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## Background

Anthrax is a disease caused by the bacterium *Bacillus anthracis*. This bacterium exists in nature in 2 forms: as an active growing cell (called the vegetative form) or as a dormant spore. The spores are very hardy and tolerant to extremes of temperature, humidity, and ultraviolet light. They can survive for long periods of time (even decades) in the environment without nutrients or water. When a spore enters a mammal host, the internal environment of the host—rich in water, sugars, and amino acids—induces that spore to germinate into a vegetative cell that leads to disease.

In nature, anthrax primarily affects herbivorous mammals such as cattle, sheep, and goats.<sup>1</sup> According to the World Health Organization (WHO), anthrax is enzootic in animal populations in much of sub-Saharan Africa and Asia as well as in some southern European countries, parts of the Americas, and some regions in Australia. Outbreaks in animals also occur sporadically in other countries around the world. Human cases of anthrax are much less frequent.<sup>2</sup>

There are 4 forms of naturally occurring human anthrax infection:

- **Cutaneous anthrax** is the result of spores entering the body through small breaks in the skin. This form of the disease is characterized by a sore at the point of infection that develops into a painless ulcer covered by a black scab (eschar). Cutaneous anthrax accounts for approximately 95% of all reported human anthrax cases. Cutaneous anthrax also could occur because of an intentional aerosol attack with *B. anthracis*.
- **Inhalational anthrax** is the result of breathing *B. anthracis* spores into the lungs. Though inhalational anthrax is less common than cutaneous, causing only about 5% of documented cases, inhalational infection is of most concern following an intentional aerosol attack with *B. anthracis*.
- **Gastrointestinal (GI) anthrax** occurs due to eating raw or undercooked meat of animals infected with *B. anthracis*. The intestinal tract, mouth, or throat (oropharyngeal anthrax) may be infected.<sup>3</sup> Though the reported incidence of gastrointestinal anthrax is low, about 1% of cases, these infections likely are underreported because they most commonly occur in underserved areas with poor access to healthcare and diagnostic testing.
- **Injection-related anthrax** is a more recent recognized route of infection. Several cases have occurred among people who inject drugs in Europe. The infection is believed to be caused by injecting heroin that is contaminated with *B. anthracis* spores.<sup>4</sup>

**Table 1. Clinical Presentation of Anthrax<sup>4,5</sup>**

Anthrax Infection	Incubation Period	Signs and Symptoms	Lethality
Cutaneous	Range of 1 to 12 days following exposure; incubation period is typically closer to 1 day	The first symptom is a small sore at the point of infection that develops into a blister and later into a painless ulcer covered by a black scab. Often there is marked swelling around the ulcer.	Approximately 20% of persons with cutaneous anthrax may die if not treated with appropriate antibiotics. With appropriate treatment, the death rate is <2%.



<b>Inhalational</b>	Ranges from as few as 2 days following exposure to spores to as long as 6 to 8 weeks after exposure	Initial symptoms are fever, head-ache, and muscle aches. If un-treated, the disease progresses to shortness of breath, chest dis-comfort, shock, and death. Men-ingitis may complicate the clini-cal course.  Chest imaging reveals widening of the mediastinum, enlarge-ment of and bleeding into lymph nodes, and bloody fluid collections around the lungs.	Historical data suggest that the case fatality rate of untreated inhalational anthrax may be as high as 90%. With appropriate treatment, a fatality rate of approximately 50% or less may be expected.
<b>Gastrointestinal</b>	Typically, 1 to 6 days following exposure	Oropharyngeal: Symptoms are fever, ulcers in the back of the mouth and throat, severe sore throat, difficulty swallowing, and lymph node and neck swelling.  Intestinal: Initial symptoms are nausea and vomiting. The disease may progress rapidly to bloody diarrhea, abdominal pain, and shock.	Without antibiotic treatment, gastrointestinal anthrax results in the death of more than 40% of affected persons.
<b>Injection-related</b>	1-2 days after injection	Inflammation or abscess at the injection site sometimes progressing to cellulitis or necrotizing fasciitis. Some patients progress to sepsis without extensive local infection.	Of reported cases, 30% of pa-tients died despite aggres-sive medical therapy.

