

Anthrax

1.5 contact hours - \$10.00

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This course was derived from Epidemiology and Prevention of Vaccine Preventable Diseases. Objectives, post test, and editing by Jo Ann O'Toole, BSN and Lauren Robertson, BA, MPT.

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Course Objectives

When you finish this course, you will be able to:

- Describe the pathogenesis and clinical features of anthrax.
- Describe the laboratory diagnosis and medical management of anthrax exposures.
- Outline the epidemiological features of anthrax including occurrence, transmission, and communicability.
- Describe current trends in the spread and surveillance of anthrax in the United States.
- Discuss major issues associated with anthrax vaccination including characteristics, recommendations, adverse reactions, and contraindications.
- Outline the guidelines for postexposure prophylaxis following exposure to anthrax.
- Discuss key concepts of anthrax bioterrorism preparedness.

Introduction

Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis*. The term anthrax is derived from the Greek word for coal, *anthrakis*, because of the black skin lesions characteristic of the disease. A disease that appears to have been anthrax was described in the biblical book of Exodus as the fifth plague in about 1490 BCE.

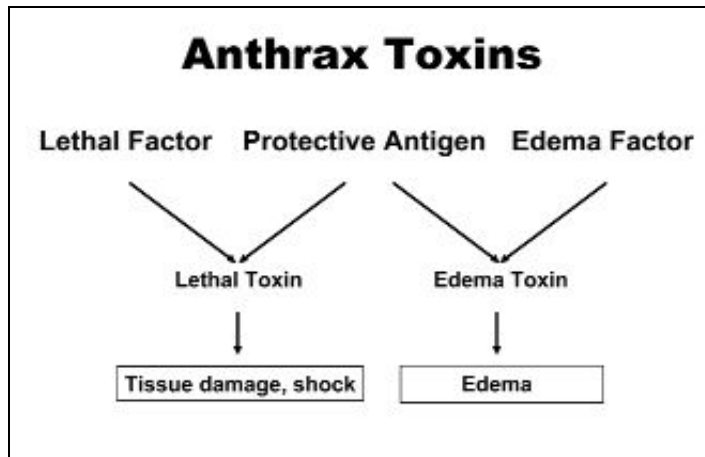
Descriptions of anthrax affecting both animals and humans are found in early Indian and Greek writings. An epidemic of anthrax in 17th century Europe caused an estimated 60,000 human deaths. The contagious nature of anthrax was described in 1823. *Bacillus anthracis* was first described in 1849, and in 1876, Robert Koch definitively established a microbial origin for anthrax making this the first disease for which this was done. A live attenuated animal vaccine was developed and tested by Louis Pasteur in 1881. An improved animal vaccine containing a suspension of an avirulent, nonencapsulated live strain of *B. anthracis* was developed in 1939. The role of toxin in the pathogenesis of anthrax was demonstrated in 1954. A human vaccine composed of cell-free culture filtrate was developed in 1954, and in 1970 an improved cell-free vaccine was licensed in the United States. Anthrax was first used effectively as a bioterrorist agent in 2001.

Bacillus Anthracis

B. anthracis is a large aerobic, spore-forming, gram-positive bacillus that grows well on common culture media, such as blood agar. Stained *B. anthracis* from culture media appears as long parallel chains of organisms with square ends, referred to as “boxcars.” *B. anthracis* spores can remain viable and infective in the soil for many years, even decades.

During this time, they are a potential source of infection for grazing livestock, but they generally do not represent a direct infection risk for humans. Animals become infected when they ingest or inhale the spores while grazing. Humans can become infected with *B. anthracis* by skin contact, ingestion, or inhalation of *B. anthracis* spores originating from products of infected animals or from inhalation of spores from the environment. Spores can be inactivated with sufficient contact with paraformaldehyde vapor, 5% hypochlorite or phenol solution, or by autoclaving.

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as the blood or tissues of an animal. The replicating bacteria produce at least three proteins—lethal factor (LF), protective antigen (PA), and edema factor (EF). These proteins combine to form two toxins known as **lethal toxin** and **edema toxin**.



Protective antigen and lethal factor form **lethal toxin**, a protease that is believed to be responsible for tissue damage, shock, and death, although the mechanism is not clear. Protective antigen and edema factor form **edema toxin**, an adenylate cyclase that upsets controls on ion and water transport across cell membranes and causes extensive edema. PA binds to receptors on mammalian cells and then binds with LF or EF. The toxin complexes are internalized to the endosome of the cell and then transported to the cytosol, where they exert their effect.

Pathogenesis

After wound inoculation or ingestion, *B. anthracis* spores are engulfed by macrophages, where they germinate. The vegetative bacterium produces a capsule that allows it to evade the immune system by resisting phagocytosis and protects the organism from lysis by cationic proteins in the serum. Lethal toxin and edema toxin are produced. If not contained, the bacteria can spread to draining lymph nodes and intracellular space, leading to further production of toxins.

