Anthrax

Anthrax also known as **Woolsorter's disease**, **Black bane** or **Ragpicker's disease** refers to any of the diseases caused by the bacterium *Bacillus anthracis*. *B. anthracis* is a organism found in soil that can infect both animals and humans. Under certain environmental conditions, it forms into **tough spores** which are dormant and can survive for decades. These spores can survive very harsh conditions while they wait for an animal or human host. Once inhaled or otherwise in contact with an animal or person, the spores germinate into harmful colonies of bacteria.

Anthrax affects livestock far more often than humans. However, as demonstrated by the 2001 anthrax attacks in the United States, anthrax can be used as a biological weapon. There are several forms of anthrax, with the most severe being inhalational anthrax. Anthrax **cannot be transmitted from one person to another**.

Types

In humans, anthrax occurs in several forms:

- **Cutaneous**, affecting the skin
- **Inhalational**, in the lungs
- **Gastrointestinal**, in the digestive tract
- **Meningoencephalitis** or **meningitis**, or infection of the brain and/or its linings

The non-cutaneous forms of the disease are sometimes loosely referred to as visceral anthrax.

Cutaneous anthrax is the most common form of the disease, accounting for about 95% of cases.[1] It is often seen in parts of Asia and sub-Saharan Africa, but the last case in the US prior to the 2001 bioterrorist attacks was in 1992.[2] [3]

Inhalational anthrax accounts for most of the remaining 5%. Gastrointestinal anthrax is rare and is contracted by eating contaminated meat.

Symptoms

Cutaneous anthrax

Cutaneous anthrax is an infection of the skin with *Bacillus anthracis*. People with cuts or open sores can get cutaneous anthrax if they come in direct contact with the bacteria or its spores, usually through **contaminated animals or animal products**. (People who handle carcasses or wool, such as rug dealers, are at particular risk.) At the point of contact with the bacterium, the skin **reddens, swells and becomes itchy**, often looking like an insect bite. Within one to two days of exposure, the spot develops into an **ulcer with blisters** surrounding it. In seven to 10 days this ulcer develops a brown or **black scab** which usually dries up in one to two weeks and drops off, leaving a permanent scar. People with this form of anthrax can also have fevers, tiredness, headaches, and swelling of lymph nodes in the area of the affected skin. If left untreated, cutaneous anthrax can be fatal about 20% of the time.[4]. However, with appropriate treatment, cutaneous anthrax is deadly in only 1% of cases. In the United States, about one to two cases occur per year, according to the CDC. [5]

Inhalational anthrax

Inhalation anthrax is the **most deadly form** of the disease. When a person inhales the spores of *B. anthracis*, the spores germinate and the bacteria infect the lungs, then spread to the lymph nodes in the chest. As the bacteria grow, they produce two kinds of deadly toxins. Symptoms usually appear one to seven days after exposure, but they may not appear for a month or more. **Fever, nausea, vomiting, body aches, and fatigue** are among the early symptoms of inhalational anthrax. The disease progresses to **labored breathing, shock, and often death**. Historically, the mortality rate for naturally-occurring inhalational anthrax has been 89%–96%.[6] But in the 2001 anthrax attacks, 11 people were infected with inhalational anthrax and six survived, a mortality rate of 45%. Prior to 2001, the last known case of inhalational anthrax worldwide was a nonfatal case in a Swiss textile worker in 1980, and the last U.S. case in 1976, when a California craftsman died after being exposed to imported yarn contaminated with anthrax spores.[6]

Gastrointestinal anthrax

People can get gastrointestinal anthrax from eating meat contaminated with anthrax bacteria or their spores. Symptoms are **stomach pain, loss of appetite, diarrhea, and fever**. Antibiotic treatment can cure this form of anthrax. However, if left untreated, it may kill half of those who get it. Gastrointestinal anthrax occurs naturally in warm and tropical regions of Asia, Africa, and the Middle East. There have been no confirmed cases of gastrointestinal anthrax in the United States, although a Minnesota farm family may have experienced symptoms

of the disease in 2000 after eating meat from a steer that had anthrax.[7] The last known case of gastrointestinal anthrax worldwide was in France in 1992, in an immigrant who also developed pulmonary and meningeal anthrax.[8]

Anthrax meningoencephalitis

Anthrax can cause an inflammation of the brain and its meninges, called meningoencephalitis. This form of the disease occurs as a **complication of pulmonary or cutaneous anthrax**.[9] It is usually quickly fatal.

