease. Direct person-to-person spread of anthrax is extremely unlikely and anthrax is not contagious. Therefore, there is no need to quarantine individuals suspected of being exposed to anthrax or to immunize or treat contacts of persons ill with anthrax, such as household contacts, friends, or coworkers, unless they also were also exposed to the same source of infection (CDC, 2001).

There are some adjunctive therapies that may be beneficial in the treatment of anthrax. Clindamycin has been suggested to have antitoxin properties (as in the treatment of toxic shock associated with group *A streptococci*, *Staphylococcus aureus,* and *Clostridium* infections). Steroids have been used to control the edema of cutaneous disease and have been suggested for the treatment of meningitis or substantial mediastinal edema. Other antitoxin agents investigated in vitro include angiotensin-converting enzyme inhibitors, calcium channel blockers, and tumor necrosis factor inhibitors. Specific anthrax IgG antisera, collected from military or other vaccines, may be an adjunct, as well as administration of the vaccine itself (CDC, 2002b).

While there are no controlled studies of ciprofloxacin use in pregnant women to show safety, an expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk. However, there are no human data available to assess the effects of long-term therapy in pregnant women such as that proposed for treatment of anthrax exposure. Ciprofloxacin is excreted into breast milk but is considered as "usually compatible with breastfeeding" by the American Academy of Pediatrics (FDA, 2001, accessed at www.fda.gov/cder/drug/infopage/cipro/cipropreg.htm).

Prophylaxis After Anthrax Exposure

Prophylaxis is recommended for any person who has been exposed to possible anthrax. The need for prophylaxis is determined by public health officials on the basis of an epidemiologic investigation. Prophylaxis is indicated for persons exposed to an airspace contaminated with aerosolized *B. anthracis*. Prophylaxis is not indicated for health-care and mortuary workers who care for patients or attend to corpses using standard precautions, for persons who handle or open mail in the absence of a credible threat, or for prevention of cutaneous anthrax (CDC, 2002b).

Ciprofloxacin, doxycycline, and penicillin G procaine have been approved by the Food and Drug Administration (FDA) for prophylaxis of inhalation *B. anthracis* infection (CDC, 2002b). While neither medication is ordinarily administered to pregnant women or children, due to the possibility of adverse effects (ciprofloxacin due to risk of fetal development to cartilage and bone, and doxycycline because of the risk of permanent stain to teeth or alteration in bone formation). The risk benefit ratio must be weighed. During the 2001 Anthrax bioterrorist attacks, interim CDC recommendations for anthrax prophylaxis include ciprofloxacin or doxycycline. Amoxicillin (in three daily doses) is an option for children and pregnant or lactating women exposed to strains susceptible to penicillin, to avoid potential toxicity of quinolones and tetracyclines. Amoxicillin is not widely recommended as a first-line prophylactic agent, however, because of lack of FDA

approval, lack of data regarding efficacy, and uncertainty about the drug's ability to achieve adequate therapeutic levels at standard doses (CDC, 2002b).

The optimal duration of prophylaxis is uncertain; however, 60 days was recommended (CDC, 2002b). The Department of Health and Human Services announced, in late 2001, that additional options for prophylaxis of inhalational anthrax for persons who wish to take extra precautions, especially those whose exposure may have been high. Three options are now offered (CDC, 2002b):

1) 60 days of antibiotic prophylaxis;
2) 100 days of antibiotic prophylaxis, and
3) 100 days of antibiotic prophylaxis, plus anthrax vaccine as investigational postexposure treatment [3 doses over a 4-week period

Prophylaxis for inhalation anthrax recommendations for adults consist of ciprofloxacin 500 mg po bid with doxycycline (100 mg po bid) or amoxicillin (500 mg po q 8 hours) serving as alternatives if strains are susceptible. In children, ciprofloxacin (10-15 mg/kg po every 12 hours) or doxycycline (>8 years and > 45 kg, 100 mg po bid; >8years and= 45 kg, 2.2 mg/kg po bid; = 8 years, 2.2 mg/kg po bid). If an anthrax exposure is confirmed, and because the anthrax vaccine is not commercially available, antibiotic prophylaxis should continue for 60 days.

According to the CDC, ciprofloxacin (500 mg, orally, two times a day for 60 days) is the antibiotic of choice for initial prophylactic therapy among asymptomatic pregnant women exposed to *B. anthracis*. In instances where the specific *B. anthracis* strain has been shown to be penicillin-sensitive, prophylactic therapy with amoxicillin (500 mg, orally, three times a day for 60 days) may be considered. CDC guidelines for treatment of anthrax infection in pregnant women recommend either ciprofloxacin or doxycycline with one or two other antibiotics added for inhalational anthrax or systemic involvement.

Prophylaxis for cutaneous anthrax is the same as postexposure prophylaxis of inhalation anthrax.

***Yersinia pestis*/Plague**

There have been 3 recorded plague pandemics throughout history. The first began in Egypt in 541AD and swept across Europe; 50% and 60% of the population of North Africa, Europe, and central and southern Asia succumbed to the plague. The second plague pandemic, known as the *Black Death* or G*reat Pestilence*, began in 1346, eventually killing 20 to 30 million people in Europe, approximately one third of the European population. This pandemic lasted over 130 years and had ramifications that extended to political, cultural and religious arenas. The third pandemic began in China in 1855, spread to all inhabited continents, and ultimately killed more than 12 million people in India and China. Throughout history, plague spread slowly from village to village by infected rats and humans or more quickly from country to country by ships (Inglesby, et al., 2000).

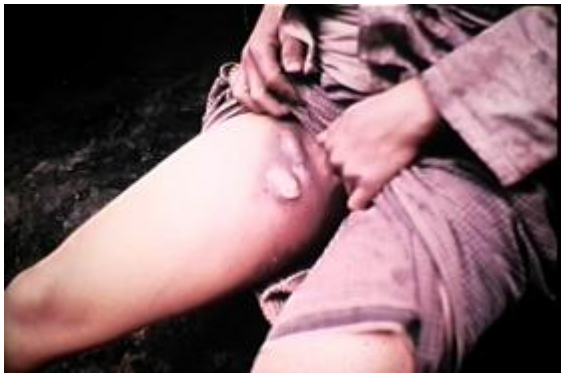
In the United States, the last urban plague epidemic occurred in Los Angeles in 1924-25. Since then, human plague in the United States has occurred as mostly scattered cases in rural areas (an average of 10 to 15 persons each year). Globally, the World Health Organization reports 1,000 to 3,000 cases of plague every year (CDC, 2002d). About 14% (1 in 7) of all plague cases in the United States are fatal (CDC, 2001e).

Yersinia pestis, a gram-negative rod-shaped bacterium causes plague. Fleas living on rodents such as rats, mice, prairie dogs, and ground squirrels, can transmit the bacteria to humans who then contract the bubonic form of plague that can progress to the septicemic and/or pneumonic forms.

The pneumonic form of plague (described later in this course) would be the predominant presenting form following an intentional bioterrorist aerosol dissemination of the bacterium. While somewhat resilient, *Y. pestis* is susceptible to heat, disinfectants, sunlight, and soap and water. Even so, when released into air, the bacterium will survive for up to one hour, depending on conditions (CDC, 2002d).

Signs and Symptoms of Plague

Bubonic plague is the most common clinical form of plague. It accounts for 80-90% of the disease in the US. It results from the bacteria being taken up by the host macrophages in the lymph nodes. These nodes become inflamed, enlarged and painful; this is acute regional lymphadenopathy, or bubo. These buboes typically involve lymph nodes that drain the site of initial infection and are most often located in the inguinal, axillary, or cervical regions. Bubonic plague occurs after an incubation period that ranges from, and rarely exceeds, two to six days. The liver and spleen are often tender and palpable. Approximately 25% of patients will have various types of skin lesions. Bubonic plague, if not treated, can progress to pneumonic plague (CDC, 2002d).



Septicemic plague, occurring when Y. pestis invades and continues to multiply in the bloodstream, can occur secondarily to bubonic plague, or it can develop without detectable lymphadenopathy. In the US from 1947-1977, approximately 10% of plague cases presented as septicemic plague; 50% of those cases resulted in death. Complications from this form of plague include septic shock, coagulopathy, meningitis and coma (ACIP, 1996).

Pneumonic plague is the least common, but most fatal form of plague. It begins after an incubation period of one to six days. It can develop as a secondary complication of septicemic plague, or it can result from inhalation of infectious respiratory droplets from a human or animal with pneumonic plague. Symptoms include high fever, chills, headache, malaise, cough and hemoptysis. It progresses quickly to dyspnea, stridor, cyanosis, and death due to respiratory failure and circulatory collapse. Treatment needs to be instituted within 18 hours of onset of respiratory symptoms; pneumonic plague is essentially fatal without antibiotic treatment (ACIP, 1996, CDC, 2002d).

In a biological attack, the inhaled aerosolized *Y. pestis* bacilli would cause primary pneumonic plague. The time of exposure to when symptoms first develop ranges from 1 to 6 days, most often 2-4 days (Inglesby, et.al., 2000). Early signs of illness are fever with cough and dyspnea, sometimes with the production of bloody, watery, or less commonly, purulent sputum. Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present (Inglesby, et al., 2000).

Chest X-rays will likely show bilateral infiltrates and consolidation. Laboratory studies may indicate leukocytosis with toxic granulations, coagulation abnormalities, aminotransferase elevations, azotemia, and other evidence of multiorgan failure. All are nonspecific findings associated with sepsis and systemic inflammatory response syndrome (Inglesby, et al., 2000).

There are no effective environmental warning systems to detect an aerosol of plague bacilli therefore the early diagnosis of plague is critical and requires a high index of suspicion in any case of plague, as one case may be indicative of a larger epidemic (Inglesby, et al., 2000). The first clinical or laboratory suspicion of plague must lead to immediate notification of the hospital epidemiologist or infection control practitioner, health department, and the local or state health laboratory. Definitive tests can thereby be arranged rapidly through a state reference laboratory or, as necessary, the Diagnostic and Reference Laboratory of the CDC and early interventions instituted (Inglesby, et al., 2000).