The toxins result in necrosis of lymphatic tissue, which leads to the release of large numbers of bacteria. Bacteremia may ensue and lead to overwhelming septicemia, widespread tissue destruction, organ failure, and death. In inhalation anthrax, spores are transported from the alveoli to the tracheobronchial and mediastinal lymph nodes. Lethal toxin and edema toxin are produced and cause tissue necrosis and extensive edema. Production of toxins leads to the massive hemorrhagic lymphadenitis and mediastinitis characteristic of inhalational disease.

Studies in animals indicate that inhaled spores may not immediately germinate within the alveoli but reside there potentially for weeks, perhaps months, until taken up by alveolar macrophages. Spores then germinate and begin replication within the macrophages and lymphatic tissue.

Antibiotics are effective against germinating or vegetative *B. anthracis* but are not effective against the non-vegetative or spore form of the organism. Consequently, disease development can be prevented as long as a therapeutic level of antibiotics is maintained to kill germinating *B. anthracis* organisms. After discontinuation of antibiotics, if the remaining non-germinated spores

are sufficiently numerous to evade or overwhelm the immune system when they germinate, disease will then develop. This phenomenon of delayed onset of disease is not recognized to occur with cutaneous or gastrointestinal exposures.

Clinical Features

There are three clinical forms of anthrax: cutaneous, gastrointestinal, and inhalation. The symptoms and incubation period of human anthrax are determined by the route of transmission of the organism.

Cutaneous Anthrax

Most (more than 95%) naturally occurring *B. anthracis* infections are cutaneous and occur when the bacterium enters a cut or abrasion on the skin (e.g., when handling *B. anthracis*-contaminated animals, animal products, or other objects). The reported incubation period for cutaneous anthrax ranges from 1 to 12 days. Skin infection begins as a small papule that may be pruritic, progresses to a vesicle in 1–2 days, and erodes leaving a necrotic ulcer (eschar) with a characteristic black center. Secondary vesicles around the primary lesions may develop. The lesion is usually painless.

Other symptoms may include swelling of adjacent lymph nodes, fever, malaise, and headache. The diagnosis of cutaneous anthrax is suggested by the presence of the eschar, the presence of edema out of proportion to the size of the lesion, and the lack of pain during the initial phases of the infection. The case-fatality rate of cutaneous anthrax is 5%–20% without antibiotic treatment and less than 1% with antibiotic treatment.

Gastrointestinal Anthrax

The intestinal form of anthrax usually occurs after eating contaminated meat. The incubation period for intestinal anthrax is believed to be 1–7 days. Involvement of the pharynx is characterized by lesions at the base of the tongue or tonsils, with sore throat, dysphagia, fever, and regional lymphadenopathy. Involvement of the lower intestine is characterized by acute inflammation of the bowel. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and bloody diarrhea. The case-fatality rate of gastrointestinal anthrax is unknown but is estimated to be 25%–60%.

Inhalation Anthrax

Originally known as Woolsorter's disease, inhalation anthrax results from inhalation of 8,000–50,000 spores of *B. anthracis*. This form of anthrax would be expected to be the most common following an intentional release of *B. anthracis*. The incubation period for inhalation anthrax for humans appears to be 1–7 days, but may be as long as 43 days. The median incubation period for the first 10 bioterrorism-related inhalation anthrax cases in 2001 was 4 days, with a range of 4–6 days. However, the incubation period for inhalation anthrax may be inversely related to the dose of *B. anthracis*. Data from studies of laboratory animals suggest that *B. anthracis* spores continue to vegetate in the host for several weeks after inhalation, and antibiotics can prolong the incubation period for developing disease.

Initial symptoms of inhalation anthrax can include a nonproductive cough, myalgia, fatigue, and fever. Profound, often drenching sweat was a prominent feature of the first 10 bioterrorism-related cases in 2001. A brief period of improvement has been reported following the prodromal symptoms, but was not seen in the 2001 cases. Rapid deterioration then occurs, with

high fever, dyspnea, cyanosis, and shock. Chest x-ray often shows pleural effusion and mediastinal widening due to lymphadenopathy.

Meningitis, often hemorrhagic, occurs in up to half of patients with inhalation anthrax. Prior to the bioterrorist attacks in 2001, the case-fatality estimates without antibiotics were 85%–97%. With antibiotics, the case-fatality rate is estimated to be 75%. For inhalation anthrax cases in 2001, the case-fatality rate with intensive therapy was 45% (5 of 11 cases).

Death sometimes occurs within hours of onset. Initial symptoms of an influenza-like illness (ILI) could be similar to early symptoms of inhalation anthrax. ILI is a nonspecific respiratory illness characterized by fatigue, fever, cough, and other symptoms. Most cases of ILI are not caused by influenza but by other viruses, such as rhinovirus and adenovirus. Nasal congestion and rhinorrhea (runny nose) are common with ILI, but not common with inhalation anthrax. Shortness of breath is common with inhalation anthrax but not common with ILI. Most persons with inhalation anthrax have abnormalities on chest x-ray, whereas most persons with ILI do not have abnormal chest x-rays (although primary influenza pneumonia or secondary bacterial pneumonia may occur in persons with influenza).