## Anthrax as a Biological Weapon

Anthrax is currently considered one of the most serious bioterrorism threats. A 1993 analysis conducted by the Office of Technology Assessment of the US Congress estimated that 130,000 to 3 million deaths could occur following the release of 100 kilograms of aerosolized *B. anthracis* over Washington, DC, making such an attack as lethal as a hydrogen bomb.<sup>6</sup> (See “The History of Bioterrorism: Anthrax,” a short video from the US Centers for Disease Control and Prevention [CDC], <https://www.youtube.com/watch?v=CmtLYQKT21I>.) The use of genetically engineered *B. anthracis* strains that are resistant to first-line antimicrobial drugs for postexposure prophylaxis (PEP) and treatment would complicate any intentional wide-area aerosol release of *B. anthracis*.<sup>7</sup>

Several additional factors contribute to concern about the potential use of *B. anthracis* as a biological weapon:

- *B. anthracis* is widely available in microbe banks around the world
- *B. anthracis* is widely available naturally in endemic areas
- Evidence suggests techniques for mass production and aerosol dissemination of anthrax exist
- Anthrax spores' hardiness in the environment may make its aerosol dissemination more effective than other potential agents
- Untreated inhalational anthrax has a high fatality rate
- Antibiotic-resistant strains of *B. anthracis* exist in nature and could be used in an intentional release
- Anthrax has been used in the past as a biological weapon.<sup>5</sup>

## History as a Biological Weapon

Beginning in the second half of the 20<sup>th</sup> century, several countries used *B. anthracis* as part of their biological weapons (BW) programs.<sup>8</sup> Although more than 180 states parties have signed on to the 1975 Biological Weapons Convention prohibiting the development, production, acquisition, transfer, stockpiling, and use of bioweapons, development of *B. anthracis* as a bioweapon remains a concern.<sup>7</sup>

Autonomous groups have demonstrated intent to use *B. anthracis* in acts of terrorism. For example, as evidenced in a March 10, 2007, US Department of Defense transcript of the Tribunal Hearing of Khalid Sheikh Muhammad, al Qaeda leadership has shown interest in and has worked to develop anthrax and other biological weapons.<sup>9</sup> In 1993, the Japanese cult Aum Shinrikyo sprayed aerosols containing *B. anthracis* several times in attempted terrorist attacks in Tokyo. Fortunately, the material used turned out to be ineffective, and consequently no one was sickened.<sup>10</sup>

Most notably, in September 2001, anthrax attacks were perpetrated in the US via mail, when 7 envelopes containing *B. anthracis* spores were sent through the US postal system (4 were recovered). Twenty-two cases of anthrax resulted (11 inhalational, 11 cutaneous), and 5 people died from inhalational anthrax. In 2008, the FBI announced a breakthrough in the case, code named "Amerithrax," concluding that Dr. Bruce Ivins, an anthrax researcher at the US Army Medical Research Institute of Infectious Diseases, had perpetrated the attack. Dr. Ivins committed suicide before charges could be filed, and the case was never tried.<sup>11</sup> Other organizations have questioned the FBI's conclusion.<sup>12</sup>

## Transmission

Humans may contract anthrax following contact with infected animals or contaminated animal products, or by breathing in aerosolized spores. Anthrax is *not* contagious, meaning it cannot be transmitted from person to person like influenza or common cold viruses.<sup>1</sup> Though anthrax is not contagious, few cases of person-to-person transmission have resulted from contact with discharges from cutaneous lesions; therefore, standard barrier isolation precautions are recommended for

hospitalized patients with all forms of anthrax infection. There is no data to support the use of use of high-efficiency particulate air filter masks or other measures to provide protection from airborne or droplet transmission when in close proximity to an infected individual. Additionally, there is no need to provide prophylaxis to close contacts of an infected patient.<sup>3</sup>

