

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 was the first disease for which a microbial origin was definitively established, by Robert Koch in 1876. 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 an improved cell-free vaccine was licensed in the United States in 1970. 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 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 animal 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 - protective antigen (PA), lethal factor (LF), and edema factor (EF). These proteins combine to form two toxins known as lethal toxin and edema toxin. PA and LF form lethal toxin, a protease that is believed to be responsible for tissue damage, shock and death, although the mechanism is not clear. PA and EF form edema toxin, an adenylate cyclase that upsets controls on ion and water transport across cell membranes and causes extensive edema.

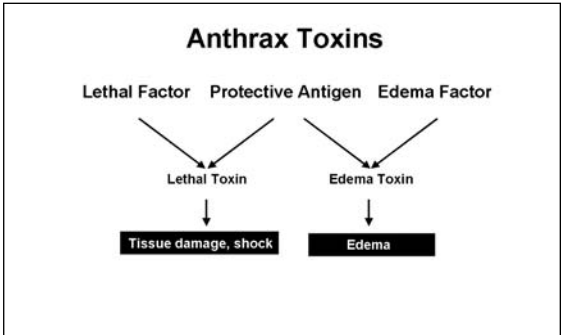
PA binds to receptors on mammalian cells then binds with LF or EF. The toxin complexes are internalized to the endosome of the cell, then transported to the cytosol where they exert their effect.

**Anthrax**

- Zoonotic disease caused by *Bacillus anthracis*
- Described in biblical times
- First animal vaccine developed by Louis Pasteur in 1881
- Used for bioterrorism in 2001

***Bacillus anthracis***

- Gram-positive aerobic bacteria
- Spores may remain viable in soil for years
- Spores inactivated by paraformaldehyde vapor, hypochlorite, phenol, or autoclave
- Toxins responsible for tissue damage and edema



## Anthrax Pathogenesis

- Spores enters through broken skin or mucous membranes
- Germinate in macrophages, replicate in lymph nodes and intracellular space
- Bacteria produce antiphagocytic capsule
- Production of toxins cause tissue destruction and edema

## Anthrax Pathogenesis

- Inhaled spores may reside in alveoli without germination for weeks
- Antibiotics effective against vegetative form but not spores
- Disease may develop after antibiotics discontinued
- Delayed onset not described for cutaneous or gastrointestinal forms

## Anthrax Clinical Features

- Three clinical forms
  - cutaneous (most common in natural exposure situations)
  - gastrointestinal (rare)
  - inhalation

## Cutaneous Anthrax

- Incubation period 1-12 days
- Papule, then vesicle, then necrotic ulcer (eschar) with black center
- Usually painless
- Case-fatality:
  - without antibiotics – 5%-20%
  - with antibiotics - <1%

## PATHOGENESIS

After wound inoculation or ingestion, macrophages engulf *B. anthracis* spores where the spores germinate. The vegetative bacteria 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. A 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 nonvegetative 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 nongerminated 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

**The symptoms and incubation period of human anthrax are determined by the route of transmission of the organism.**

There are three clinical forms of anthrax: cutaneous, gastrointestinal, and inhalation.

## CUTANEOUS ANTHRAX

Most (>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 0.5 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% to 20% without antibiotic treatment and <1% with antibiotic treatment.

### **GASTROINTESTINAL ANTHRAX**

The intestinal form of anthrax usually occurs after eating contaminated meat. The incubation period for intestinal anthrax is suspected 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

#### **Gastrointestinal Anthrax**

- Incubation period 1-7 days
- Pharyngeal involvement includes oropharyngeal ulcerations with cervical adenopathy and fever
- Intestinal involvement includes abdominal pain, fever, bloody vomiting or diarrhea
- Case-fatality estimated at 25-60%

#### **Inhalation Anthrax**

- Incubation period: 1-7 days (range up to 43 days)
- Prodrome of cough, myalgia, fatigue, and fever
- Rapid deterioration with fever, dyspnea, cyanosis and shock, often with radiographic evidence of mediastinal widening
- Case fatality:
  - without antibiotic treatment – 86%- 97%
  - with antibiotic treatment - 75% (45% in 2001)

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 diagnosis because of its similarity to other severe gastrointestinal diseases. A history of ingesting potentially contaminated meat and 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 cerebral spinal 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.