Laboratory Diagnosis

The diagnosis of cutaneous anthrax should be suspected by the characteristic painless, shallow ulcer with a black crust. Gram stain of vesicular fluid will reveal typical gram-positive bacteria. Diagnosis can be confirmed by culture.

Gastrointestinal anthrax is difficult to diagnose because of its similarity to other severe gastrointestinal diseases. A history of ingesting potentially contaminated meat and presence of typical symptoms may be helpful. Diagnosis of inhalation anthrax can also be difficult. Mediastinal widening on chest x-ray is a useful clinical finding. The bacterial burden may be so great in advanced infection that bacteria are visible on Gram stain of unspun peripheral blood.

Gram-positive bacteria may be present in other clinical specimens, such as pleural fluid, skin biopsy lesion material, oropharyngeal ulcers, or cerebrospinal fluid. Diagnosis is usually confirmed with a positive culture for *B. anthracis*. Standard blood cultures should show growth in 6–24 hours.

Other laboratory tests that may assist in the diagnosis are polymerase chain reaction (PCR), which detects *B. anthracis* DNA in pleural fluid or blood, serology (PA-based ELISA), and tissue immunohistochemistry, in which tissue is stained with specific cell wall and capsular antibodies.

Medical Management

Antibiotics are the most important therapeutic intervention in any form of anthrax and should be started as soon as the disease is suspected. Naturally occurring strains of *B. anthracis* are typically sensitive to several antibiotics, including penicillin, tetracycline, and oral fluoroquinolones (ciprofloxacin and ofloxacin). *B. anthracis* produces a cephalosporinase that inhibits the antibacterial activity of cephalosporins such as ceftriaxone. Consequently, cephalosporins should not be used for treatment of anthrax. Naturally occurring *B. anthracis* may also be resistant to other commonly used antibiotics, such as sulfamethoxazole, trimethoprim, and aztreonam.

All patients with bioterrorism-related inhalation anthrax in 2001 received combination

antimicrobial therapy with more than one agent active against *B. anthracis*. The survival rate among these patients was higher (55%) than in previous descriptions. The apparent improvement in survival suggests that the antibiotic combinations used in these patients may have therapeutic advantage compared with previous regimens.

Limited data on treatment suggest that early intravenous treatment with a fluoroquinolone (e.g., ciprofloxacin) and at least one other active drug may improve survival. Treatment should initially be intravenous, then oral (PO) when clinically appropriate. Antibiotics should be continued for 30–60 days, or longer. In addition to antibiotics, aggressive supportive care, such as draining of pleural effusions, correction of electrolyte and acid-base disturbances, and early mechanical ventilation appear to increase the likelihood of survival for inhalation anthrax.

Anthrax Medical Management

- Antibiotics
 - Ciprofloxacin or doxycycline and >1 additional drug active against *B. anthracis**
- IV, then PO
- 30–60 days duration

*Rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin

For cutaneous anthrax, ciprofloxacin or doxycycline is recommended as first-line therapy. Intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head and neck. Cutaneous anthrax is typically treated for 7–10 days. However, in the setting of a bioterrorism attack, the risk for simultaneous aerosol exposure may be high. As a result, persons with cutaneous anthrax associated with a bioterrorism attack should be treated for 60 days. Even if promptly treated with appropriate antibiotics, cutaneous anthrax will continue to progress through the eschar phase.

The most current recommendations on treatment of anthrax can be found on the CDC Public Health Emergency Preparedness and Response website at <http://www.bt.cdc.gov>.

Epidemiology

Occurrence

Anthrax occurs worldwide and is most common in agricultural regions with inadequate control programs for anthrax in livestock. These regions include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Prior to 2001, anthrax was very rare in the United States, with no human cases reported during 1993–1999.

Reservoir

The main reservoirs of anthrax are infected animals and soil. Anthrax spores are highly resistant to physical and chemical agents and persist in the environment for many years. The spores may remain dormant in certain types of soil for decades.

Transmission

The most common method of transmission of anthrax is through direct contact with an infected

animal. *B. anthracis* may enter the body through a preexisting skin lesion or may be inadvertently introduced through an injury from a contaminated object. The result of this source of transmission is cutaneous anthrax. Vectors such as flies and vultures may mechanically spread the organism in some circumstances, but vectors are not believed to be important in human infection. Meat from an infected animal can transmit *B. anthracis* if the infected meat is eaten undercooked.

B. anthracis can also be transmitted by inhalation of airborne or aerosolized spores. In nature, *B. anthracis* spores are 2–6 microns in diameter. If aerosolized by industrial processing of contaminated products, or as a result of a bioterrorist attack, particles larger than 5 microns in diameter quickly fall from the atmosphere and bond to any surface.