## Decontamination

The greatest risk of anthrax infection occurs during the period when spores are first aerosolized (primary aerosolization). After this primary period, *B. anthracis* spores will settle on the ground and other surfaces, possibly in high concentrations, at which point there is a risk that *B. anthracis* may become airborne again (secondary aerosolization). However, the extent to which re-aerosolized spores are infectious is not known. Re-aerosolization depends on several variables, including:

- Concentration of spores present
- Type of surface where spores land
- Type of movement in the area that could disturb spores (ie, wind, foot traffic, indoor air movement/ventilation, etc.).<sup>3</sup>

Surfaces should be decontaminated to help eliminate the risk of secondary aerosolization, and this should be done in coordination with local health, public health, and environmental authorities.<sup>13</sup>

## Diagnosis

The diagnosis of naturally occurring anthrax should be considered if there are symptoms and signs consistent with the disease and a history of contact with sick animals or animal skins, or travel to an area where anthrax is endemic. The symptoms of anthrax—both the physical signs of cutaneous anthrax and the radiographic signs of inhalational anthrax—are often quite characteristic if the clinician is attuned and clinical presentation is consistent with the diagnosis. Thorough evaluation may be required, as several differential diagnoses are possible in the case of each form of anthrax infection.<sup>4</sup> The expected hallmark of the use of an aerosolized anthrax weapon would be a sudden surge of patients presenting with symptoms of severe pneumonia, meningitis, and/or sepsis.<sup>7</sup>

*B. anthracis* grows quickly and easily in routine culture. In addition, there are several rapid diagnostic tests for identifying anthrax at reference laboratories, but none are available widely in ordinary hospital laboratories.<sup>3</sup>

## Post-Exposure Prophylaxis and Treatment

Early diagnosis and prompt initiation of appropriate treatment are crucial for improving survival in anthrax cases. In November 2023, CDC published updated recommendations for both PEP and treatment for natural and intentional exposures to anthrax, such as a wide-area aerosol release of *B. anthracis* spores. The recommendations are based on systematic reviews of the literature regarding antimicrobial drug activity against *B. anthracis*, antimicrobial drug efficacy for PEP and treatment, and antitoxin efficacy for PEP and treatment.



Many antimicrobial drugs can be used to prevent or treat anthrax infection, including 6 approved for those indications by the Food and Drug Administration (FDA) and about 20 others that are not FDA-approved for anthrax prevention or treatment. While empiric treatment or prophylaxis after exposure is necessary to save lives, it is essential to conduct antimicrobial drug susceptibility testing. Based on the results, modifications to antimicrobial drug choices may be required. CDC recommends several first-line antimicrobials, including ciprofloxacin, doxycycline, levofloxacin, or, less commonly, minocycline; however, suggested antimicrobials or combinations with other drug classes such as antitoxins, dosing, and length of treatment vary by type of infection and population.<sup>7</sup>

**Table 2. CDC Recommendations for Prevention and Treatment of Anthrax<sup>7</sup>**

Condition (exposure to or infection with <i>B. anthracis</i> )	Corresponding Table in 2023 Guidelines
Empiric PEP after exposure to <i>B. anthracis</i>	Nonpregnant adults: <a href="#">Table 6</a> Pregnant or lactating adults: <a href="#">Table 9</a> Children aged ≥1 mo to <18 yrs: <a href="#">Table 12</a> Preterm and full-term newborns: <a href="#">Table 15</a>
Empiric treatment regimens for individuals with cutaneous anthrax without signs and symptoms of meningitis	Nonpregnant adults: <a href="#">Table 7</a> Pregnant or lactating adults: <a href="#">Table 10</a> Children aged ≥1 mo to <18 yrs: <a href="#">Table 13</a> Preterm and full-term newborns: <a href="#">Table 16</a>
Empiric treatment regimens for individuals with systemic anthrax with or without meningitis	Nonpregnant adults: <a href="#">Table 8</a> Pregnant or lactating adults: <a href="#">Table 11</a> Children aged ≥1 mo to <18 yrs: <a href="#">Table 14</a> Preterm and full-term newborns: <a href="#">Table 17</a>