Cause

Anthrax is caused by *Bacillus anthracis*, a bacterium that lives in soil and, like some other related bacteria, has developed a survival tactic that allows it to endure for decades under the harshest conditions. An anthrax bacterial cell can transform itself into a spore, a very hardy dormant phase that can withstand extreme heat, cold, and drought, without nutrients or air. When environmental conditions are favorable, the spores will germinate into colonies of bacteria. For example, a grazing animal may ingest spores that begin to grow, spread, and eventually kill the animal. The bacteria form spores in the carcass and then return to the soil to infect other animals in the future. While its spore form allows the bacteria to survive in any environment, the ability to produce toxins is what makes *B. anthracis* such a potent killer. Together, the hardiness and toxicity of *B. anthracis* make it a formidable bioterror agent.

Its **toxin** is made of three proteins: protective antigen, edema factor, and lethal factor.

- **Protective antigen** binds to certain cells of an infected person or animal and forms a channel that permits the other two toxins to enter those cells.
- **Edema factor**, once inside the cell, causes fluid to accumulate at the site of infection. Edema factor can contribute to a fatal build-up of fluid in the cavity surrounding the lungs. It also can inhibit some of the body's immune functions.
- **Lethal factor** also works inside the cell, disrupting a key molecular switch that regulates the cell's functions. Lethal factor can kill infected cells or prevent them from working properly.

Diagnosis

Anthrax is diagnosed by isolating the bacteria *B. anthracis* from tissues or blood of suspected cases, or by finding specific antibodies against *B. anthracis* in the blood of persons with suspected cases. The first identification that is often made is the genus of the organism, *Bacillus*. This is done with a common, easily-performed test called a Gram stain and by growing colonies on a culture plate.

When *Bacillus* organisms are noted, then the species has to be determined. (The only other *Bacillus* species that is dangerous to humans is called *Bacillus cereus*.) Further tests include looking at the bacteria under the microscope; tests for motility (the germ's ability to move), lysis (breaking apart the outer coat of the bacteria) by a special virus called a gamma phage; tests for capsule production and visualization; tests for red blood cell rupture; and special staining called malachite green staining, which helps visualize spores. Confirmation of B. anthracis includes more specific and intricate tests. Epidemiologic investigation in response to threats of exposure to *B. anthracis* may employ taking nasal swabs of potentially exposed persons in addition to environmental sampling to determine the extent of exposure. Nasal swabs and screening, however, should not be relied upon as guides for prevention or treatment.

Molecular tests for anthrax

PCR

Polymerase chain reaction (PCR) is a laboratory method used to detect genetic material, such as DNA, from organisms. It can be used to diagnose disease by identifying DNA commonly found in **Bacillus anthracis** strains. PCR can also be used to classify the organism into subtypes by amplifying specific genetic material and comparing it with known strains of *B. anthracis* to see if it matches. When PCR is used for subtyping, the amplified genetic material is usually further analyzed by other molecular methods, such as DNA sequencing.

MLVA

For subtyping, CDC uses a method called multi-locus variable-number of tandem (consecutive) repeat analysis (MLVA). MLVA examines a number of B. anthracis' DNA segments within the that have specific repeated patterns. These repeats may differ by sequence, length, and the number of times that they are repeated. Different types of repeats and the number of times they are repeated provide a specific pattern that will identify different strains of the organism. More than 100 different strains of *B. anthracis* have been identified with this method.