These particles are difficult to resuspend in the air, but may remain in the environment for years. Spores 2–5 microns in diameter behave as a gas and move through the environment without settling. Spores of this size are able to pass through the pores in paper, as occurred in mail processing facilities subsequent to the anthrax attacks in 2001. Particles smaller than 5 microns in diameter, if inhaled, are small enough to reach the lower respiratory tract and can lead to inhalation anthrax.

Naturally-occurring anthrax is extremely rare in the United States (see Trends). Persons at risk of anthrax are primarily those who have contact with infected animals. However, although animal anthrax occurs in the United States, this mode of transmission is rare. Laboratory personnel or other persons who come into contact with *B. anthracis* spores could be at increased risk, although only two laboratory-associated anthrax cases have been reported (both were inhalation anthrax). In the past, persons involved in processing wool, hair, hides, and/or bones from infected animals could be infected. However, improvements in animal husbandry and strict importation requirements for animal products have made this source of infection extremely rare. Exposure to *B. anthracis* through an effective bioterrorist attack occurred for the first time in 2001.

Temporal Pattern

Anthrax may occur throughout the year. Animal-related cases occur primarily in the spring and summer.

Communicability

Persons with inhalation anthrax are not contagious. Human-to-human transmission of cutaneous anthrax has been reported but is very rare.

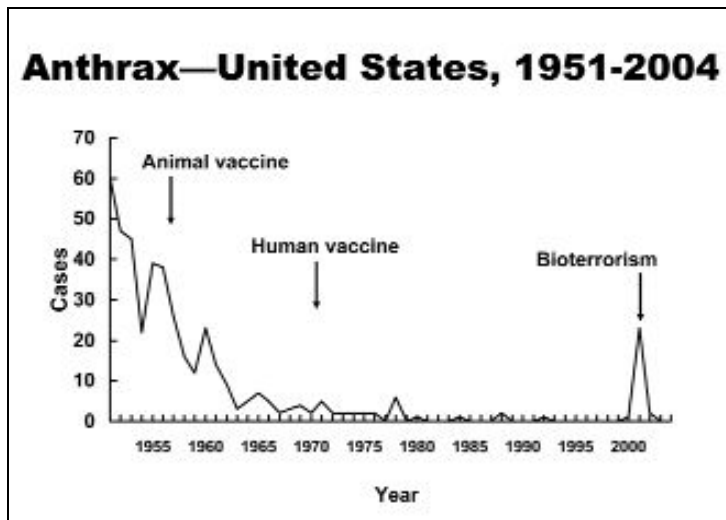
Anthrax Epidemiology	
•	Reservoir
○	Infected animals
○	Soil
•	Transmission
○	Direct contact (cutaneous)
○	Ingestion (gastrointestinal)
○	Inhalation
•	No temporal pattern
•	Communicability
○	Not communicable (inhalation)

- Very rare (cutaneous)

Trends

Anthrax most commonly occurs in herbivores, which are infected by ingesting or inhaling spores from the soil. Humans are infected naturally following contact with anthrax-infected animals or anthrax-contaminated animal products. Estimation of the true incidence of human anthrax worldwide is difficult because reporting of anthrax cases is unreliable. The largest recent epidemic of human anthrax occurred in Zimbabwe during 1978–1980; 9,445 cases were reported, including 141 (1.5%) deaths.

In the United States, the annual incidence of human anthrax declined from approximately 130 cases annually in the early 1900s to no cases during 1993–1999. Most cases reported in the United States have been cutaneous. A single case of cutaneous anthrax was reported in 2000, and two cases were reported in 2002. During the 20th century, only 18 cases of inhalation anthrax were reported, the most recent in 1976. Gastrointestinal anthrax has not been reported in the United States.



Anthrax continues to be reported among domestic and wild animals in the United States. The incidence of anthrax in U.S. animals is not known. However, reports of animal infection have occurred in the Great Plains states from Texas to North Dakota.

Except for the single case in 2000 and two cases in 2002, all other cases of anthrax in the United States since 1993 were related to intentional exposure from a bioterrorist attack.

Most infected persons were exposed in mail-sorting facilities or had direct contact with a contaminated envelope. The source of the *B. anthracis* used in these attacks has not been determined.

Case Definition

A confirmed case of anthrax is defined as a clinically compatible case of cutaneous, respiratory, or gastrointestinal illness that is laboratory confirmed by isolation of *B. anthracis* from an affected tissue or site, or other laboratory evidence of *B. anthracis* infection based on at least two supportive laboratory tests. A suspect case of anthrax is a clinically compatible case of illness

without isolation of *B. anthracis* and no alternative diagnosis, but with laboratory evidence of *B. anthracis* by one supportive laboratory test, or a clinically compatible case of anthrax epidemiologically linked to a confirmed environmental exposure, but without corroborative laboratory evidence of *B. anthracis* infection. Any person suspected of having any type of anthrax must be reported immediately to the local or state health department.