Table 5:

Epidemiology and symptoms	Sudden appearance of many persons with fever, cough, shortness of breath, hemoptysis, and chest pain
	Gastrointestinal symptoms common (eg, nausea, vomiting, abdominal pain, and diarrhea)
	Patients have fulminant course and high mortality
Clinical signs	Tachypnea, dyspnea, and cyanosis
	Pneumonic consolidation on chest examination
	Sepsis, shock, and organ failure
	Infrequent presence of cervical bubo
	(Purpuric skin lesions and necrotic digits only in advanced disease)
Laboratory studies	Sputum, blood, or lymph node aspirate
	Gram-negative bacilli with bipolar (safety pin) staining on Wright, Giemsa, or Wayson stain
	Rapid diagnostic tests available only at some health departments, the Centers for Disease Control and Prevention, and military laboratories
	Pulmonary infiltrates or consolidation on chest radiograph
Pathology	Lobular exudation, bacillary aggregation, and areas of necrosis in pulmonary parenchyma

(Inglesby, et al., 2000)

Treatment for Plague

Antibiotic therapy must begin immediately, no more than 24 hours after the onset of any symptoms (CDC, 2002d). Several categories of antibiotics are effective for curing the disease and 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. Antibiotics for 10-14 days are the recommended treatment. According to the CDC (2002d), early in the response to a bioterrorism attack, these medications would be tested to determine which is most effective against the particular weapon that was used.

Patients with the disease should be isolated and medically supervised for at least the first 48 hours of antibiotic treatment. Standard precautions are adequate for bubonic plague while droplet precautions are required for suspected pneumonic plague (CDC, 2002d). Patients with pneumonic plague will likely require substantial advanced medical supportive care in addition to antimicrobial therapy. Complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure (Inglesby, et al., 2000).

People who have been exposed to a contagious person can be protected from developing plague by receiving prompt antibiotic treatment (CDC, 2002d). For asymptomatic exposed persons, doxycycline (100 mg po bid) for 7 days, or the duration of exposure risk plus 7 days, serves as prophylaxis.

Vaccination for Plague

The CDC identifies that there is no currently available vaccine for bubonic, septicemic or pneumonic plague prophylaxis available in the US (CDC, 2002d). From 1896 until 1999, when it was discontinued, there was a US-licensed formalin-inactivated whole bacilli vaccine. This killed vaccine was effective in preventing or ameliorating bubonic disease, but was not effective in primary pneumonic plague (Inglesby, et al., 2000).

Botulism

Clostridium botulinum and two additional *Clostridia* species are extremely potent spore-forming bacillus neurotoxins that cause the clinical syndrome known as botulism. They have been used therapeutically to treat spastic conditions such as strabismus, tetanus and cosmetic wrinkles. Clostridia spores germinate into vegetative bacteria that produce toxins during anaerobic incubation and can be produced in large quantities as a biological agent to contaminate food and water supplies. *C. botulinum* exists in three forms: food borne, infantile, and wound. The toxin is inactivated by sunlight within 1-3 hours. Heat and chlorine also destroy the toxin.

Although an aerosol attack is the most likely scenario for the use of botulin toxins, this agent could also be used to sabotage food supplies.

Signs and Symptoms of Botulism

Symptom onset of inhaled botulism usually begins within 12 to 36 hours after exposure. Clinical features include symmetric cranial nerve neuropathies are evident early with blurred vision, ptosis, photophobia, dysphonia and dysphagia. Symmetric, progressive skeletal muscle weakness in a proximal to distal pattern, and respiratory dysfunction from respiratory muscle paralysis or upper airway obstruction without sensory deficits follows. Weakened oropharyngeal musculature may lead to upper airway collapse and sudden respiratory failure. Autonomic effects include dry mouth and urinary retention. Severe food borne botulism can progress to death within as little as 24 hours.

Inhalational botulism has a similar clinical presentation as food borne botulism. However, the gastrointestinal symptoms that accompany food borne botulism may be absent.

Treatment of Botulism

Bioassays of the patient's serum in addition to environmental sampling help confirm cases. Early administration of the botulinum antitoxin or heptavalent antitoxin is essential since the antitoxin only neutralizes circulating toxin. Respiratory assistance will be required if symptoms progress to respiratory collapse. Standard precautions are adequate for patient care. Decontamination with soap and water is also adequate.

Vaccination

The pentavalent toxoid vaccine is recommended for selected individuals or groups judged to be at high risk for exposure to botulinum toxin aerosols.

***Francisella tularensis*/Tularemia**

Tularemia, caused by *Francisella tularensis,* a small, nonmotile, aerobic, gram-negative coccobacillus.is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to cause disease. Humans can become infected through diverse environmental exposures and can develop severe, sometimes fatal illness. Human to human transmission does not occur in tularemia. The Working Group on Civilian Biodefense (Dennis, et al., 2001) considers *F. tularensis* to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death (Dennis, et al., 2001).

F. tularensis has been studied and possibly used as a biological weapon. The Japanese germ warfare research units operating in Manchuria between 1932 and 1945 studied the potential use of *F. tularensis*. It is speculated that tularemia outbreaks which affected tens of thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use (Dennis, et al., 2001). In the 1950s and 1960s, the US military developed weapons that would disseminate *F. tularensis* aerosols; concurrently, researched the development of vaccines and antibiotic prophylaxis and treatment regimens. A live attenuated vaccine was developed that partially protected against respiratory and intracutaneous challenges with *F. tularensis*, and treatment with regimens of streptomycin, tetracyclines, and chloramphenicol were found to be effective in both prophylaxis and treatment. By the late 1960s the US military as well as the Soviet Union, stockpiled *F. tularensis* as a biological weapon. Allegedly, the Soviets engineered antibiotic-resistant strains of *F.* (Dennis, et al., 2001).

Tularemia occurs naturally in North America, Europe and Asia. It is generally a rural disease, spread through diverse animal hosts and habitats. A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares, are natural reservoirs of infection. They acquire infection through bites by ticks, flies, and mosquitoes, and by contact with contaminated environments (Dennis, et al., 2001).

Exposure to Tularemia

Humans become infected with *F tularensis* by various modes, including bites by infective arthropods, handling infectious animal tissues or fluids, direct contact with or ingestion of contaminated water, food, or soil, and inhalation of infective aerosols. *F. tularensis* can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. Although *F tularensis* is highly infectious and pathogenic, its transmission from person to person has not been documented (Dennis, et al., 2001).

Tularemia disease

The major target organs are the lymph nodes, lungs and pleura, spleen, liver, and kidney. Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to regional lymph nodes and further multiply, and then may disseminate to organs throughout the body (CDC, 2002e).

Airborne *F tularensis* would be expected to principally cause **primary pleuropneumonic infection** through inhalation; some exposures might contaminate the eye, resulting in **ocular tularemia**; penetrate broken skin, resulting in **ulceroglandular** or glandular disease; or cause **oropharyngeal** disease with cervical lymphadenitis (Dennis, et al., 2001). A large airborne tularemia outbreak occurred in 1966-67 in Sweden where 600 persons were infected during a farming incident (rodent infested hay was being moved to a barn). In that outbreak conjunctivitis was reported in 26% of 140 confirmed cases and an infected ulcer of the skin was reported in nearly 12%; pharyngitis was reported in 31% and oral ulcers in about 9% of the cases; and 32% of these patients had various exanthemas, such as erythema multiforme and erythema nodosum. Tularemia outbreaks arising from similar agricultural exposures have been reported from Finland, mostly presenting with general constitutional symptoms rather than specific manifestations of

pneumonia; enlargement of hilar nodes was the principal radiographic finding in these cases (Dennis, et al., 2001).

A terrorist release of aerosolized *F tularensis* would have the most significant adverse health consequences. In a densely populated area, an aerosolized release would be expected to result in an abrupt onset of large numbers of cases of acute, nonspecific febrile illness beginning 3 to 5 days later (incubation range, 1-14 days), with pleuropneumonitis soon developing in a significant proportion of cases (Dennis, et al., 2001).

Public health authorities would most likely become aware of an outbreak of unusual respiratory disease in its early stages, but this could be difficult to distinguish from a natural outbreak of community-acquired infection, especially influenza or various atypical pneumonias. The abrupt onset of large numbers of acutely ill persons, the rapid progression in a relatively high proportion of cases from upper respiratory symptoms and bronchitis to life-threatening pleuropneumonitis and systemic infection affecting, among others, young, previously healthy adults and children should, however, quickly alert medical professionals and public health authorities to a critical and unexpected public health event and to bioterrorism as a possible cause. Until the etiology became clear, clinicians would need to work closely with epidemiologists and diagnostic laboratories to differentiate the illness from various community-acquired pneumonias and to determine if it could have resulted from use of one of several potential bioterrorism weapons agents (Dennis, et al., 2001).

The onset of tularemia is usually abrupt, with fever (38°C–40°C), headache, chills and rigors, generalized body aches (often prominent in the low back), coryza, and sore throat. Bacteremia may be common in the early phase of infection. A pulse-temperature dissociation has been noted in as many as 42% of patients. A dry or slightly productive cough and substernal pain or tightness frequently occur with or without objective signs of pneumonia, such as purulent sputum, dyspnea, tachypnea, pleuritic pain, or hemoptysis. Nausea, vomiting, and diarrhea may occur (CDC, 2002e).

Sweats, fever, chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness (CDC, 2002e).

In general, tularemia would be expected to have a slower progression of illness and a lower case-fatality rate than either inhalational plague or anthrax. Milder forms of inhalational tularemia would be indistinguishable from Q fever; another potential bioterrorism agent; establishing a diagnosis of either would be problematic without reference laboratory testing (CDC, 2002e).

Once a substantial cluster of cases of **inhalational tularemia** had been identified, epidemiological findings should suggest a bioterrorist event. The abrupt onset and single peak of cases would implicate a point-source exposure without secondary transmission. Among exposed persons, attack rates would likely be similar across sex and age groups, and risk would be related to degree of exposure to the point source. An outbreak of inhalational tularemia in an urban setting should trigger a high level of suspicion of an intentional event, since all reported inhalational tularemia outbreaks have occurred in rural areas (Dennis, et al., 2001).