Survival of patients with bioterrorism-related inhalation anthrax was higher (55%) than in previous descriptions. All patients received combination antimicrobial therapy with more than one agent active against *B. anthracis*. The apparent improvement in survival suggests that the antibiotic combinations used in these patients may have therapeutic advantage compared to previous

### Anthrax Laboratory Diagnosis

- Gram stain of clinical samples (skin lesion, blood, pleural fluid, CSF)
- Culture
- Adjunct Assays
  - PCR
  - Serology (PA based ELISA)
  - Immunohistochemistry

### Anthrax Medical Management

- Antibiotics
  - ciprofloxacin or doxycycline and  $\geq 1$  additional drug active against *B. anthracis*\*
  - IV, then PO
  - 30 to 60 days duration
- Aggressive supportive care

\*rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin

regimens. Limited data on treatment suggests 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 when clinically appropriate. Antibiotics should be continued for 30 to 60 days, or longer. In addition to antibiotics, survival of persons with inhalation anthrax appears to be more likely with aggressive supportive care, such as draining of pleural effusions, correction of electrolyte and acid-base disturbances, and early mechanical ventilation.

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 in 1993-2000.

**RESERVOIR**

The main reservoirs of anthrax are infected animals and the 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 pre-existing 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

Anthrax Epidemiology	
• Reservoir	Infected animals, soil
• Transmission	Direct contact (cutaneous) Ingestion (gastrointestinal) Inhalation
• Temporal pattern	None
• Communicability	Not communicable (inhalation) or rare (cutaneous)

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 >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 <5 microns in diameter, if inhaled, are small enough to reach the lower respiratory tract and can lead to inhalation anthrax.

## Anthrax Epidemiology

- Agricultural exposure to animals (rare)
- Laboratorians exposed to *B. anthracis* spores (rare)
- Processors of wool, hair, hides, bones or other animal products (extremely rare)
- Biological terrorism

Naturally-occurring anthrax is extremely rare in the United States (see Secular Trends, below). Persons at risk of anthrax are primarily those who have contact with infected animals. 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 had inhalation anthrax). In the past, persons involved in the processing of 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.

## SECULAR 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 occurred, 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. A single case of cutaneous anthrax was reported in 2000, and was associated with an outbreak of anthrax in farm animals in North Dakota. Most cases reported in the United States have been cutaneous. 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 unknown. However, reports of animal infection have occurred in the Great Plains states from Texas to North Dakota.

Except the single case in 2000, all cases of anthrax in the United States since 1993 were related to intentional exposure from a bioterrorist attack. A total of 22 cases (11 inhalation, 11 cutaneous) were reported from Florida, New Jersey, Connecticut, New York City, and the District of Columbia in October and November 2001. *B. anthracis* was contained in at least 2 envelopes sent through the U.S. postal system. Most cases were exposed in mail sorting facilities or had direct contact with a contaminated envelope. Cross-contamination of mail in sorting facilities is suspected as the source for cases without known exposure to a contaminated facility or envelope. The source of the *B. anthracis* used in these attacks has not been determined.