Anthrax Vaccine

Louis Pasteur successfully attenuated *B. anthracis* and produced the first live attenuated bacterial vaccine for animals in 1881. An improved live vaccine containing an unencapsulated avirulent variant of *B. anthracis* (the Stern vaccine) was developed for livestock in 1939. This vaccine continues to be used as the principal veterinary vaccine in the Western Hemisphere. The use of livestock vaccines was associated with occasional death in the animal, and live vaccines were considered unsuitable for humans. In the early 20th century, filtrates of artificially cultivated *B. anthracis* were explored as potential vaccines. The first human culture filtrate vaccine was developed in 1954. This vaccine used alum as an adjuvant. It provided protection in monkeys, caused minimal reactivity and short-term adverse reactions in humans, and was used in the only efficacy study of human vaccination against anthrax in the United States.

In the late 1950s the vaccine was improved through the selection of a *B. anthracis* strain that produced a higher fraction of protective antigen, the production of a protein-free medium, and the use of aluminum hydroxide rather than alum as the adjuvant. This vaccine—anthrax vaccine adsorbed (AVA)—was licensed for use in the United States in 1970.

Characteristics

AVA is the only FDA-licensed human anthrax vaccine in the United States. It is prepared from a cell-free culture filtrate of a toxigenic, nonencapsulated strain of *B. anthracis*. The vaccine does not contain dead or live bacteria. The filtrate contains a mix of cellular products and contains all three toxin components (LF, EF, and PA). The vaccine is adsorbed to aluminum hydroxide as an adjuvant. AVA contains no more than 0.83 mg aluminum per 0.5-mL dose, 0.0025% benzethonium chloride as a preservative, and 0.0037% formaldehyde as a stabilizer.

Immunogenicity and Vaccine Efficacy

The principal antigen responsible for producing immunity is PA. Approximately 83% of recipients of AVA develop detectable antibody to PA by 2 weeks after the first dose, and 91% after two or more doses. Approximately 95% of vaccinees seroconvert with a fourfold rise in anti-PA IgG titers after three doses. However, the precise correlation between antibody titer (or concentration) and protection against infection is not known with certainty.

The only controlled clinical human trial of anthrax was performed among mill workers in 1955–1959 using the alum-precipitated vaccine (the PA-based precursor to the currently licensed AVA). In this controlled study, 379 employees received the vaccine, 414 received a placebo, and 340 received neither the vaccine nor the placebo.

The study documented a vaccine efficacy of 92.5% for protection against anthrax (cutaneous and inhalation combined). During the study, an outbreak of inhalation anthrax occurred among the study participants. Overall, five cases of inhalation anthrax occurred in persons who were either placebo recipients or did not participate in the controlled part of the study. No cases occurred in

anthrax vaccine recipients. No data are available regarding the efficacy of anthrax vaccine for persons younger than 18 years or older than 65 years of age.

The protective efficacy of the alum-precipitated vaccine (the earlier form of the PA filtrate vaccine) and AVA has been demonstrated in several animal studies using different routes of spore exposure. Inhalation anthrax in macaque (Rhesus) monkeys is believed to best reflect human disease, and AVA has been shown to be protective for up to 100 weeks after pulmonary challenge with *B. anthracis*. The duration of immunity in humans following vaccination with AVA is unknown. Data from animal studies suggest that the duration of efficacy after two inoculations might be 1–2 years.

Vaccination Schedule and Use

Primary vaccination with AVA consists of three subcutaneous (SC) injections at 0, 2, and 4 weeks, followed by doses at 6, 12, and 18 months. To maintain immunity, the manufacturer recommends an annual booster dose. The basis for the schedule of vaccinations at 0, 2, and 4 weeks, and 6, 12, and 18 months followed by annual boosters is not well defined.

As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. Interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses.

Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions, studies are being conducted to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) rather than subcutaneous administration. Preliminary results indicate that schedules using fewer doses at longer intervals, and IM rather than SC route, produce similar concentrations of antibody to PA. However, no alternate schedule has yet been approved for use by the FDA.

Preexposure Vaccination

Routine preexposure vaccination with AVA is indicated for persons engaged in work involving production of quantities or concentrations of *B. anthracis* cultures and in activities with a high potential for aerosol production. Laboratory personnel using standard Biosafety Level 2 practices in routine processing of clinical samples are not at increased risk for exposure to *B. anthracis* spores. The risk for persons who come in contact in the workplace with imported animal hides, furs, bone meal, wool, animal hair, or bristles has been reduced by changes in industry standards and import restrictions.

Routine preexposure vaccination is recommended only for persons in this group for whom these standards and restrictions are insufficient to prevent exposure to anthrax spores. Routine vaccination of veterinarians in the United States is not recommended because of the low incidence of animal cases. However, vaccination might be indicated for veterinarians and other persons handling potentially infected animals in areas with a high incidence of anthrax cases.

Preexposure vaccination may be indicated for certain military personnel and other select groups who may be exposed to an intentional release of *B. anthracis*. Preexposure vaccination is not currently recommended for emergency first responders, federal responders, medical practitioners, or private citizens.