In **ulceroglandular tularemia**, the form that typically arises from handling a contaminated carcass or following an infective arthropod bite, a local cutaneous papule appears at the inoculation site at about the time of onset of generalized symptoms, becomes pustular, and ulcerates within a few days of its first appearance. The ulcer is tender, generally has an indolent character, and may be covered by an eschar. Typically, one or more regional afferent lymph nodes may become enlarged and tender within several days of the appearance of the papule. Even with antibiotic treatment, the affected nodes may become fluctuant and rupture. In **oculoglandular tularemia**, which follows direct contamination of the eye, ulceration occurs on the conjunctiva, accompanied by pronounced chemosis, vasculitis, and regional lymphadenitis. **Glandular tularemia** is characterized by lymphadenopathy without an ulcer (CDC, 2002e).

Oropharyngeal tularemia is acquired by drinking contaminated water, ingesting contaminated food, and, sometimes, by inhaling contaminated droplets or aerosols. Affected persons may develop stomatitis but more commonly develop exudative pharyngitis or tonsillitis, sometimes with ulceration. Pronounced cervical or retropharyngeal lymphadenopathy may occur (CDC, 2002e).

Prior to the advent of antibiotics, the overall mortality from infections with the more severe strains was in the range of 5% to 15%, and fatality rates as high as 30% to 60% were reported for untreated pneumonic and severe systemic forms of disease. Currently, the overall case-fatality rate of reported cases in the United States is less than 2% (CDC, 2002e).

Diagnosis of Tularemia

Rapid diagnostic testing for tularemia is not widely available. Healthcare providers who suspect inhalational tularemia in patients presenting with atypical pneumonia, pleuritis, and hilar lymphadenopathy should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures (CDC, 2002e).

F. tularensis may be identified through direct examination of secretions, exudates, or biopsy specimens using Gram stain, direct fluorescent antibody, or immunohistochemical stains. Microscopic demonstration of *F. tularensis* using fluorescent-labeled antibodies is a rapid diagnostic procedure performed in designated reference laboratories in the National Public Health Laboratory Network; test results can be available within several hours of receiving the specimens, if the laboratory is alerted and prepared (CDC, 2002e).

Growth of *F. tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. It can be grown from pharyngeal washings, sputum specimens, and even fasting gastric aspirates in a high proportion of patients with inhalational tularemia. It is only occasionally isolated from blood (CDC, 2002e).

Tularemia Vaccination

In the United States, a live attenuated vaccine derived from avirulent *F. tularensis* biovar palaearctica (type B) has been used to protect laboratorians routinely working with the bacterium. Until recently, this vaccine was available as an investigational new drug. It is currently under review by the Food and Drug Administration (CDC, 2002e).

Correlates of protective immunity appear about 2 weeks following natural infection or vaccination. Given the short incubation period of tularemia and incomplete protection of current vaccines against inhalational tularemia (CDC, 2002e).

Treatment of Tularemia

The Working Group recommends parenteral antimicrobial therapy for tularemia (see Table 6). Streptomycin is the drug of choice; Gentamicin, which is more widely available and may be used intravenously, is an acceptable alternative (Dennis, et al., 2001). Treatment with aminoglycosides should be continued for 10 days. Tetracyclines and chloramphenicol are also used to treat tularemia; however, relapses and primary treatment failures occur at a higher rate with these bacteriostatic agents than with aminoglycosides, and they should be given for at least 14 days to reduce chance of relapse. Fluoroquinolones, which have intracellular activity, are promising candidates for treating tularemia. Ciprofloxacin, which is not labeled for use in tularemia, has been shown to be active against *F tularensis* in vitro and in animals and has been used to successfully treat tularemia in both adults and children. Treatment with ciprofloxacin should be continued for 10 days. In persons beginning treatment with parenteral doxycycline, ciprofloxacin, or chloramphenicol, therapy can be switched to oral antibiotic administration when clinically indicated. Very limited experiences in treating tularemia patients with beta-lactam and macrolide antibiotics have been reported, and treatment failures have occurred. Use of beta-lactam and macrolide antibiotics in treating tularemia is neither FDA-approved nor recommended by the working group (Dennis, et al., 2001).

Table 6. Working Group Consensus Recommendations for Treatment of Patients With Tularemia in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis* (CDC, 2002e)	
Patient Category	**Recommended Therapy**
Contained Casualty	
Adults	**Preferred choices:** Streptomycin, 1g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily† **Alternative choices:** Doxycycline, 100 mg IV twice daily Chloramphenicol, 15 mg/kg IV 4 times daily Ciprofloxacin, 400 mg IV twice daily†
Children	**Preferred choices:** Streptomycin, 15 mg/kg IM twice daily (should not exceed 2 gm/d) Gentamicin, 2.5 mg/kg IM or IV 3 times daily† **Alternative choices:** Doxycycline, If weight >= 45 kg, 100 mg IV If weight < 45 kg, give 2.2 mg/kg IV twice daily Chloramphenicol, 15 mg/kg IV 4 times daily† Ciprofloxacin, 15 mg/kg IV twice daily‡
Pregnant Women	**Preferred choices:** Gentamicin, 5 mg/kg IM or IV once daily† Streptomycin, 1 g IM twice daily **Alternative choices:** Doxycycline, 100 mg IV twice daily Ciprofloxacin, 400 mg IV twice daily†
Mass Casualty Setting and Postexposure Prophylaxis	
Adults	**Preferred choices:** Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily†
Children	**Preferred choices:** Doxycycline, and If >=45kg give 100 mg orally twice daily If <45 kg then give 2.2 mg/kg orally twice daily Ciprofloxacin, 15 mg/kg orally twice daily‡
Pregnant Women	**Preferred choices:** Ciprofloxacin, 500 mg orally twice daily† Doxycycline, 100 mg orally twice daily
* One antibiotic, appropriate for treatment for patient age, should be chosen from among the alternatives. Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14-21 days. Persons beginning treatment with intramuscular (IM) or intravenous (IV) doxycycline,	

ciprofloxacin, or chloramphenicol can switch to oral antibiotic administration when clinically indicated.

† Not a U.S. Food and Drug Administration-approved use.

‡ Ciprofloxacin dosage should not exceed 1 g/d in children.

In **children**, streptomycin or gentamicin is recommended by the working group as first-line treatment in a contained casualty situation (see Table 6). Doxycycline, ciprofloxacin (≤1 g/d), and chloramphenicol can be used as alternatives to aminoglycosides. Fluoroquinolones have been reported to cause cartilage damage in immature animals and are not FDA-approved for use in children. However, short courses of these agents have not been associated with arthropathy in pediatric patients, and the potential risks of their use must be weighed against their benefits in treating serious infections (Dennis, et al., 2001).

Doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment in the mass casualty setting, for both adults and children (see Table 6). The ciprofloxacin dosage for children should not exceed 1 g/d. In a mass casualty situation, the working group believes the benefits to children from short courses of doxycycline or fluoroquinolones outweigh the risks of their use (CDC, 2002e).

For **pregnant women** in a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat tularemia in pregnant women (see Table 6). Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women.

There is scant experience in treating tularemia in **immunocompromised patients**. However, considering the greater occurrence in immunocompetent patients of tularemia relapses and treatment failures following use of bacteriostatic antimicrobial agents compared with aminoglycosides, streptomycin or gentamicin should be used when possible to treat patients with known immune dysfunction in either contained casualty or mass casualty situations (see Table 4).

Tularemia Prophylaxis

Persons beginning treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin in the incubation period of tularemia and continuing treatment daily for 14 days might be protected against symptomatic infection. Therefore, if an attack is discovered before individuals become ill, exposed persons should be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin (CDC, 2002e).

If an attack is discovered only after individuals become ill, persons potentially exposed should begin a fever watch. Those who develop an otherwise unexplained fever or flu-like illness within 14 days of presumed exposure should begin treatment as outlined above (CDC, 2003e).

Postexposure prophylactic treatment of close contacts of tularemia patients is not recommended because person-to-person transmission is not known to occur (CDC, 2002e).

Tularemia Infection Control and Environmental Decontamination

Isolation is not recommended for tularemia patients, given the lack of person-to-person transmission. In hospitals, standard precautions are recommended (CDC, 2002e).

Laboratory personnel should be alerted when tularemia is suspected. Routine diagnostic procedures can be performed in biosafety level 2 conditions. Examination of cultures in which *F. tularensis* is suspected should be done in a biological safety cabinet. Manipulation of cultures and

other procedures that might produce aerosols or droplets (e.g., grinding, centrifuging, vigorous shaking, animal studies) should be conducted under biosafety level 3 conditions (CDC, 2002e).

Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to produce aerosols or droplets should be avoided (CDC, 2002e).

Clothing or linens contaminated with body fluids of patients with tularemia should be disinfected per standard hospital procedure.

Under natural conditions, *F. tularensis* can survive for extended periods in a cold, moist environment. Information is not available about survivability of an intentionally released aerosol form of *F. tularensis*, but the working group predicts a short half-life due to desiccation, solar radiation, oxidation, and other environmental factors and a very limited risk from secondary dispersal. Following an urban release, the risk to humans of acquiring tularemia from infected animals or arthropods is likely small and can be reduced by educating the public to avoid sick or dead animals and to take precautions to protect against biting arthropods.

Hemorrhagic Fever Viruses

Viral Hemorrhagic Fever

Viral Hemorrhagic Fever (VHF) is a clinical disease characterized by fever and bleeding, caused by viruses belonging to one of 4 families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae (Borio, et al., 2002).

While multiple viruses can cause VHF, only those that may be weaponized or have high morbidity and mortality will be addressed. The Working Group on Civilian Biodefense (Borio, et al., 2002) identified VHFs that meet criteria for a serious biological terror risk. Among them are: Ebola, Marburg, Lassa Fever, Rift Valley Fever and Yellow Fever. These specific VHF will be covered in this course. An overview of VHF will occur first in this course, then specifics VHFs will be addressed.