Environmental sampling

Environmental sampling is means testing air, soil, dust, water, and/or physical surfaces for bacteria, chemicals, and radiological materials. In the case of anthrax, this is used to identify its location and presence in the environment. Sampling is conducted if there is a possibility of *B. anthracis* contamination. Environmental sampling to determine the presence of Bacillus anthracis spores in indoor environments is an important tool for assessing risk for

exposure, though, the presence of *B. anthracis* does not necessarily mean people will get the disease. Environmental sampling can also be used to determine the extent and degree of contamination, to support decisions regarding the need for medical treatment or cleanup, and to provide guidance regarding when cleanup is adequate to permit re-entry into an area. Currently, no occupational or environmental exposure standards exist for *B. anthracis* spores. In addition, there are presently no validated sampling and analytical methods specifically for *B. anthracis* in environmental samples. It isn't known how efficient various collection methods are (e.g, swabs, wipes, filters) for typical indoor surfaces (e.g., furniture, carpet, letters, clothing, vent filters). The effect of varying concentrations of *B. anthracis*-containing particles and dust loading on sampling efficiency has not been studied. Further, the efficiency of removal of *B. anthracis* spores from the sample collection media has not been adequately evaluated, nor have limits of detection been established. Culture with positive identification of *B. anthracis* (CDC culture method) is the confirmatory test for environmental samples. At the present time, PCR- or immune-based assays for B. anthracis should not be used alone, but should be confirmed with samples analyzed by culture methods.[10]

Treatment

If diagnosed early, anthrax is easily treated with antibiotics. Unfortunately, infected people often confuse early symptoms with more common illnesses and do not seek medical help until severe symptoms appear. By that time, the destructive anthrax toxins are at high levels, making treatment difficult. This is because antibiotics can kill the bacteria, but they have no effect on the anthrax toxins which cause most of the damage. The CDC has provided recommendations for treatment.[11][12] For prompt diagnosis and effective treatment of anthrax, the **disease must be suspected and antibiotics rapidly given**. Because of the death rate of inhalational anthrax, two or more antibiotics are used, although no controlled studies in humans have been performed to validate this. There is some informal clinical experience to support a multiple drug approach. Studies in nonhuman primates and other animals and in vitro data (experiments done "under glass", e.g. in a test tube), show that ciprofloxacin or doxycycline should be used for initial intravenous therapy (medicine given through a needle in a vein) until the bacteria can be grown on a plate and tested for drug sensitivities. Other agents that may be used with ciprofloxacin or doxycycline include rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, and clarithromycin. Other than for penicillin, limited or no data exist regarding the use of the other antibiotics. Cephalosporins and trimethoprim-sulfamethoxazole (Bactrim) should not be used for therapy. Penicillin is labelled for use in treating inhalational anthrax. However, penicillin resistance genes have been found in some *B. anthracis*. For this reason, penicillin is not recommended for use alone in the treatment of anthrax that has spread throughout the body (called "systemic" anthrax). Toxin-mediated sickness is a major complication of systemic anthrax. Corticosteroids have been suggested for inhalational anthrax associated with extensive edema (collection of fluid in the tissues, leading to swelling), life-threatening breathing problems, and meningitis (infection of the tissues surrounding the brain and spinal cord).

Specific antibiotic guidelines at the present time are as follows:

- Cutaneous (skin) anthrax: **Ciprofloxacin** 500 mg by mouth twice a day for 60 days; alternatively **doxycycline** 100 mg by mouth twice a day for 60 days.
- Inhalation and gastrointestinal anthrax: **Ciprofloxacin** 400 mg every 12 hours plus **clindamycin** 900 mg every 8 hours, with or without **rifampin** 300 mg every 12 hours. All given by vein for 60 days.

Which antibiotics are used will depend on the severity of the illness, whether the infected person is allergic to specific medications, and whether *B. anthracis* is susceptible to a particular antibiotic.

Prevention

General precautions

In areas where anthrax is common, such as South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East, people should avoid contact with livestock and animal products, and should not eat potentially contaminated meat. Anthrax cannot be transmitted from person to person.

Vaccine

In 1970, the Food and Drug Administration (FDA) approved an anthrax vaccine for humans, which is licensed for limited use. It is currently given to members of the military and individuals most at risk for exposure to the bacteria in their jobs, such as slaughterhouse workers, veterinarians, laboratory workers, and livestock handlers. The vaccine does not contain the entire bacteria. Rather, it is made mostly of the anthrax protective antigen protein, so people cannot get anthrax infection from the vaccine. Health experts currently do not recommend the vaccine for general use by the public because anthrax illness is rare and the vaccine has potential serious side effects in some people. Researchers have not determined the safety and effectiveness of the vaccine in children, the elderly, and people with weakened immune systems. Although research trials indicate that three to four doses of anthrax vaccine can provide protective immunity, the recommended vaccination schedule is **six doses given over an 18-month period**. There is also research underway to develop a new vaccine that can be used to protect the public quickly in the event of a bioterror attack.