Postexposure Vaccination

Limited data are available regarding the postexposure efficacy of AVA. Studies in nonhuman primates indicate that postexposure vaccination alone is not protective. However, studies have shown that antibiotics in combination with postexposure vaccination are effective at preventing disease in animals after exposure to *B. anthracis* spores.

The current vaccine is approved by FDA only for preexposure vaccination. The optimal number of doses for postexposure prophylaxis use of the vaccine is not known. An estimated 83% of human vaccinees develop a vaccine-induced immune response after two doses of the vaccine, and more than 95% develop a fourfold rise in antibody titer after three doses. Although the precise correlation between antibody titer and protection against disease is not clear, these studies of postexposure vaccine regimens used in combination with antibiotics in nonhuman primates have consistently documented that one or two doses of vaccine were sufficient to prevent development of disease once antibiotics were discontinued.

Adverse Reactions Following Vaccination

The most common adverse reactions following AVA are local reactions. In AVA prelicensure evaluations, minor local reactions (defined as erythema, edema, and induration less than 30 mm) occurred after 20% of vaccinations, moderate local reactions (edema and induration of 30–120 mm) occurred after 3% of vaccinations, and severe local reactions (edema or induration more than 120 mm) occurred after 1% of vaccinations. Local reactions usually occur within 24 hours and subside within 48 hours.

Subcutaneous nodules occur at the injection site in 30%–50% of recipients and persist for several weeks. In multiple Department of Defense studies, systemic reactions (i.e., chills, muscle aches, malaise, or nausea) occurred in 5%–35% of vaccine recipients. Systemic reactions are usually mild and transient. Fever is not common following AVA. Severe (e.g., allergic) reactions are rare.

Adverse reactions following anthrax vaccination have been assessed in several studies conducted by the Department of Defense in the context of the routine anthrax vaccination program. In one of these studies, 1.9% of vaccine recipients reported limitations in work performance or had been placed on limited duty due to a local reaction. Only 0.3% reported more than 1 day lost from work; 0.5% consulted a clinic for evaluation; and one person (0.02%) required hospitalization for an injection-site reaction. Adverse reactions were reported more commonly among women than among men.

No studies have documented occurrence of chronic diseases (e.g., cancer or infertility) following anthrax vaccination. In an assessment of the safety of anthrax vaccine, the Institute of Medicine (IOM) noted that published studies reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies. One published follow-up study of laboratory workers at Fort Detrick, Maryland, concluded that during the 25-year period following receipt of anthrax vaccine, the workers did not develop any unusual illnesses or unexplained symptoms associated with vaccination. The IOM found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse reactions immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that an elevated risk of developing long-term adverse health effects is associated with receiving AVA, although data are limited in this regard (as they are for all vaccines). CDC has conducted two epidemiologic investigations of the health concerns of Persian

Gulf War (PGW) veterans that examined a possible association with several factors, including anthrax vaccination. Current scientific evidence does not support an association between anthrax vaccine and PGW illnesses.

No data are available regarding the safety of anthrax vaccine for persons younger than 18 years and older than 65 years of age. Adverse reactions can occur in persons who must complete the anthrax vaccination series because of high risk of exposure or because of employment requirements. Several protocols have been developed to manage specific local and systemic adverse reactions (available at www.anthrax.osd.mil). However, these protocols have not been evaluated in randomized trials.

Contraindications and Precautions

As with all vaccines, AVA is contraindicated for persons who have experienced a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of AVA. Anthrax vaccine is contraindicated for persons who have recovered from anthrax because of observations of more severe adverse reactions among recipients with a history of anthrax disease. A moderate or severe acute illness is a precaution, and vaccination should be postponed until recovery. This prevents superimposing the adverse reactions from the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccine can be administered to persons who have mild illnesses with or without low-grade fever.

No studies have been published regarding use of anthrax vaccine among pregnant women. The vaccine is neither licensed nor recommended during pregnancy. Pregnant women should be vaccinated against anthrax only if the potential benefits of vaccination outweigh the potential risks to the fetus. No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breastfeeding women or breastfed children. AVA may be administered to an immunosuppressed person if necessary, but response to the vaccine may be suboptimal.

Postexposure Prophylaxis with Antibiotics

Ciprofloxacin, doxycycline, and procaine penicillin G, are approved by FDA for the treatment of anthrax and are considered the drugs of choice for the treatment of naturally occurring anthrax. In addition, ofloxacin has also demonstrated in vitro activity against *B. anthracis*. Although naturally occurring *B. anthracis* resistance to penicillin is rare, such resistance has been reported.

Antibiotics are effective against the germinated form of *B. anthracis* but are not effective against the spore form of the organism. Following inhalation exposure, spores can survive in tissues for months without germination in nonhuman primates. This phenomenon of delayed vegetation of spores resulting in prolonged incubation periods has not been observed for routes of infection other than inhalation.