A number of countries and political organizations have developed weaponized hemorrhagic fever viruses. The former Soviet Union and Russia produced Marburg, Ebola, Lassa, and New World arenaviruses (specifically, Junin and Machupo) until 1992. Soviet Union researchers quantified the aerosol infectivity of Marburg virus for monkeys, determining that no more than a few virions are required to cause infection. Yellow Fever and Rift Valley Fever viruses were developed as weapons by the US offensive biological weapons program prior to its termination in 1969.There are reports that Yellow Fever may have been weaponized by North Korea. The Japanese terrorist cult Aum Shinrikyo unsuccessfully attempted to obtain Ebola virus as part of an effort to create biological weapons (Borio, et al., 2002).

A high index of suspicion will be required to diagnose VHF among persons exposed to a bioterrorist attack; the variable clinical presentation of these diseases presents a major diagnostic challenge (Borio, et al., 2002).

Any suspected cases of HFV disease should be immediately reported to local and/or state health departments who would then notify the CDC. The World Health Organization has developed surveillance standards for acute VHF syndrome with the aim of early detection of naturally occurring outbreaks and notification of cases, even before identification of the causal agent. This includes prompt reporting to public health authorities of any patient with acute onset of fever greater than or equal to 101 degrees Fahrenheit of less than 3 weeks' duration who is severely ill, has no known predisposing host factors for hemorrhagic manifestations, and has any 2 of the following (Borio, et al., 2002):

- hemorrhagic or purpuric rash,
- epistaxis,
- hematemesis,
- hemoptysis,
- blood in stool, or
- other hemorrhagic symptoms.

This broad definition may be useful in the early period following a confirmed bioterrorist-related case of VHF as well. Public health authorities may develop more specific case definitions after the etiologic agent is identified (Borio, et al., 2002.

It is recommended that in any suspected case of VHF treatment should begin prior to the confirmation of the diagnosis. Initiation of supportive and ribavirin (a nucleoside analog) therapy

should begin immediately (see Table 5.) (Borio, et al., 2002). It should be noted however, that ribavirin is not approved by the Food and Drug Administration (FDA) for the treatment of VHF and ribavirin has been shown to have efficacy only to the arenaviruses or the bunyaviruses and has shown no benefit in the treatment of filoviruses and flaviviruses.

However, the mainstay of treatment of VHF is supportive. Careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure must be insured. Intravenous fluids may reverse hypotension, however, caution is needed as in some cases intravenous fluids may have contribute to pulmonary edema; consideration should be given to early vasopressor support with hemodynamic monitoring. Mechanical ventilation, renal dialysis, and antiseizure therapy may be needed. Intramuscular injections, aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulant therapies are contraindicated. Steroids are not indicated (Borio, et al., 2002).

Table 7. Recommendations for Ribavirin Therapy in Patients with Clinically Evident Viral Hemorrhagic Fever of Unknown Etiology or Secondary to Arenaviruses or Bunyaviruses*

	Contained Casualty Setting	Mass Casualty Setting†
Adults	Loading dose of 30 mg/kg intravenously (IV) (maximum, 2 g) once, followed by 16 mg/kg IV (maximum, 1 g per dose) every 6 hours for 4 days, followed by 8 mg/kg IV (maximum, 500 mg per dose) every 8 hours for 6 days	Loading dose of 2000 mg orally once, followed by 1200 mg/d orally in 2 divided doses (if weight >75 kg), or 1000 mg/d orally in 2 doses (400 mg in AM and 600 mg in PM) (if weight ≤75 kg) for 10 days‡
Pregnant women§	Same as for adults	Same as for adults
Children	Same as for adults, dosed according to weight	Loading dose of 30 mg/kg orally once, followed by 15 mg/kg per day orally in 2 divided doses for 10 days

*Recommendations are not approved by the US Food and Drug Administration for any of these indications and should always be administered under an investigational new drug protocol. However, in a mass casualty setting, these requirements may need to be modified to permit timely administration of the drug.
†The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local health care resources.
‡Although a similar dosage (1000 mg/d in 3 divided doses) has been used in a small number of patients with Lassa fever,[106] this regimen would be impractical because the current formulation of oral ribavirin in the United States consists of 200-mg capsules, and ribavirin capsules may not be broken open.
§Refer to the section in text on treatment of pregnant women for details.

Recommendations for Protective Measures Against Nosocomial Transmission of Hemorrhagic Fever Viruses (Borio, et al., 2002)

- Strict adherence to hand hygiene: Healthcare workers should clean their hands prior to donning personal protective equipment for patient contact. After patient contact, healthcare workers should remove gown, leg and shoe coverings, and gloves and immediately clean their hands. Hands should be cleaned prior to the removal of facial protective equipment (ie, personal respirators, face shields, and goggles) to minimize exposure of mucous membranes with potentially contaminated hands, and once again after the removal of all personal protective equipment.
- Double gloves;
- Impermeable gowns;
- N-95 masks or powered air-purifying respirators;

- a negative isolation room with 6-12 air changes per hour, as required by Healthcare Infection Control Practices Advisory Committee standards for airborne precautions*;
- Leg and shoe coverings;
- Face shields†;
- Goggles for eye protection†;
- Restricted access of nonessential staff and visitors to patient's room;
- Dedicated medical equipment, such as stethoscopes, glucose monitors, and, if available, point-of-care analyzers;
- Environmental disinfection with an Environmental Protection Agency–registered hospital disinfectant or a 1:100 dilution of household bleach.
- If there are multiple patients with viral hemorrhagic fever in one health care facility, they should be cared for in the same part of the hospital to minimize exposures to other patients and health care workers

*These resources may not be possible in many health care facilities or in a mass casualty situation. In this case, all other measures should be taken and would, in combination, be expected to substantially diminish the risk of nosocomial spread.

†Face shields and eye protection may be already incorporated in certain personal protective equipment, such as powered air-purifying respirators.

Ebola Hemorrhagic Fever

Ebola virus belongs to the Filoviridae virus family, as does the Marburg Virus (discussed later in this course); both cause severe hemorrhagic fever in humans. Four species of Ebola virus have been identified: Ivory Coast, Sudan, Zaire, and Reston. Ebola-Reston is the only known filovirus that does not cause severe disease in humans (CDC, 2003f).

Ebola virus was first identified in 1976 when two outbreaks of Ebola hemorrhagic fever (Ebola HF) occurred in the Democratic Republic of Congo (formerly called Zaire) and southern Sudan. The outbreaks involved what eventually proved to be two different species of Ebola virus; both were named after the nations in which they were discovered. Both viruses showed themselves to be highly lethal, as 90% of the Zairian cases and 50% of the Sudanese cases resulted in death (CDC and WHO, 2003g).

Despite numerous attempts to locate the natural reservoir or reservoirs of Ebola and Marburg viruses, their origins remain undetermined (CDC, 2003f). In an outbreak or isolated case among humans, just how the virus is transmitted from the natural reservoir to a human is unknown. Once a human is infected, however, person-to-person transmission involves close personal contact between an infected individual or their body fluids, and another person (CDC, 2003f). Nosocomial transmission through contact with infected body fluids – via reuse of unspecialized syringes, needles, or other medical equipment contaminated with these fluids – has also been an important factor in the spread of disease (CDC, 2003f). Percutaneous exposure to very low inocula can result in Ebola infection; mortality was substantially higher when the disease was acquired percutaneously. During the 1976 Ebola epidemic in the Democratic Republic of the Congo (formerly Zaire), 85 (26.7%) of 318 cases occurred in individuals who had received an injection, and every case of disease acquired by contaminated syringes resulted in death (Borio, et al., 2002).

Filoviruses can also be transmitted by mucosal exposure. Experiments in nonhuman primates have documented transmission of infection after direct administration of Marburg virus into the mouths and noses of experimental animals and after direct administration of Ebola virus into the

mouths or conjunctiva of experimental animals. Human infections might occur through contact of contaminated fingers with oral mucosa or conjunctiva, but direct evidence is lacking (Borio, et al., 2002). Large numbers of Ebola viral particles have been found on human skin and the lumina of sweat glands; this has raised concern that disease transmission may occur from touching an infected patient or corpse (Borio, et al., 2002).

In 1995, an outbreak of Ebola hemorrhagic fever (Ebola HF) affected more than 300 people in and around the city of Kikwit, Democratic Republic of the Congo (formerly, Zaire); approximately 80% of the patients died (CDC and WHO, 2003g). More than 25% of all the patients in the 1995 outbreak were health care workers (CDC, et al., 2003g). Persons preparing bodies for burial acquired the infection. According to local custom, burial practices may involve washing the body and cutting the hair and nails of the corpse (Borio, et al., 2002).

This outbreak prompted the CDC and the World Health Organization to develop infection control procedures for use in Africa—where resources are very scarce (CDC and WHO, 2003g). Since barrier precautions have been in place, only 3 healthcare workers have become infected (Borio, et al., 2002).

There has been some concern about the potential for person-to-person transmission by way of small-droplet airborne nuclei. However, to date, Ebola epidemics in Africa were ultimately controlled and ended without use of specific airborne precautions (Borio, et al., 2002). (HICPAC's definitions of standard, contact, droplet, and airborne precautions are at http://www.cdc.gov/ncidod/dhqp/gl_isolation_ptII.html

.)

In 2000, 224 people died in Uganda during an Ebola outbreak. Fourteen (64%) of 22 medical personnel were infected after institution of isolation wards and infection control measures including donning gowns, gloves, and shoe covers, standard surgical masks, and either goggles or eye glasses. It is not clear whether lack of adherence to guidelines contributed to nosocomial cases in this outbreak, but airborne transmission could not be ruled out (Borio, et al., 2002).

Infections with Ebola virus are acute. There is no carrier state. Because the natural reservoir of the virus is unknown, the manner in which the virus first appears in a human at the start of an outbreak has not been determined. However, researchers have hypothesized that the first patient becomes infected through contact with an infected animal (CDC, 2003h).

The incubation period for Ebola HF ranges from 2 to 21 days. The onset of illness is abrupt and is characterized by fever, headache, joint and muscle aches, sore throat, and weakness, followed by diarrhea, vomiting, and stomach pain. A rash, red eyes, hiccups and internal and external bleeding may be seen in some patients (CDC, 2003h).