Research

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, conducts and funds research to improve our ability to prevent, diagnose, and treat anthrax. Anthrax research was underway prior to the 2001 bioterror attack, but it has expanded since then. New research findings are improving our understanding of how *B. anthracis* causes disease and how to better prevent and treat it. Several biologic factors contribute to *B. anthracis*' ability to cause disease. NIAID researchers and grantees are uncovering the molecular pathways that enable the bacterium to form spores, survive in people, and cause illness. Scientists envision this basic research to be the pathway to new vaccines, drugs, and diagnostic tools.

Natural history of anthrax

One goal of NIAID researchers is to look at the infectious disease process over time, from initial infection through the clinical course and beyond recovery. Some of the survivors from the 2001 anthrax attacks are enrolled in a long-term clinical study for this purpose. In this type of study, many years of clinical observation are needed for definitive results. Because the medical literature does not include findings regarding long-term complications in anthrax survivors, information gained in this study will be valuable to patients and health care workers.

Toxin biology

Scientists are studying anthrax toxins to learn how to block their production and action. Recently, NIAID-supported scientists have shown that protective antigen can bind edema factor and lethal factor at the same time, forming a greater variety of toxin complexes than were previously known. This finding could help researchers develop antitoxin therapies. Previously, scientists discovered the three-dimensional molecular structure of the anthrax protective antigen protein bound to one of the receptors (CMG2) it uses to enter cells. Using a specific fragment of the CMG2 receptor protein, researchers have been able to block the attachment of protective antigen in test-tube experiments, thereby inhibiting anthrax toxin activity. NIAID-funded scientists also have synthesized a small molecule that blocks anthrax toxin in cell culture and in rodents. The molecule blocks the pore formed by anthrax protective antigen. Blocking the pore effectively prevents lethal factor and edema factor toxins from entering cells. Scientists anticipate that these findings will lead to new and effective treatments.

Anthrax bacterium genome

Genes are the instructions for making proteins, which in turn build components of the cell or carry out its processes. The instructions that dictate how bacteria work are encoded within their genes. Bacteria keep most of their genes in a chromosome, a very long stretch of DNA. Smaller circular pieces of DNA called plasmids also carry genes that bacteria can swap with each other. Because plasmids often contain genes for toxins and antibiotic resistance, knowing the DNA sequence of such plasmids is important. Scientists have sequenced plasmids carrying the toxin genes of *B. anthracis*. In addition, researchers have sequenced the complete chromosomal DNA sequence of several B. anthracis strains, including one that killed a Florida man in the 2001 anthrax bioterror attack. By comparing the DNA blueprints of different B. anthracis strains, researchers are learning why some strains are more deadly than others. Small variations among the DNA sequences of different strains may also help investigators pinpoint the origin of an anthrax outbreak. Knowing the genetic fingerprint of B. anthracis might lead to gene-based detection mechanisms that can alert scientists to the bacteria in the environment. It could also allow rapid diagnosis of anthrax in infected people. Variations between strains might also point to differences in antibiotic susceptibility. Knowing these susceptibilities allows doctors to start the appropriate treatment right away. Scientists are now analyzing the *B. anthracis* genome sequence to determine the function of each of its genes. Scientists are also learning how those genes interact with each other or with host-cell components to cause disease. Knowing the sequence of *B. anthracis* genes will help scientists discover key bacterial proteins that can then be targeted by new drugs or vaccines.

Spore biology

B. anthracis spores are essentially dormant and must wake up, or germinate, to become reproductive, disease-causing bacteria. Researchers are studying the germination process to learn more about the signals that cause spores to become active once inside an animal or person. Efforts are under way to develop models of spore germination in laboratory animals. Scientists hope those models will enable discoveries leading to drugs that block the germination process in *B. anthracis* spores.