In one study, macaques were exposed to four times the LD50 dose of anthrax spores (the dose of spores that will result in the death of 50% of the exposed animals). The proportion of spores that survived in the lung tissue was estimated to be 15%–20% at 42 days, 2% at 50 days, and less than 1% at 75 days. Spores have been detected in animals up to 100 days following exposure. Although the LD50 dose for humans is believed to be similar to that for nonhuman primates, the length of persistence of *B. anthracis* spores in human lung tissue is not known. The length of persistence probably depends on the dose inhaled. The prolonged incubation period reported in

an outbreak of inhalation anthrax in the former Soviet Union suggests that lethal amounts of spores might have persisted up to 43 days after initial exposure.

Postexposure Prophylaxis Following Inhalation Exposure

Postexposure prophylaxis against *B. anthracis* with antibiotics is recommended following an aerosol exposure to *B. anthracis* spores. Such exposure might occur following an inadvertent exposure in a laboratory setting or a biological terrorist incident. Inhalation anthrax in humans has not been reported to result from contact with naturally occurring anthrax among animals. Currently, ciprofloxacin, doxycycline, and procaine penicillin G are approved by FDA for use as antibiotic prophylaxis for inhalation *B. anthracis* infection.

Because of concern about the possible antibiotic resistance of *B. anthracis*, ciprofloxacin or doxycycline should be used initially for antibiotic prophylaxis until organism susceptibilities are known. Antibiotic chemoprophylaxis can be switched to penicillin VK or amoxicillin, particularly for children, once antibiotic susceptibilities are known and the organism is found to be penicillin susceptible with minimum inhibitory concentrations (MICs) attainable with oral therapy.

Because of the potential persistence of spores following an aerosol exposure, antibiotic therapy should be continued for at least 60 days if used alone. If vaccine is available, antibiotics can be discontinued after three doses of vaccine have been administered according to the standard schedule (0, 2, and 4 weeks). Although the shortened (3-dose) vaccine regimen has been effective when used in a postexposure regimen that includes antibiotics, the duration of protection after vaccination is not known. Therefore, if subsequent exposures occur, additional vaccinations might be required.

Postexposure Antibiotic Prophylaxis Following Cutaneous or Gastrointestinal Exposure

No controlled studies have been conducted in animals or humans to evaluate the use of antibiotics alone or in combination with vaccination following cutaneous or gastrointestinal exposure to *B. anthracis*. Cutaneous and rare gastrointestinal exposures of humans are possible following outbreaks of anthrax in livestock. In these situations, on the basis of pathophysiology, reported incubation periods, current expert clinical judgment, and lack of data, postexposure prophylaxis might consist of antibiotic therapy for 7–14 days. Antibiotics could include ciprofloxacin, ofloxacin, doxycycline, penicillin, or amoxicillin.

Vaccine Storage and Handling

AVA must be stored at 35°–46°F (2°–8°C). The vaccine should not be frozen. The manufacturer (Bioport Corporation, Lansing, Michigan [877-BIO-THRAX]) should be contacted for advice should the vaccine be exposed to freezing temperature or a prolonged period at room temperature.

Bioterrorism Preparedness

Research on anthrax as a biological weapon began more than 90 years ago. In 1999, at least 17 nations were believed to have offensive biological weapons programs; it is not known how many are working with anthrax. Iraq has acknowledged producing and weaponizing anthrax. One terrorist group, Aum Shinrikyo, dispersed aerosols of anthrax and botulism throughout Tokyo, Japan, on at least eight occasions. For unknown reasons the attacks failed to produce illness.

B. anthracis is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax, and the greater stability of *B. anthracis* spores compared with other potential biological warfare agents. The World Health Organization estimates that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations, far more deaths than predicted in any other scenario of agent release.

A total of 22 anthrax cases in four states and the District of Columbia occurred in October and November 2001 as a result of a series of bioterrorist attacks with *B. anthracis*. Eleven cases were inhalation anthrax, of which five were fatal. The organism was sent through the U.S. postal system.

Nine of the cases of inhalation anthrax occurred in persons with direct exposure to an envelope containing *B. anthracis*. The envelopes contaminated several office buildings and mail processing centers. Cross-contamination of mail in the processing centers is suspected as the source of exposure in those cases without known direct exposure to a contaminated letter. Several thousand persons required postexposure antibiotic prophylaxis because of exposure to contaminated buildings. Information on the 2001 anthrax attacks, recommendations for management of anthrax infection and exposure, and information on bioterrorism preparedness is available on the CDC Public Health Emergency Preparedness and Response website at <http://www.bt.cdc.gov>.

Reference

Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds. 9th ed., Washington DC: Public Health Foundation, 2006. <http://www.cdc.gov/vaccines/pubs/pinkbook/pink-chapters.htm>

Post Test

Circle one answer per question.