Ebola may lead to thrombocytopenia, and data suggest that platelet dysfunction is present in Ebola (Borio, et al., 2002). Reduced levels of coagulation factors may be secondary to hepatic dysfunction and/or disseminated intravascular coagulation and are most prominent in Rift Valley fever and yellow fever. In addition, Ebola and Marburg viruses may lead to a hemorrhagic diathesis through direct damage of cells involved in hemostasis (such as platelets and endothelial cells) and/or indirectly through immunological and inflammatory pathways (Borio, et al., 2002).

Filoviruses are extremely virulent in humans. Necrosis of visceral organs, such as liver, spleen, and kidneys, has been associated with both direct viral-induced cellular damage and impairment of the microcirculation; filoviruses are cytotoxic to cells. In general, inflammatory infiltration is absent in the affected visceral organs. Even when viral titers in the lungs of monkeys are elevated, the virus is not apparent in the alveoli or airways, occurring primarily in the vascular structures. All experimentally infected monkeys develop disseminated intravascular coagulation. Ebola, but not Marburg virus, makes a secreted form of its glycoprotein that has been suggested to have a role in virulence (Borio, et al., 2002).

Researchers do not understand why some people recover from Ebola HF and others do not. However, it is known that patients who die usually have not developed a significant immune response to the virus at the time of death (CDC, 2003h).

Diagnosing Ebola HF in an individual who has been infected only a few days is difficult because early symptoms, such as red eyes and a skin rash, are nonspecific to the virus and are seen in other patients with diseases that occur much more frequently. However, if a person has the constellation of symptoms described above, and infection with Ebola virus is suspected, isolate the patient and notify local and state health departments and the CDC (CDC, 2003h).

Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, IgM ELISA, polymerase chain reaction (PCR), and virus isolation can be used to diagnose a case of Ebola HF within a few days of the onset of symptoms. Persons tested later in the course of the disease or after recovery can be tested for IgM and IgG antibodies; the disease can also be diagnosed retrospectively in deceased patients by using immunohistochemistry testing, virus isolation, or PCR (CDC, 2003h).

There is no standard treatment for Ebola HF. Patients receive supportive therapy. This consists of balancing the patient's fluids and electrolytes, maintaining their oxygen status and blood pressure, and treating them for any complicating infections (CDC, 2003h).

Ebola HF has occurred primarily on the African continent; the prevention of Ebola HF in Africa presents many challenges. Because the identity and location of the natural reservoir of Ebola virus are unknown, there are few established primary prevention measures. When cases have appeared, scarce resources as well as current social and economic conditions often favor the spread of an epidemic within health-care facilities. Therefore, healthcare providers must be able to recognize a case of Ebola HF should one appear. Recognizing Ebola HF elsewhere in the world, should it occur as a bioterrorist attack, also will likely fall to healthcare providers to quickly identify and intervene. They must also have the capability to perform diagnostic tests and be ready to employ practical viral hemorrhagic fever isolation precautions, and standard precautions. These techniques include the wearing of protective clothing, such as masks, gloves, gowns, and goggles; the use of infection-control measures, including complete equipment sterilization; and the isolation of Ebola HF patients from contact with unprotected persons. The aim of all of these techniques is to avoid any person's contact with the blood or secretions of any patient. If a patient with Ebola HF dies, it is equally important that direct contact with the body of the deceased patient be prevented (CDC, 2003h).

Marburg Hemorrhagic Fever

The Marburg virus was the first filovirus to be identified in 1976 after laboratory workers in Germany and the former Yugoslavia became ill after handling tissue from monkeys imported from Uganda (CDC, 2003i). A total of 31 cases and seven deaths were associated with these outbreaks. The virus was named after Marburg, Germany, the site of one of the outbreaks (CDC and WHO, 2003g).

As with Ebola virus, the actual animal host for Marburg virus also remains a mystery (CDC, 2003i). Just how the animal host first transmits Marburg virus to humans is unknown. However, humans who become ill with Marburg hemorrhagic fever may spread the virus to other people (CDC, 2003i).

Spread of the virus between humans has occurred in a setting of close contact, often in a hospital. Droplets of body fluids, or direct contact with persons, equipment, or other objects contaminated with infectious blood or tissues are all highly suspect as sources of disease (CDC, 2003i).

After an incubation period of 5-10 days, the onset of the disease is sudden and is marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea then may appear. Symptoms become increasingly severe and may include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction (CDC, 2003i).

Marburg fever may lead to thrombocytopenia (Borio, et al., 2002). Reduced levels of coagulation factors may be secondary to hepatic dysfunction and/or disseminated intravascular coagulation In addition, Marburg virus may lead to a hemorrhagic diathesis through direct damage of cells involved in hemostasis (such as platelets and endothelial cells) and/or indirectly through immunological and inflammatory pathways (Borio, et al., 2002).

Because many of the signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases, such as malaria or typhoid fever, diagnosis of the disease can be difficult, especially if only a single case is involved (CDC, 2003i).

Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, IgM-capture ELISA, polymerase chain reaction (PCR), and virus isolation can be used to confirm a case of Marburg hemorrhagic fever within a few days of the onset of symptoms. The IgG-capture ELISA is appropriate for testing persons later in the course of disease or after recovery. The disease is readily diagnosed by immunohistochemistry, virus isolation, or PCR of blood or tissue specimens from deceased patients (CDC, 2003i).

Recovery from Marburg hemorrhagic fever may be prolonged and accompanied by orchititis, recurrent hepatitis, transverse myelitis or uvetis. Other possible complications include inflammation of the testes, spinal cord, eye, parotid gland, or by prolonged hepatitis. The case-fatality rate for Marburg hemorrhagic fever is between 23-25% (CDC, 2003i).

Specific treatment for this disease is unknown. However, supportive hospital therapy should be utilized. This includes balancing the patient's fluids and electrolytes, maintaining their oxygen status and blood pressure, replacing lost blood and clotting factors and treating them for any complicating infections (CDC, 2003i). Sometimes treatment also has used transfusion of fresh-frozen plasma and other preparations to replace the blood proteins important in clotting. One controversial treatment is the use of heparin (which blocks clotting) to prevent the consumption of clotting factors. Some researchers believe the consumption of clotting factors is part of the disease process (CDC, 2003i).

Lassa Fever

Lassa fever is an acute viral illness that thus far has occurred in West Africa. The illness was discovered in 1969 when two missionary nurses died in Nigeria, West Africa. The cause of the illness was found to be Lassa virus, named after the town in Nigeria where the first cases originated. The virus, a member of the virus family Arenaviridae, is a single-stranded RNA virus and is zoonotic, or animal-borne (CDC, 2003j).

In areas of Africa where the disease is endemic, Lassa fever is a significant cause of morbidity and mortality. While Lassa fever is mild or has no observable symptoms in about 80% of people infected with the virus, the remaining 20% have a severe multisystem disease. Lassa fever is also associated with occasional epidemics, during which the case-fatality rate can reach 50% (CDC, 2003j).

The reservoir, or host, of Lassa virus is a rodent known as the "multimammate rat" of the genus *Mastomys*. *Mastomys* rodents breed very frequently, produce large numbers of offspring, and are numerous in the savannas and forests of West, Central, and East Africa. In addition, *Mastomys* generally readily colonize human homes. All these factors together contribute to the relatively efficient spread of Lassa virus from infected rodents to humans (CDC, 2003j).

Lassa fever may also spread through person-to-person contact. This type of transmission occurs when a person comes into contact with virus in the blood, tissue, secretions, or excretions of an individual infected with the Lassa virus. The virus cannot be spread through casual contact (including skin-to-skin contact without exchange of body fluids). Person-to-person transmission is common in both village and health care settings, where, along with the above-mentioned modes of transmission, the virus also may be spread through nosocomial infection (CDC, 2003j).

Signs and symptoms of Lassa fever typically occur 1-3 weeks after the patient comes into contact with the virus. These include fever, retrosternal pain, sore throat, back pain, cough, abdominal pain, vomiting, diarrhea, conjunctivitis, facial swelling, proteinuria, and mucosal bleeding. Neurological problems have also been described, including hearing loss, tremors, and encephalitis. Because the symptoms of Lassa fever are so varied and nonspecific, clinical diagnosis is often difficult (CDC, 2003j).

Lassa fever may lead to thrombocytopenia, and data suggest that platelet dysfunction is present (Borio, et al., 2002).

Lassa fever is most often diagnosed by using enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen. The virus itself may be cultured in 7 to 10 days. Immunohistochemistry performed on tissue specimens can be used to make a post-mortem diagnosis. The virus can also be detected by reverse transcription-polymerase chain reaction (RT-PCR); however, this method is primarily a research tool (CDC, 2003j).

The most common complication of Lassa fever is deafness. Various degrees of deafness occur in approximately one-third of cases, and in many cases hearing loss is permanent. As far as is known, severity of the disease does not affect this complication: deafness may develop in mild as well as in severe cases. Spontaneous abortion is another serious complication. Approximately 15%-20% of patients hospitalized for Lassa fever die from the illness. However, overall only about 1% of infections with Lassa virus result in death. The death rates are particularly high for women in the third trimester of pregnancy, and for fetuses, about 95% of which die in the uterus of infected pregnant mothers (CDC, 2003j).

Ribavirin has been used with success in Lassa fever patients, although it is not FDA approved for use in this illness. It has been shown to be most effective when given early in the course of the illness. Patients should also receive supportive care consisting of maintenance of appropriate fluid and electrolyte balance, oxygenation and blood pressure, as well as treatment of any other complicating infections (CDC, 2003j).

When caring for patients with Lassa fever, further transmission of the disease through person-to-person contact or nosocomial routes can be avoided by taking preventive precautions against contact with patient secretions (together called VHF isolation precautions or barrier nursing methods). Such precautions include wearing protective clothing, such as masks, gloves, gowns, and goggles; using infection control measures, such as complete equipment sterilization; and isolating infected patients from contact with unprotected persons until the disease has run its course (CDC, 2003j).