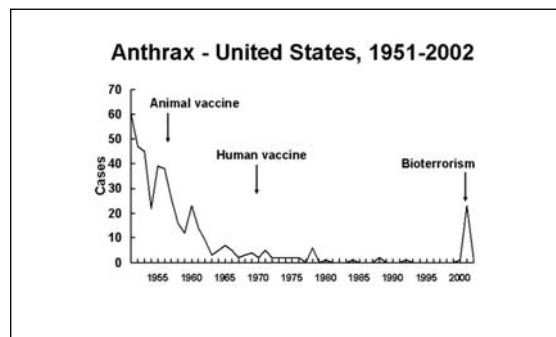
## CASE DEFINITION

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 veteri-



- ### Anthrax Bioterrorism Attacks – United States, 2001
- 22 cases (11 inhalation, 11 cutaneous) in 4 states and DC
  - *B. anthracis* sent through U.S. mail
  - Most exposures occurred in mail sorting facilities and sites where mail was opened

- ### Anthrax Vaccines
- 1881 Pasteur develops first live attenuated veterinary vaccine for livestock
  - 1939 Improved live veterinary vaccine
  - 1954 First cell-free human vaccine
  - 1970 Improved cell-free vaccine licensed

## Anthrax Vaccine

- Cell-free culture filtrate of toxigenic strain of *B. anthracis*
- Filtrate contains protective antigen (PA) and other cellular products
- Adsorbed to aluminum hydroxide as an adjuvant
- Contains small amounts of benzethonium chloride (preservative) and formaldehyde (stabilizer)

## Anthrax Vaccine Efficacy

- 95% seroconversion following 3 doses
- One controlled human trial using earlier vaccine  
–92.5% efficacy (cutaneous and inhalation disease combined)
- Animal models suggest protection against inhalation anthrax
- Duration of immunity unknown

nary 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 twentieth 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 media, 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 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 in 91% of vaccinees who received 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. This 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 among 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 aged <18 years and >65 years.



The protective efficacy of the alum-precipitated vaccine (the earlier form of the PA filtrate vaccine) and AVA have 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 (see Adverse Reactions), studies are being conducted to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration 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.**

**PRE-EXPOSURE VACCINATION**

Routine pre-exposure vaccination with AVA is indicated for **persons engaged in work involving production 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 the 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 pre-exposure 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

**Anthrax Vaccine Efficacy in Macaques**

Year	Vaccine	Challenge	Time	Survival
1954	alum	50 x LD50	16 d	7 of 7
1954	alum	100 x LD50	16 d	4 of 4
			34 d	4 of 4
1956	alum	100 x LD50	7 d	10 of 10
			1 yrs	10 of 10
			2 yrs	8 of 7
1995	alum. hyd.	200 x LD50	8 wks	10 of 10
			38 wks	3 of 3
			100 wks	7 of 8
1995	alum. hyd.	200 x LD50	12 wks	10 of 10

**Anthrax Vaccine Schedule**

- Initial doses at 0, 2, and 4 weeks
- Additional doses at 6, 12, and 18 months
- Annual booster doses thereafter
- Alternative schedules being investigated

**Anthrax Vaccine Pre-exposure Vaccination**

- Persons working with production quantities or concentrations of *B. anthracis* cultures
- Persons engaged in activities with a high potential for production of aerosols containing *B. anthracis*
- Persons with increased risk of exposure to intentional release of *B. anthracis* (e.g., certain military personnel)

cases. However, vaccination might be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax cases.

**Pre-exposure vaccination may be indicated for certain military personnel and other select groups who may be exposed to an intentional release of *B. anthracis*.** Pre-exposure 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 pre-exposure 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 >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 <30 mm) occurred after 20% of vaccinations, moderate local reactions (edema and induration of 30 mm - 120 mm) occurred after 3% of vaccinations, and severe local reactions (edema or induration >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 reactions (*e.g.*, allergic) 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 >1 day lost from work; 0.5% consulted a clinic for evaluation; and one person (0.02%) required

### Anthrax Vaccine Postexposure Vaccination

- No efficacy data for postexposure vaccination of humans
- Postexposure vaccination alone not effective in animals
- Combination of vaccine and antibiotics appears effective in animal model