1. Anthrax disease:
 - a) Is a human disease that has never been seen in animals.
 - b) Is caused by a large spore-forming bacillus that can remain viable and infective in soil for many years.
 - c) Was first used as a bioterrorism agent during World War I.
 - d) Is characterized by white skin lesions over the face and trunk.
2. After wound inoculation or ingestion:
 - a) Anthrax spores produce lethal and edema toxins that result in necrosis of lymphatic tissue and the release of large numbers of bacteria.
 - b) Macrophages engulf and kill any bacillus anthracis that has entered the body.
 - c) The bacteria spreads to the heart and brain and death soon follows.
 - d) Production of toxins leads to the massive hemorrhagic lymphadenitis and mediastinitis characteristic of ingestion disease.
3. The only two forms of anthrax are gastrointestinal and inhalation.
 - a) True
 - b) False
4. The most common type of anthrax is:
 - a) Gastrointestinal anthrax.
 - b) Inhalation anthrax.
 - c) Cutaneous anthrax.
 - d) Woolsorter's disease.
5. Inhalation anthrax:
 - a) Has an incubation period of 7–10 days.
 - b) May include hemorrhagic meningitis which occurs in up to half of patients.
 - c) Has a fatality rate of 85–97% even with intensive antibiotic treatment.
 - d) Usually occurs after eating contaminated meat from animals who ingested spores while grazing.
6. Medical management of anthrax:
 - a) Includes the use of ceftriaxone and sulfa drugs for all forms of anthrax.
 - b) Is only aggressive supportive care because there is no known antimicrobial agent effective against the disease.
 - c) Includes aggressive supportive care, Cipro and at least one other active drug.
 - d) Includes penicillin as a first-line therapy for cutaneous anthrax.

7. Transmission of anthrax:

- a) Is most common through inhalation of airborne or aerosolized spores.
- b) Occurs worldwide most commonly in agricultural regions with inadequate control programs for anthrax in livestock.
- c) Is common in the United States animal husbandry and animal products importation businesses due to lax importation requirements.
- d) Can not occur through vectors such as flies and vultures.

8. Human anthrax infection in the United States:

- a) Continues to be reported in the Great Plains states from Texas to North Dakota.
- b) Is mainly gastrointestinal.
- c) Most commonly occurs after ingesting or inhaling spores from the soil.
- d) Since 1993 (except for 3 cases) were related to a bioterrorist attack.

9. The anthrax vaccine used in humans is:

- a) The Stern vaccine which contains an unencapsulated avirulent variant of *B. anthracis*.
- b) The AVA vaccine which gives lifelong immunity.
- c) Is the AVA vaccine which gives immunity for 1–2 years.
- d) Safe and effective for persons younger than 18 years and older than 65 years.

10. Preexposure vaccination is recommended for:

- a) All veterinarians in the United States.
- b) Laboratory personnel using standard Biosafety Level 2 practices in routine processing of clinical samples.
- c) Military personnel who may be exposed to an intentional release of *B. anthracis*.
- d) Emergency first responders, federal responders and medical practitioners.

11. The use of postexposure vaccination:

- a) Has been proven to protect against anthrax if given within 2 days of onset of symptoms.
- b) Has been effective in animals when used in combination with antibiotics.
- c) Has not been approved by the FDA because it may increase the severity of anthrax symptoms.
- d) Is contraindicated due to the high frequency of severe allergic reactions in persons already exposed to anthrax.

12. Adverse reactions following anthrax vaccination:

- a) Are more common among men than women.
- b) Include injection site nodules, chills, muscle aches and nausea that are usually mild and transient.
- c) Have been shown to occur as long as 25 years after vaccination and may cause permanently disabling disease in a small percentage of cases.
- d) Include pneumonia and meningitis which occur in about 1% of cases.

13. Persons who should not receive the anthrax vaccine are:

- a) Those with mild illness and low-grade fever.
- b) Anyone who has recovered from anthrax.
- c) Immunocompromised patients who may develop the disease if vaccinated.
- d) Pregnant women in their first trimester.

14. Postexposure treatment for anthrax:

- a) Should include vancomycin that must be given for at least 60 days because spores may survive in the lung tissue for prolonged periods of time.
- b) Includes Cipro or doxycycline which may be discontinued after 3 doses of vaccine have been administered according to the standard schedule.
- c) Includes initial use of sulfa drugs until organism susceptibilities are known because of concerns about possible antibiotic resistance.
- d) Consists of antibiotics and AVA vaccine, which confers immunity for subsequent anthrax exposures and probably is lifelong.

15. The use of anthrax as a biological weapon:

- a) Is considered unlikely due to the instability of anthrax spores.
- b) Has not occurred, but is considered a potential biological warfare agent because of its high mortality rate.
- c) Resulted in 22 anthrax cases with 5 fatalities in 2001 in the United States.
- d) Occurred in Japan on 8 occasions resulting in thousands of deaths.

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* 1. This course met the goals and learning objectives.

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* 2. The author was well prepared to write about the content in a way that facilitated my learning.

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* 3. This course was free from commercial bias.

Yes No

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