Yellow Fever

Yellow fever is a mosquito-borne viral disease. Illness ranges in severity from an influenza-like syndrome to severe hepatitis and hemorrhagic fever. Yellow fever is caused by a zoonotic virus that is maintained in nature by transmission between nonhuman primates and mosquito vectors. In some situations, humans may serve as the primary host in the transmission cycle ("urban yellow fever") (CDC, 2004).

The disease occurs only in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic. In Africa, a variety of vectors are responsible for the disease, and it is in Africa where most cases are reported. The case-fatality rate is >20%, and infants and children

are at greatest risk for infection. In South America, cases occur most frequently in young men who have occupational exposure to mosquito vectors in forested or transitional areas of Bolivia, Brazil, Colombia, Ecuador, Venezuela, and Peru (CDC, 2004).

Information about Yellow Fever used in a terrorist attack is limited. The information provided here related to Yellow Fever among persons who travel to those endemic regions. The risks of illness and of death due to yellow fever in an unvaccinated traveler are estimated to be 1:1,000 and 1:5,000 per month, respectively. (For a 2-week journey, the risks of illness and death are 1:2,000 and 1:10,000, respectively.) These estimates, which are based on risk to indigenous populations, may overestimate the risk to travelers, who may have a different immunity profile, take precautions against getting bitten by mosquitoes, and have less outdoor exposure than do indigenous residents. Based on data for U.S. travelers, the risk for illness in a traveler due to yellow fever has been estimated to be 0.4–4.3 cases per million travelers to yellow fever-endemic areas (CDC, 2004).

Initial symptoms of Yellow Fever include fever, headache, vomiting and backache. As the disease progresses, the pulse slows and weakens, and bleeding of the gums and bloody urine occur. Jaundice may also occur (NYSDOH, 2003).

With the exception of yellow fever live attenuated 17D vaccine, which is highly effective when administered to travelers to endemic areas, there is no licensed vaccine for any of the HFVs. The yellow fever vaccine is produced in limited supply, and world stocks are not sufficient to meet a surge. This vaccine would not be useful in preventing disease if given in the postexposure setting because yellow fever has a short incubation period of 3 to 6 days, and neutralizing antibodies take longer to appear following vaccination (Borio, et al., 2002).

Rift Valley Fever

Rift Valley Fever (RVF) is an acute, fever-causing viral disease that affects domestic animals (such as cattle, buffalo, sheep, goats, and camels) and humans. RVF is most commonly associated with mosquito-borne epidemics during years of unusually heavy rainfall (CDC, 2003l) .

The disease is caused by the RVF virus, a member of the genus *Phlebovirus* in the family Bunyaviridae. The disease was first reported among livestock by veterinary officers in Kenya in the early 1900s (CDC, 2003l).

RVF is generally found in regions of eastern and southern Africa where sheep and cattle are raised, but the virus also exists in most countries of sub-Saharan Africa and in Madagascar. In September 2000, a RVF outbreak was reported in Saudi Arabia and subsequently Yemen. These cases represent the first Rift Valley fever cases identified outside Africa (CDC, 2003l).

RVF virus primarily affects livestock and can cause disease in a large number of domestic animals (this situation is referred to as an "epizootic"). The presence of an RVF epizootic can lead to an epidemic among humans who are exposed to diseased animals. The most notable epizootic of RVF, which occurred in Kenya in 1950-1951, resulted in the death of an estimated 100,000 sheep. In 1977, the virus was detected in Egypt (probably exported there in infected domestic animals from Sudan) and caused a large outbreak of RVF among animals and humans. The first epidemic of RVF in West Africa was reported in 1987 and was linked to construction of the Senegal River Project. The project caused flooding in the lower Senegal River area and altered interactions between animals and humans resulting in transmission of the RVF virus to humans (CDC, 2003l).

An epizootic of RVF is generally observed during years in which unusually heavy rainfall and localized flooding occur. The excessive rainfall allows mosquito eggs, usually of the genus *Aedes*, to hatch. The mosquito eggs are naturally infected with the RVF virus, and the resulting mosquitoes transfer the virus to the livestock on which they feed. Once the livestock is infected, other species of mosquitoes can become infected from the animals and can spread the disease. In addition, it is possible that the virus can be transmitted by other biting insects (CDC, 2003l).

Humans can get RVF as a result of bites from mosquitoes and possibly other bloodsucking insects that serve as vectors. Humans can also get the disease if they are exposed to either the blood or other body fluids of infected animals. This exposure can result from the slaughtering or handling of infected animals or by touching contaminated meat during the preparation of food. Infection through aerosol transmission of RVF virus has resulted from contact with laboratory specimens containing the virus (CDC, 2003l).

RVF virus can cause several different disease syndromes. People with RVF typically have either no symptoms or a mild illness associated with fever and liver abnormalities. However, in some patients the illness can progress to hemorrhagic fever, encephalitis, or ocular disease. Patients who become ill usually experience fever, generalized weakness, back pain, dizziness, and extreme weight loss at the onset of the illness. Typically, patients recover within two days to one week after onset of illness (CDC, 2003l).

The most common complication associated with RVF is inflammation of the retina. As a result, approximately 1% - 10% of affected patients may have some permanent vision loss (CDC, 2003l).

Approximately 1% of humans that become infected with RVF die of the disease. Case-fatality proportions are significantly higher for infected animals. The most severe impact is observed in pregnant livestock infected with RVF, which results in abortion of virtually 100% of fetuses (CDC, 2003l).

There is no established course of treatment for patients infected with RVF virus. However, studies in monkeys and other animals have shown promise for ribavirin, an antiviral drug, for future use in humans. Additional studies suggest that interferon, immune modulators, and convalescent-phase plasma may also help in the treatment of patients with RVF (CDC, 2003l).

A person's chances of becoming infected can be reduced by taking measures to decrease contact with mosquitoes and other bloodsucking insects through the use of mosquito repellents, protective clothing and bed nets. Avoiding exposure to blood or tissues of animals that may potentially be infected is an important protective measure for persons working with animals in RVF-endemic areas (CDC, 2003l).

Table 8. Category A Biological Agents/Diseases: Mode of Transmission and Precautions, Incubation Period, Symptoms, Treatment

Disease/Biological Agent	Mode of Transmission and Precautions	Incubation Period	Symptoms	Treatment
Anthrax/ *Bacillus anthracis*	Inhalation (Droplet/Airborne precautions) Skin contact (Contact precautions) Ingestion	1-6 days	**Inhaled** – fever, fatigue, general malaise, non-productive cough, and mild chest discomfort **Cutaneous** – fluid-filled vesicle dries to form eschar **Gastrointestinal** – fever, nausea, abdominal pain, bloody diarrhea	Supportive airway management; ciprofloxacin or doxycycline
Smallpox/ *Variola major*	Inhalation (Droplet/Airborne precautions) Skin contact (contact precautions)	1-3 weeks	Malaise, fever, rigors, vomiting, headache, and backache; within 2-3 days, lesions on face, hands, and forearms progressing from pustular vesicles	Supportive treatment; isolation until scab separation
Plague/ *Yersinia pestis*	Inhalation (Droplet/Airborne precautions) Contact precautions if draining buboes present	2-10 days	High fever, chills, headache, malaise, cough, often hemoptysis, progresses quickly to dyspnea, stridor, cyanosis, and death	Antibiotic therapy (streptomycin, gentamicin, doxycycline, or choramphenicol) within 24 hours of symptom onset
Botulism/ *Clostridium botulinum*	Inhalation (Droplet/Airborne precautions) Ingestion	12-36 hours	Dry mouth and urinary retention; blurred vision, ptosis, photophobia, dysphonia and dysphagia followed by skeletal muscle paralysis in a symmetrical, descending, progressive manner; upper airway collapse, sudden respiratory failure	Botulinum antitoxin or heptavalent antitoxin; Respiratory assistance as needed
Tularemia/ *Franciscella tularensis*	Inhalation (Droplet/Airborne precautions) Ingestion Skin contact (Contact precautions)	3-6 days (incubation range 2-14 days)	Fever, headache, chills; rigors, generalized body aches, coryza, and sore throat; bacteremia; dry or slightly productive cough; substernal pain or tightness with or without objective signs of pneumonia, nausea, vomiting, and diarrhea; sweats, progressive weakness,	Streptomycin, Gentamicin Alternatively, Doxycycline, Chloramphenicol, Ciprofloxacin Postexposure prophylactic treatment of close

			malaise, anorexia, and weight loss characterize the continuing illness	contacts is not recommended because person-to-person transmission is not known to occur.
Ebola Hemorrhagic Fever	Blood and Body Fluids (Standard Precautions) Mucosal transmission (mask, goggles) Airborne transmission has not been ruled out (Droplet/Airborne Precautions)	2 to 21 days	Abrupt onset of fever, headache, joint and muscle aches, sore throat, weakness, diarrhea, vomiting, stomach pain, rash, red eyes, hiccups, internal and external bleeding, thrombocytopenia, platelet dysfunction, necrosis of visceral organs	No standard treatment for Ebola HF; supportive therapy consisting of the balance of fluids and electrolytes, maintenance of oxygen status and blood pressure; treatment of any complicating infections
Marburg Hemorrhagic Fever	Blood and Body Fluids (Standard Precautions) Airborne droplets (Airborne/Droplet Precautions)	5-10 days	Sudden fever, chills, headache, myalgia; on 5th day a maculopapular rash on trunk; nausea, vomiting, chest pain, sore throat, abdominal pain, diarrhea, jaundice, pancreatic inflammation, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction, thrombocytopenia; Recovery may be prolonged and accompanied by orchititis, recurrent hepatitis, transverse myelitis or uvetis, inflammation of the testes, spinal cord, eye, parotid gland, or by prolonged hepatitis; the case-fatality rate is between 23-25%.	Specific treatment is unknown; supportive hospital therapy including balance of fluids and electrolytes, maintenance of oxygen status and blood pressure, replacement of lost blood and clotting factors; treatment of any complicating infections
Lassa Hemorrhagic Fever	Blood and body fluids (Standard Precautions) Airborne Transmission has not been ruled out.	7-21 days	Fever, retrosternal pain, sore throat, back pain, cough, abdominal pain, vomiting, diarrhea, conjunctivitis, facial swelling, proteinuria, mucosal bleeding; Neurological problems including hearing loss, tremors, and encephalitis;	Ribavirin (not FDA approved for use in this illness); most effective when given early in the course of the illness; supportive care consisting of maintenance of appropriate fluid and electrolyte balance,