Host immunity

People who get anthrax make antibodies to the protective antigen protein. Similar antibodies appear to block infection in animals. Recent studies also suggest that some animals can produce antibodies to components of *B. anthracis* spores. Those antibodies, when studied in a test tube, prevent spores from germinating and increase their uptake by the immune system's bacteria-eating cells. These discoveries suggest that scientists might be able to develop a vaccine to fight both B. anthracis cells and spores. Researchers also are studying how the immune system responds to B. anthracis infection. Part of the immune system response, known as adaptive immunity, consists of B and T cells (types of white blood cells) that specifically recognize components of the anthrax bacterium. The other type of immune response, innate immunity, aims more generally to combat a wide range of microbial invaders. Innate immunity likely plays a key role in the body's front-line defenses. Scientists are conducting studies of how these two arms of the immune system fight infection, including how *B. anthracis* spore germination affects individual immune responses. In another study, NIAID-supported scientists have discovered a potential target for developing new measures to prevent and treat anthrax toxicity. Their study shows that a human gene called LRP6 plays a role in the delivery of anthrax toxins into cells. Antibodies directed against LRP6 were found to protect cell cultures from anthrax lethal toxin. These results suggest that targeting LRP6 may prove useful in developing ways to protect against the effects of accumulated toxin.

Vaccine

NIAID is supporting research on anthrax vaccines that might prevent infect with fewer doses than the currently licensed vaccine. The new vaccines, called recombinant protective antigen, or rPA vaccines, are based on the gene for just one anthrax toxin. These vaccines have been tested in rabbits and monkeys. They have completed two phases of clinical trials in humans. The rPA vaccines appear to produce an effective immune response in people with intact immune systems. In general, the goal is to make rPA vaccines that are safer, more reliable, can be produced in large quantities, and may also be given to people with compromised immune systems.

Diagnostics

Research is under way to develop improved techniques for spotting *B. anthracis* in the environment and diagnosing it in infected individuals. As mentioned previously, a key part of that research is the functional genomic analysis of the bacterium. This should lead to new genetic markers for sensitive and rapid identification. Genomic analysis will also reveal differences in individual *B. anthracis* strains that may affect how those bacteria cause disease or respond to treatment. Several companies market rapid tests for detecting anthrax. The US Postal Service employs some of these systems for detecting mail contaminated with anthrax spores.

Therapies

Following the discoveries of how the protective antigen and lethal factor proteins interact with cells, researchers are screening thousands of small molecules in hopes of finding an anti-anthrax drug. In addition, NIAID is working with FDA, CDC, and the Department of Defense to accelerate testing of collections of compounds for their effectiveness against inhalational anthrax. Many of those compounds already have been approved by FDA for other conditions and therefore could quickly be approved for use in treating anthrax. NIAID is also seeking new drugs that attack *B. anthracis* at different levels. These include agents that prevent the bacterium from attaching to cells, compounds that inhibit spore germination, and inhibitors that block the activity of key enzymes such as anthrax lethal factor. NIAID also plans to develop anti-anthrax compounds in sufficient purity and quantity for preclinical testing. NIAID-supported scientists have solved the structure of enzymes called sortases, which are known to anchor bacterial surface proteins to the cell walls. These enzymes may be essential to bacterial survival, and therefore could be an attractive potential target for therapies. Scientists have designed a compound that blocks anthrax toxins from attaching to receptors on the surface of host cells in animal models. If the toxin cannot attach to and enter the cell, it is effectively neutralized. The new inhibitor is much more potent than current therapies and shows promise against some antibiotic-resistant strains as well. The general concept could also be applied to designing inhibitors for other pathogens. Researchers have also found that certain types of human antibodies protect against inhalation anthrax in three animal models. New anthrax therapies, such as monoclonal and polyclonal antibodies that can neutralize anthrax toxins, are being further developed.

History

Although anthrax has been known since antiquity, it was not always clearly distinguished from other diseases with similar manifestations. Scholars think that the fifth and sixth biblical plagues, as well as the "burning plague" described in Homer's Iliad, were anthrax.[13] However, it was Virgil (70-19 BC) who provided one of the earliest and most detailed descriptions of an anthrax epidemic in his Georgics. Virgil also noted that the disease could spread to humans.