## Countermeasures

### Vaccines

The FDA has licensed 2 anthrax vaccines, both manufactured by Emergent BioSolutions, Inc. BioThrax® (Anthrax Vaccine Adsorbed [AVA]) is approved for pre-exposure prophylaxis of disease in persons aged 18-65 years at high risk of exposure to anthrax and for PEP following suspected or confirmed anthrax exposure in conjunction with antibiotic treatment. The vaccine can be used under an appropriate regulatory mechanism, such as emergency use authorization, for individuals aged < 18 years or >65 years who are exposed to anthrax.<sup>7</sup> As pre-exposure prophylaxis, a 5-dose series is required for immunization, with annual boosters. When used as PEP in conjunction with a course of antimicrobials, a 3-dose series is required at 0 weeks, 2 weeks, and 4 weeks after exposure.<sup>14</sup>

In July 2023, the FDA approved a second-generation anthrax vaccine from Emergent BioSolutions, marketed as CYFENDUS™ (Anthrax Vaccine Adsorbed, Adjuvanted), for PEP following suspected or confirmed exposure to *B. anthracis* in persons aged 18-65 years when administered in conjunction with recommended antimicrobial drugs.<sup>15</sup> The vaccine is based on the same AVA platform as BioThrax® with an additional adjuvant, CPG7909, to induce a rapid immune response to *B. anthracis*. Unlike the 3-dose, 28-day primary series dosing schedule for BioThrax®, CYFENDUS™ is administered as a 2-dose series, 2 weeks apart, providing a more rapid onset to protection.<sup>16</sup> Notably, CYFENDUS™ elicited a higher immune response compared with BioThrax® in persons aged >65 years; however, anthrax vaccine use in older adults, pregnant or lactating individuals, or children would be informed by data available at the time of an anthrax event.<sup>7</sup>

### Antitoxins

There are currently 3 FDA-approved antitoxins available for treatment of inhalational anthrax, in combination with antimicrobials: obiltoximab (ANTHIM®) and raxibacumab, both monoclonal antibody injections, and anthrax immunoglobulin intravenous (AIGIV; ANTHRASIL™), which contains polyclonal antibodies.<sup>7,17-21</sup> Antitoxins are important tools used in conjunction with antimicrobial treatment, and, less often, vaccination, as they neutralize the toxins released into the body by the bacteria, while the antimicrobials target the bacteria.<sup>19-21</sup> If coadministration of an anthrax vaccine and antitoxin is indicated, the only antitoxin that should be used is raxibacumab.

Notably, because antitoxins are administered intravenously and are somewhat (ie, the monoclonals) to moderately (ie, the polyclonal) less efficacious than antimicrobial drugs, all oral antimicrobial drugs are preferred over antitoxins for PEP. Additionally, in the case of a wide-area aerosol release of *B. anthracis* spores, prioritizing antitoxins for treatment over PEP is recommended, as they are likely to provide greater benefit as adjunctive treatments. Both monoclonal antibodies can cause hypersensitivity reactions and anaphylaxis, so patients should receive diphenhydramine before receiving either monoclonal antitoxin.<sup>7</sup>

### Strategic National Stockpile

The US government has purchased the 2 anthrax vaccines and 3 antitoxins to be held in the Strategic National Stockpile (SNS) and deployed in the case of an anthrax emergency.<sup>22-24</sup> In fact, anthrax vaccines and medicines for PEP were deployed quickly from the SNS to more than 50 sites in 11 states and Washington, DC, within 5 hours of recognizing the September 2001 anthrax attacks.<sup>25</sup> From fiscal years 2015 through 2021, the US Department of Health and Human Services (HHS) obligated nearly US\$5 million in non-COVID-19 appropriations to purchase medical countermeasures for the SNS, with 50% of this funding going toward anthrax supplies.<sup>26</sup>

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## See also:

US Centers for Disease Control and Prevention. Anthrax. Updated November 20, 2020. Accessed November 20, 2023. <https://www.cdc.gov/anthrax/index.html>