			may lead to thrombocytopenia, and platelet dysfunction	oxygenation and blood pressure, and treatment of any other complicating infections
Yellow Hemorrhagic Fever	Vector-borne transmission: mosquitoes (Use of mosquito repellant, protective clothing, mosquito netting) Airborne transmission has not been ruled out.	3-6 days	Initial symptoms include fever, headache, vomiting and backache. As the disease progresses, the pulse slows and weakens, and bleeding of the gums and bloody urine occur. Jaundice may also occur.	No specific treatment. Yellow fever live attenuated 17D vaccine is highly effective prophylaxis.
Rift Valley Hemorrhagic Fever	Vector-borne: mosquitoes and other blood sucking insects (Use of mosquito repellents, protective clothing, mosquito netting) Blood and body fluids of infected animals (Avoidance of contact with infected animals) Airborne transmission has not been ruled out.	2-6 days	Several different disease syndromes possible with either no symptoms or a mild illness associated with fever and liver abnormalities; in some patients the illness can progress to hemorrhagic fever, encephalitis, or ocular disease. Those who become ill usually experience fever, generalized weakness, back pain, dizziness, and extreme weight loss at the onset of the illness. Typically, recovery occurs within two days to one week after onset of illness; the most common complication is inflammation of the retina with approximately 1% - 10% having some permanent vision loss	No established course of treatment; animal studies show some promise for future use ribavirin in humans; additional studies suggest that interferon, immune modulators, and convalescent-phase plasma may also be helpful.

Preparation for Potential Bioterrorist Attacks

Nurses as healthcare professionals are likely to be one of the "first responders" to a bioterrorist event. An increase in the number of patients presenting with clinical features caused by the exposure to a biological agent will be the first indicator of a bioterrorist attempt. Initial clinical suspicion, detection, and response will be critical in order to avert or contain outbreaks in disease.

Prompt reporting of cases of communicable disease allows public health agencies at the local, state and federal levels to identify newly emerging infectious diseases, detect naturally occurring disease outbreaks, prevent secondary transmission and evaluate the effectiveness of control measures. All of these efforts may be compromised when cases are not reported in a timely manner. Physicians, healthcare facilities, laboratories, and local and State health departments all share the responsibility for reporting, follow-up, and control of communicable diseases (Novello, 2002).Therefore, such preparedness on the part of the registered professional nurse is essential. Emerging epidemiologic patterns and subsequent investigations and containment will be triggered only if initial detection and response is successful when the victims of a biological attack begin arriving in emergency rooms and ambulatory care clinics.

Ten Critical Steps for Handling Possible Bioterrorist Events (NYSDOH, 2002)

1. **Maintain an index of suspicion**

   In an otherwise healthy population, some associations are very suggestive, especially when seen in clusters, high numbers, or unusual presentations: Hemoptysis - Plague, Flaccid Paralysis - Botulism, Purpura - Viral Hemorrhagic Fevers (VHF), Wide Mediastinum – Anthrax, Centrifugal Rash – Smallpox.

2. **Protect yourself and your patients**

   Use appropriate personal protection equipment (PPE). Prophylaxis: vaccines, if available; or antibiotics, if risks are known.

3. **Adequately assess the patient**

   Review and assess the patient's history; also ask the following:

   - Are others ill?
   - Were there any unusual events, when, where?
   - Was there a possible contaminated food item?
   - Was there vector exposure?
   - Has the patient been traveling?
   - What is the patient's immunization record?
   - What is the patient’s occupation?

Perform a physical examination with special attention to the respiratory system, nervous system, skin condition, and hematologic and vascular status.

4. Decontaminate as appropriate

Do not use bleach on exposed people. Soap, water and shampoo are perfectly adequate for all biological and most chemical agents. Chemically contaminated clothes should be removed and discarded safely. Biologically contaminated clothes can be laundered with soap, water and, perhaps, bleach.

5. Establish a diagnosis.

Think clinically and epidemiologically; always send specimens for culture.

Symptom (individuals)	**Possible Diagnosis**
Pulmonary	Anthrax, tularemia, plague, staph enterotoxin B (SEB)
Neuromuscular	Botulism, Venezuelan Equine Encephalitis (VEE)
Bleeding/purpura	VHF, ricin, plague (late)
Rash (various types)	VHF, T2 mycotoxin, smallpox, plague
Flu-like symptoms	Varies
Immediate Symptoms (large numbers)	Possible Diagnosis
Pulmonary	SEB, mustard, Lewisite, phosgene, cyanide
Neurological	Nerve gases, cyanide
Delayed Symptoms (large numbers)	Possible Diagnosis Biologic agents,
Pulmonary	Biological agents, mustard, phosgene
Neurological	Botulism, VEE, other encephalitis

6. Render prompt treatment.

Doxycycline can be used to treat virtually everything (except virals or toxins) while awaiting lab results. Observe pediatric precautions as appropriate. Prophylaxis (antibiotics and/or vaccines) should be administered according to Public Health recommendations.

7. **Provide good infection control.**

   Recommended isolation precautions (in addition to standard precautions) for biologic agents include:

Anthrax	Contact precautions for cutaneous anthrax; airborne precautions for inhalation anthrax
Pneumonic plague	Droplet precautions; contact precautions if draining buboes present
Smallpox	Airborne and contact precautions
Tularemia	Contact precautions if lesions present
Viral Hemorrhagic Fevers	Contact and airborne precautions

8. **Alert the proper authorities.**

Agency	**Telephone Number**
FBI	518.465.7551 (Albany) 212.384.1000 (NYC) 716.856.7800 (Buffalo)
Municipal Police/County Sheriff	*
New York State Police	*
County Health Unit	*
New York State Health Dept.	518.473.4436 (daytime) 518.465.9720 (after hours)
Local Emergency Medical Services Unit	*
Local Hospitals	*
Centers for Disease Control And Prevention	770.488.7100
NYS Wadsworth Laboratory	518.474.2821 (daytime) 518.465.9720 (after hours)

*Check your local telephone directory for numbers in your area.

9. **Assist in the epidemiologic investigations so as to determine who else may be at risk.**

   Steps in an epidemiological investigation:

   - Count cases
   - Relate to the at-risk population
   - Make comparisons
   - Develop hypotheses
   - Test hypotheses
   - Make inferences
   - Conduct studies
   - Interpret and evaluate

10. Know and spread this information.

Additionally, the Centers for Disease Control and Prevention has developed documents to assist healthcare facilities to prepare for potential bioterrorism attacks: Bioterrorism Readiness Plan: A Template for Healthcare Facilities (make this a link to http://www.cdc.gov/ncidod/hip/Bio/13apr99APIC-CDCBioterrorism.PDF).

The American Hospital Association has also developed a plan for the management of mass casualties in hospitals. This document can be accessed at http://www.hospitalconnect.com/ahapolicyforum/resources/disaster.html. These resources are available to healthcare providers to assist in preparation for a bioterrorist attack. Most healthcare facilities have developed emergency plans for the specific management of casualties related to a terrorist attack; refer to your facility's plan for specific information.

Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents (CDC, October 24, 2001)

For nurses working in hospitals or ambulatory care sites, who have come into contact with patients who have anthrax, utilizing standard precautions is required. Standard disinfectants can be used for infection control in the health care setting. However, healthcare providers may be first responders to the incidents of bioterrorism, either at the site of an attack, or in the course of their usual work. The need for decontamination and treatment of first responders should be decided in consultation with local public health authorities.

When using respiratory protection, the type of respirator is selected on the basis of the hazard and its airborne concentration. For a biological agent, such as B. Anthracis, the air concentration of infectious particles will depend upon the method used to release the agent. Current data suggests that the self-contained breathing apparatus (SCBA) which first responders currently use for entry into potentially hazardous atmospheres will provide responders with respiratory protection against biological exposures associated with a suspected act of biological terrorism.

Protective clothing, including gloves and booties, also may be required for the response to a suspected act of biological terrorism. Protective clothing may be needed to prevent skin exposures and/or contamination of other clothing. The type of protective clothing needed will depend upon the type of agent, concentration, and route of exposure.

The interim recommendations for personal protective equipment, including respiratory protection and protective clothing, are based upon the anticipated level of exposure risk associated with different response situations, as follows:

1. Responders should use a NIOSH-approved, pressure-demand SCBA in conjunction with a Level A protective suit in responding to a suspected biological incident where any of the following information is unknown or the event is uncontrolled:
    a. The type(s) of airborne agent(s)
    b. The dissemination method
    c. If dissemination via an aerosol-generating device is still occurring or it has stopped but there is no information on the duration of dissemination, or what the exposure concentration might be
2. Responders may use a Level B protective suit with an exposed or enclosed NIOSH-approved pressure-demand SCBA if the situation can be defined in which:
    a. The suspected biological aerosol is no longer being generated
    b. Other conditions may present a splash hazard

3. Responders may use a full facepiece respirator with a P100 filter or powered air-purifying respirator (PAPR) with high efficiency particulate air (HEPA) filters when it can be determined that:
    a. An aerosol-generating device was not used to create high airborne concentration
    b. Dissemination was by a letter or package that can be easily bagged

These type of respirators reduce the user's exposure by a factor of 50 if the user has been properly fit tested.

Care should be taken when bagging letters and packages to minimize creating a puff of air that could spread pathogens. It is best to avoid large bags and to work very slowly and carefully when placing objects in bags. Disposable hooded coveralls, gloves, and foot coverings also should be used. NIOSH recommends against wearing standard firefighter turnout gear into potentially contaminated areas when responding to reports involving biological agents.