Over the next fifteen hundred years, Europe witnessed sporadic outbreaks of anthrax. The most severe outbreaks occurred in fourteenth-century Germany and seventeenth-century Russia and Central Europe. Despite the threat these outbreaks posed to livestock, it was only in 1769 that Jean Fournier classified the disease as anthrax or charbon malin ("malignant carbon"), a name undoubtedly derived from the black skin lesions of cutaneous anthrax. Fournier also noted a link between those who worked with animal hair or wool and a susceptibility to anthrax.

By the mid 1870s, most researchers believed that anthrax was an infectious disease, but there was disagreement as to its specific cause. In 1876, Robert Koch, a Prussian physician, isolated the anthrax bacillus and pointed out that the bacillus could form spores which remained viable, even in hostile environments. According to Koch, "this remove[d] all doubt that *Bacillus anthracis* is the actual cause and contagium of anthrax." Shortly after this, John Bell linked anthrax with "woolsorter disease" and developed a procedure to disinfect wool.

William Greenfield was the first to immunize livestock successfully against anthrax in 1880. However, credit for the use of a live vaccine against anthrax is usually given to Louis Pasteur, who tested a heat-cured vaccine on sheep in 1881. Celebrated in the contemporary French press, Pasteur's vaccine solidified his status as one of France's greatest scientists. By the late twentieth century, extensive animal vaccination programs led to an overall decline in anthrax, although the disease still occurred in poor and unstable regions. For example, between 1978 and 1980, a civil war in Zimbabwe caused a breakdown in veterinary care; the result was an anthrax epidemic that spread from animals to humans.

Without the vaccine, animals are highly vulnerable to this disease, which makes it an effective form of biological warfare. During World War I, German agents were sent to five neutral countries (Romania, Spain, Norway, the United States and Argentina) with instructions to infect animal shipments sent to the Allies. Targeted animals included sheep, cattle, horses, mules, and, in Norway, reindeer. Animals were infected either by having anthrax injected directly into their blood or by being fed sugar laced with anthrax.

In the inter-war period, attention shifted to human anthrax and its potential as a biological weapon. Although the Geneva Protocol of 1925 prohibited biological weapons, several nations, including the United States, experimented with anthrax during the 1930s and 1940s. In the late 1930s, the Japanese Imperial Army performed covert experiments on anthrax and began deploying biological weapons in Manchuria. During World War II, American, British and Canadian laboratories began developing biological weapons, especially anthrax. By 1944, the Allies had developed thousands of anthrax bombs. Even though Hitler had officially forbidden biological weapons research, the Nazis conducted anthrax and biological weapons research at a secret facility in Poland.

Following World War II, the Americans and British continued to research anthrax and its potential for biological warfare. The American program was centered at Fort Detrick, Maryland. In 1969, Richard Nixon limited biological weapons research to defensive purposes only, saying "mankind already carries in its own hands too many of the seeds of its own destruction."

Throughout the 1950s, the Communicable Disease Center (later re-named The Centers for Disease Control and Prevention) investigated outbreaks in Pennsylvania, Colorado, North Carolina, New Hampshire, and Louisiana. Most of the studies were concentrated in Pennsylvania, and the CDC's goal was fivefold:

1. To discover the cause of anthrax among workers in wool and animal hair industries
2. To determine the particle size of anthrax-contaminated aerosols in industry
3. To assess the effectiveness of an anthrax vaccine for humans
4. To study the epidemiology and epizootiology of anthrax in selected outbreaks
5. To collect and study different strains of *Bacillus anthracis*.

In 1955, five human cases of anthrax occurred within a three-month period at a mill in Monroe, North Carolina. The source of the disease was ultimately traced to a shipment of wool from Iran and Iraq. In 1957, nine human cases occurred at a mill in Manchester, New Hampshire. Four workers ultimately died of inhalation anthrax. The potential of anthrax to resurface because of its sporulated form was made clear when nine years later a worker at a machine shop across from the mill died of inhalation anthrax. The New Hampshire mill was sealed in 1968 and ultimately decontaminated in 1971.