### Anthrax Postexposure Prophylaxis Vaccine Combined with Antibiotics

- Henderson, et al (1956): earlier PA-based vaccine
  - Methods: 5 days of penicillin compared to penicillin plus postexposure vaccination
  - Results: 9 of the 10 receiving just penicillin died, while all of the macaques receiving both penicillin and vaccine survived
- Friedlander et al (1993): aluminum hydroxide PA filtrate vaccine (current FDA-licensed vaccine)
  - Methods: 30 days of various antibiotics compared to 30 days of doxycycline plus postexposure vaccination
  - Results: 9 of the 10 animals in the doxycycline-alone arm survived, while all receiving doxycycline and vaccine survived

### Anthrax Vaccine Adverse Reactions

- Local reactions
  - minor 20%-50%
  - severe 1%
- Systemic symptoms 5%-35%
- Severe reactions rare

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 people face elevated risk of developing long term adverse health effects, 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 aged <18 years and >65 years.

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](http://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 in persons who have recovered from anthrax** because of observations of more severe adverse reactions among recipients with a vaccine history of anthrax than among nonrecipients. **A moderate or severe acute illness** is a precaution, and vaccination should be postponed until recovery. This prevents superimposing the adverse effects of 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

**Anthrax Vaccine  
Precautions and Contraindications**

- Severe allergic reaction to a vaccine component or following a prior dose
- Previous anthrax disease
- Moderate or severe acute illness

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.

## VACCINE STORAGE AND HANDLING

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

## POSTEXPOSURE PROPHYLAXIS WITH ANTIBIOTICS

Procaine penicillin G, ciprofloxacin, and doxycycline 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 <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 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 Postexposure Antibiotic Prophylaxis

- Ciprofloxacin, doxycycline, and procaine penicillin G approved for postexposure prophylaxis after aerosol exposure to *B. anthracis*
- Due to latency of spores in lung, antibiotics should continue for 30-60 days or more
- Discontinue antibiotics after third dose of vaccine

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 antimicrobial 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.

**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 8 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

Adults (including pregnant women and immunocompromised)	Initial Therapy Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID	Duration 60 days
Children	Ciprofloxacin 10-15 mg/kg PO Q 12 hrs* OR Doxycycline: >8 yrs and >45 kg: 100 mg PO BID >8 yrs and ≤45 kg: 2.2 mg/kg PO BID ≤8 yrs: 2.2 mg/kg PO BID	60 days

\*Ciprofloxacin dose should not exceed 1 gram per day in children.

**Anthrax in Biological Terrorism**

- *B. anthracis* considered likely biological terrorism threat
  - aerosolized stable spore form
  - human LD50 8,000 to 40,000 spores (one deep breath at site of release)
  - acute illness with high fatality rate

Information about anthrax and  
bioterrorism preparedness

<http://www.bt.cdc.gov>

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 5 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>.

## SELECTED REFERENCES

Brachman PS, Friedlander AM, Grabenstein JD. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders; 2003:887-904.

CDC. Use of anthrax vaccine in the United States. Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2000;49(RR-15):1-20.

CDC. Update: investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR* 2001;50:889-93.

CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001;50:909-19.

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

Cieslak TJ, Eitzen EM. Clinical and epidemiologic principles of anthrax. *Emerg Infect Dis* 1999;5:552-5.

Demicheli V, Rivetti D, Deeks JJ, et al. The effectiveness and safety of vaccines against human anthrax: a systematic review. *Vaccine* 1998;16:880-4.

Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a bio-

logical weapon. *J Am Med Assoc* 1999;281:1735-45.

Jernigan JA, Stephens DS, Ashford DA. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933-44.

Joellenbeck LM, Zwanziger L, Durch JS, et al (eds). *The anthrax vaccine: is it safe? Does it Work?* Washington DC:National Academy Press, March 2002. (Institute of Medicine Report)

LaForce MF. Anthrax. *Clin Infect Dis* 1994;19:1009-14.

Turnbull PCB. *Guidelines for the surveillance and control of anthrax in humans and animals*. Geneva, Switzerland: World Health Organization, Department of Communicable Diseases Surveillance and Response, 1998; publication no. WHO/EMC/ZDI./98.6.

Young JAT, Collier RJ. Attacking anthrax. *Sci Amer* 2002;286:48-59.