Decontamination of protective equipment and clothing is an important precaution to make sure that any particles that might have settled on the outside of protective equipment are removed before taking off gear. Decontamination sequences currently used for hazardous material

emergencies should be used as appropriate for the level of protection employed. Equipment can be decontaminated using soap and water, and 0.5% hypochlorite solution (one part household bleach to 10 parts water) can be used as appropriate or if gear had any visible contamination. Note that bleach may damage some types of firefighter turnout gear (one reason why it should not be used for biological agent response actions). After taking off gear, response workers should shower using copious quantities of soap and water.

Strategic National Stockpile

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

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

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

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

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

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

Conclusion

Unfortunately, the global threat of bioterrorism is likely here to stay. The registered professional nurse performing triage in the local emergency room or ambulatory clinic will be the first line of response to bioterrorist exposure. As potential first-line responders, all registered professional nurses must educate themselves about early detection and response to a bioterrorist exposure. Our decisions can have dire consequences on the public's health.

Resources

The Centers for Disease Control and Prevention (CDC)
www.cdc.gov

The CDC has published a template entitled "Bioterrorism Readiness Plan: A Template for Healthcare Facilities" (http://www.cdc.gov/ncidod/dhqp/pdf/bt/13apr99APIC-CDCBioterrorism.PDF) which discusses infection control activities, laboratory policy, public inquiry, in addition to disease specific information.

The CDC has also published "The Public Health Response to Biological and Chemical Terrorism - Interim Planning Guidance for State Public Health Officials."

The CDC has a free videotape, "Anthrax: What Every Clinician Should Know". To receive a copy, in the US, contact 877.252.1200; outside the US, contact 301.645.7773

Center for Disease Control, Bioterrorism Preparedness and Response
www.bt.cdc.gov

Center for Civilian Biodefense Studies, Johns Hopkins University

US Army Medical Research Institute of Chemical Defense

USAMRIID-US Army Medical Research Institute of Infectious Disease

Department of Defense, Nuclear, Biological, Chemical Medical reference site

Department of Health and Human Services

Association for Professional in Infection Control (APIC)

Federal Bureau of Investigation

New York State Department of Health, Bureau of Communicable Disease Control

OSHA's Website has information about Defining Personal Protective Equipment.

http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9765

Environmental Protection Agency

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Biological Agents and Terrorism: A Worldwide Threat
Course Exam

After studying the downloaded course and completing the course exam, you need to enter your answers online. **Answers cannot be graded from this downloadable version of the course.** To enter your answers online, go to e-leaRN's Web site, www.elearnonline.net and click on the Login/My Account button. As a returning student, login using the username and password you created, click on the "Go to Course" link, and proceed to the course exam.

1. Category A biological agents are those that haven been given the highest priority for preparedness because they can be used as weapons of bioterrorism. This includes the characteristic of:

   A. Having a significant impact on the illness and death of the public: 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;
   B. Generating the perception of fear among the public and having the potential for civil disruption;
   C. Necessitating special public health preparedness needs related to stockpile requirements, enhanced surveillance, or diagnostic needs.
   D. All of the above.

2. The variola virus is the biological agent that causes smallpox; the smallpox vaccine is made from live variola virus.

   A. True.
   B. False.

3. All of the following is true regarding the transmission smallpox virus EXCEPT:

   A. Smallpox is highly communicable; the most common route of infection is person-to-person spread through direct deposit of infective droplets onto the nasal, oral, or pharyngeal mucosal membranes, or the alveoli of the lungs.
   B. People with smallpox are most infectious during the first week of illness, because that is when the largest amount of virus is present in saliva.
   C. Transmission is vector-borne; it is endemic among mosquitoes.
   D. Transmission occurs through skin contact; risk of transmission lasts until all scabs have fallen off.

4. Smallpox vaccination is unique in some ways. These include all the following EXCEPT:

   A. That It can be used as a vaccination prior to exposure to smallpox, or it can be utilized within 4 days post exposure in order to prevent or ameliorate the disease.
   B. It uses a bifurcated needle; 15 punctures are made.
   C. Vaccination should not be attempted on persons who have eczema or known cardiac disease.
   D. Persons who were vaccinated prior to 1972, when smallpox vaccination was routine, continue to have life-time immunity.

5. Of the major clinical forms of human anthrax, the most serious form, in which there high mortality rate, is:

    A. Inhalation.
    B. Gastrointestinal.
    C. Oral-pharyngeal.
    D. Cutaneous.

6. Anthrax was recently used as a weapon of bioterrorism in the United States during the fall of 2001. The following is true of those anthrax cases EXCEPT:

    A. The most common form of anthrax disease was gastrointestinal, accounting for more than 50% of the cases.
    B. With early institution of multidrug antibiotics regimens and supportive care, the survival rate of patients was markedly higher than previously reported.
    C. There were 22 suspected or confirmed cases of inhalation and cutaneous anthrax in multiple states: Florida, New York, New Jersey, the District of Columbia, and Connecticut.
    D. Current recommendations for prophylaxis after possible exposure to *B. anthracis* for adults are: ciprofloxacin 500 mg po bid with doxycycline (100 mg po bid) or amoxicillin (500 mg po q 8 hours).

7. All the following are true of treatment after exposure to anthrax EXCEPT:

    A. Standard precautions should be utilized in the treatment of anthrax disease.
    B. Individuals who have been exposed to *B. anthracis* should be treated prophylactically with the anthrax vaccine.
    C. Direct person-to-person spread of anthrax is extremely unlikely and anthrax is not contagious.
    D. There is no need to quarantine individuals suspected of being exposed to anthrax or to immunize or treat contacts of persons ill with anthrax, such as household contacts, friends, or coworkers, unless they also were also exposed to the same source of infection.

8. Symptoms of bubonic plague include:

    A. A centripedal rash, followed by eschars.
    B. Fever, headache, joint and muscle aches, sore throat, weakness, diarrhea, vomiting, and stomach pain followed by red eyes, hiccups and internal and external bleeding.
    C. Inflammed, enlarged lymph nodes, usually in the inguinal, axillary or cervical regions are the classic signs.
    D. Cervical lymphadenitis.

9. Following an attack with aerosolized *Yersinia pestis* bacilli, primary pneumonic plague would be seen within 1 to 6 days.

    A. True.
    B. False.

10. Treatment of pneumonic plague includes all the following EXCEPT:

    A. Antibiotic treatment begun within 24 hours of symptoms development; oral medications used are a tetracycline or a fluoroquinolone; intravenous medications include streptomycin or gentamicin. Antibiotics are used for 10-14 days.
    B. Substantial advanced medical supportive care in addition to antimicrobial therapy due to the complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure.
    C. For asymptomatic persons exposed to pneumonic plague, doxycycline (100 mg po bid) for 7 days, or the duration of exposure risk plus 7 days, serves as prophylaxis.
    D. Quarantine of confirmed and suspected plague cases with tracing, vaccination and close surveillance of contacts to these cases as well as vaccination of the household contacts of the contacts.

11. Treatment of botulism includes the following:

    A. A tetracycline or a floroquinolone antibiotic therapy.
    B. Botulinum antitoxin or heptavalent antitoxin.
    C. None of the above.
    D. All the above.

12. *Franciscella tularensis*, the agent that causes Tularemia can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. Although F tularensis is highly infectious and pathogenic, its transmission from person to person has not been documented.

    A. True.

    B. False

13. Generally, inhalational tularemia would be expected to have a slower progression of illness and a lower case-fatality rate than either inhalational plague or anthrax.

    A. True.

    B. False.

14. Current treatment recommendations for Tularemia include:

    A. There are no recommendations currently the effective treatment of Tularemia.

    B. The preferred choice in the treatment of adults is: Streptomycin, 1g IM twice daily or Gentamicin, 5 mg/kg IM or IV once daily.

    C. The variola vaccine has been shown to be an effective prophylactic treatment.

    D. None of the above.

15. According to the World Health Organization (WHO), any suspected cases of Viral Hemorrhagic Fever (VHF), acute onset of fever greater than or equal to 101 degrees Fahrenheit of less than 3 weeks' duration who is severely ill, has no known predisposing host factors for hemorrhagic manifestations, and has any 2 of the following hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other hemorrhagic symptoms, should be immediately reported to local and/or state health departments who then notify the CDC.

    A. True.

    B. False.

16. Ribavirin has been shown to be effective in the treatment of some VHF. Among the virus families in which its effectiveness has been identified are the arenaviruses and the bunyaviruses. So ribavirin can be used in the treatment of:

    A. Ebola and Marburg Hemorrhagic Fevers.

    B. Yellow Fever and Ebola Hemorrhagic Fevers.

    C. Lassa Fever and Rift Valley Fever.

    D. None of the above.

17. In addition to strict hand hygiene, personal protective equipment for healthcare providers to utilize when treating and caring for persons with VHF include all the following EXCEPT:

    A. Double gloves, impermeable gowns, shoe and leg coverings.

    B. N-95 masks or powered air purifying respirators.

    C. Face shields, goggles.

    D. Dialectric boots, liquid splash protective suit, head protector, ice vest

18. Ebola Hemorrhagic Fever is extremely virulent in humans; the onset of illness is abrupt and is characterized by fever, headache, joint and muscle aches, sore throat, and weakness, followed by diarrhea, vomiting, and stomach pain. A rash, red eyes, hiccups and internal and external bleeding.

    A. True.

    B. False.

19. Some of the critical steps for the handling of potential bioterrorism threats is:

    A. The maintenance of a high level of suspicion with persons who present with select symptoms, including review and assessment of the patient and the patient's history; and to be alert for symptoms in an otherwise healthy population, some associations are very suggestive, especially when seen in clusters, high numbers, or unusual presentations.

    B. Prompt diagnosis, laboratory confirmation and treatment. Some treatment should begin before laboratory confirmation is complete.

    C. Good infection control, proper personal protective equipment and immediate notification of local health departments.

    D. All of the above.

20. The National Strategic Stockpile was created to:

    A. Provide a re-supply of large quantities of essential medical materiel to states and communities during an emergency within twelve hours of the federal decision to deploy.

    B. The SNS is designed to supplement and re-supply state and local public health agencies in the event of a national emergency anywhere and at anytime within the U.S. or its territories

    C. Be the national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, IV administration, airway maintenance supplies, and medical/surgical items.

    D. All of the above.