According to CDC, the last case of inhalation anthrax in the United States before 2001 occurred in 1976. A craftsman working with imported and infected yarn in California died as a result of the disease. Before 2001, the last case of cutaneous anthrax in the United States occurred in 2000. A 67-year-old resident of North Dakota who participated in the disposal of five anthrax-infected cows contracted the cutaneous form of the disease. Upon being treated with antibiotics, the patient recovered. Treatment for anthrax has varied. In 1903, a major breakthrough occurred when anthrax was successfully treated with serum therapy—administration of blood serum which contains the antibody needed to fight anthrax. Severe adverse reactions to this treatment were common. Serum therapy was replaced by antibiotics in the 1940s. Since then, antibiotics have been the primary form of treatment. In 1970, the Food and Drug Administration licensed an anthrax vaccine. The first human vaccine, a live spore vaccine, had been developed in the Soviet Union in 1943. Two years after the development of the American vaccine, the Biological Weapons Convention (BWC) forbid development, production, stockpiling or retaining biological agents "that have no justification for prophylactic, protective or other peaceful purposes." Ultimately, 140 nations endorsed the BWC.

Several nations have, however, continued to research anthrax as a biological weapon. This was graphically demonstrated by the April 1979 anthrax outbreak in the Soviet city of Sverdlovsk (now Ekaterinburg). Soviet officials insisted that the outbreak was caused by tainted meat and that fatalities were limited to sixty-four people. American intelligence sources claim the death toll reached a thousand and that the aerosolized anthrax originated in a military compound. Records from this outbreak were destroyed in 1990, but the consensus is that the outbreak was a result of biological weapons research. Recent evidence also indicates that Russian scientists may have been experimenting on an anthrax strain which would be resistant to antibiotics. In the 1980s, Iraq bought anthrax from the American Type Culture Collection (Maryland). The 1995 defection and debriefing of a key Iraqi official provided western intelligence experts with evidence of Iraq's biological weapons program and its production of 8,500 liters of anthrax.[14] Since the Gulf War, American troops have been vaccinated against anthrax. Although only 0.007% of those vaccinated have suffered adverse reactions, many troops have resisted vaccination. The complex nature of the vaccine (six inoculations over 18 months with annual boosters) has made public health officials reluctant to endorse vaccinations for the general public.

Public Health

Bioterror

In the fall of 2001, lethal anthrax bacteria were spread deliberately through the U.S. mail. Twenty-two people became ill, and five died. The perpetrator has not been caught. Other cases of bioterrorism with anthrax have also occurred in Russia, Japan and other countries. The most serious case was a leak of anthrax bioweapons in Russia in April, 1979. This affected 94 people and killed at least 64 of them in the Soviet city of Sverdlovsk (now called Ekaterinburg), roughly 850 miles east of Moscow. The Soviet government of the time claimed it was the result of *B. anthracis* tainted meat.[15] During World War I, Germany sent agents to the US and other neutral countries to spread anthrax in livestock meant for export to European allies. However great the potential threat of anthrax in bioterrorist attacks, it is difficult to create an easily disseminated weaponized anthrax. The best illustration of this is the experiences of the Japanese cult Aum Shinrikyo. The cult attempted to release anthrax spores from its mid-rise Tokyo office building laboratory. Although some pets died, no humans were infected. This cult had sophisticated scientists and facilities available to it and later released sarin nerve gas in a Tokyo subway, killing seven people and sickening hundreds. Even before the 2001 bioterror attack, public health officials were concerned about the

potential for such an event. In 1999, the Centers for Disease Control and Prevention (CDC) created lists of high-priority biological agents that terrorists could use to harm civilians. An expert panel of doctors and scientists classified Bacillus anthracis as a Category A bioterror agent. The National Institute of Allergy and Infectious Diseases (NIAID) List of Category A organisms includes those that pose the greatest threats to national security due to their ease of transmission, high rate of death or serious illness, potential for causing public panic, and the special public health measures an epidemic would require. Since the creation of the CDC lists, public health officials and researchers have worked to plan and prepare for a possible bioterror attack. Following the 2001 anthrax attacks, federal funding for these efforts increased significantly.

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