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Review Article

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Anthrax: A Global Health Concern

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Abstract

Anthrax is a severe and extremely contagious infection that can be lethal. It is brought on by *Bacillus anthracis*, a gram-positive, toxic, and spore-forming bacillus. Anthrax has been a known source of disease in both animals and, if rarely, people for centuries. This naturally occurring sickness has been described since ancient times. The majority of herbivores that contract anthrax does so by ingesting soil-borne spores. Modern microbiology allowed Pasteur to create the first effective anthrax vaccine in 1881. Since the late 19th century, the disease's incidence has steadily declined, and animal immunization programs have been substantially scaled back. These developments formed the foundation for the final risk assessment in 1999 and the premise for the re-evaluation of the current threat. The most recent version, which was released in May 1999, served as a solid foundation for the formulation of measures to mitigate the risks that could be brought about by the use of anthrax as a chemical weapon and was useful in the response to the attacks of 2001. However, soil tests from different parts of the world continue to show the presence of anthrax spores. More than 80 years ago, anthrax was first studied as a potential biological weapon, and as of today, at least 17 countries are thought to be developing anthrax-based offensive biological weapons. The impact of both fake and actual threats posed by anthrax bioweapons on society has been demonstrated by recent occurrences in the USA. In addition to providing clinical and laboratory data helpful for biological terror readiness, this page provides a historical overview of anthrax.

Keywords: Anthrax, Contagious infection, Biologicalterrorist, Vaccination

Introduction

Anthrax is particularly appropriate among the many biological agents that could be employed as a biological weapon since it can result in widespread illness and death and eventually cripple a city or region (1, 2). The bacteria Bacillus anthracis is categorized as a category of organism by the Centers for Disease Control and Prevention (CDC). These organisms are easily spread and/or passed from person to person, leading to significant fatality rates (e.g., B. anthracis, smallpox, Yersinia pestis). But Bacillus anthracis, which spreads quickly with the right technical know-how, does not spread from person to person.Despite receiving the proper antibiotic treatment, inhalational anthrax patient mortality rates are significant. Most nations signed the Biological Weapons and Toxins Convention of 1972, which forbade the creation of offensive bioweapons. Though they both signed the agreement, the former Soviet Union (FSU) and Iraq have both admitted to developing offensive bioweapons. Reviewing the anthrax disease and the organism that causes it, B. anthracis, is appropriate in light of the events that occurred after the World Trade Center attacks on September 11, 2001.The Consensus Statements of the Working Group on Civilian Biodefense about anthrax were a part of the broad literature study used to inform this article in the series of papers addressing biowarfare and bioterrorism (3). This consensus article remains a weapon of bioterrorism, so it is important to periodically review the findings and suggestions when new information becomes available. To ensure a cool-headed and reasoned reaction to those risks, the medical community should keep up its education and readiness activities.

Anthrax's history and the present threat

Anthrax has been a known source of illness in animals for ages, as well as, albeit rarely, in people. In the past, people who came into contact with animals or animal products contaminated with B. anthracis spores were at risk of developing human anthrax, which can present as gastrointestinal, cutaneous, or inhalational forms. Ancient manuscripts provide detailed descriptions of the illness, and it has been proposed that the infamous Plague of Athens (430–427 BC) was caused by an epidemic of inhalational anthrax (4). The word "anthrax" actually derives from the Greek word "antracites," which means "coallike," and refers to the typical black eschar found in the cutaneous manifestation of the illness.Virgil, a Roman poet, provided a wonderful description of the murrain of Noricum, the ancient name for the Danube River delta and the eastern Alps (5). Aeneid is Virgil's most famous work, but he also produced four Georgics, which are instructional verse works about agriculture. The third Georgic features a section on veterinary medicine and is devoted to animal husbandry. It describes a zoonosis that took place in the Roman town of Noricum. Sheep, cattle, horses, dogs, and other domestic and wild animals were also impacted by the sickness. The anthrax symptoms are described in great depth, and although if the story has several inaccuracies and indications of artistic license, it also contains a lot of real information, demonstrating that Virgil did, in fact, comprehend the tenacity of the infectious source.

Animals and people were still susceptible to anthrax during the Middle Ages. Anthrax outbreaks in Europe during the 18th century wiped out around half the sheep population (6). As a result of the disease's frequent occurrence among mill employees who had contact with animal fibers tainted with B. anthracis spores, the condition was given the name "woolsorters' disease" in Victorian England. The name is slightly misleading, too, as contact with goat or alpaca hair rather than wool or sheep was more frequently the cause of the infection (7). The illness was also known as "ragpickers' disease," "tanners' disease," "charbon disease," "milzbrand disease," and "Siberian (splenic) illness."Anthrax was a prominent focus of growing biomedical research in the 19th century. Small filiform entities "about twice the length of a blood corpuscle" was found in the circulation of anthrax-infected lambs in 1850 by Pierre Rayer and Casimir-Joseph Davaine (8). This discovery was initially not considered significant since

filiform entities were thought to be illness byproducts. Davaine later asserted that the described corpuscles were the disease-causing germs.

Researchers in Europe, such as Robert Koch in Berlin and Louis Pasteur in Paris, conducted in-depth studies on anthrax in the 1870s (Figure 1). For the first time ever, Koch was able to follow the anthrax bacillus' whole life cycle in 1876 using suspended drop culture methods. He discovered that even in harsh environmental conditions, the bacillus could produce spores that could survive for extended periods of time (8). In 1877, he produced the anthrax bacillus in vitro and infected healthy animals with material from these bacterial cultures to induce the disease. He also hypothesized that the anthrax bacillus might be passed from one host to another. For Koch's well-known hypotheses about the spread of infectious diseases, anthrax served as the model.

At the same time, Louis Pasteur declared his intention to present his own unquestionable proof of the spread of infectious diseases since he thought Koch's study was inconclusive. As one might expect, this led to a protracted argument between the two guys. Louis Pasteur administered his anthrax vaccination to 25 cattle in May 1881 at a farm in Pouilly-le-Fort, a tiny village west of Paris (8, 9). This original vaccination was made with live, weakened microbes. Pasteur then injected a virulent strain of B. anthracis into the vaccinated animals as well as additional cattle. All of the animals who had received vaccinations lived; the others perished. Pasteur believed that this experiment, not Robert Koch's work, had established the validity of the germ hypothesis of illness.Whose study ultimately gave the proof for the germ hypothesis of illness may appear minor to us. The combined efforts of highly renowned medical authorities Koch and Pasteur led to widespread acceptance of their theories and created opportunities for additional research in medical microbiology. Human cases of inhalational anthrax among employees in the textile and tanning industries who handled goat hair, goat skin, and wool were reported in the USA in the early 1900s (7, 10, 11). Human cases of anthrax continued to occasionally occur in humans during this time.

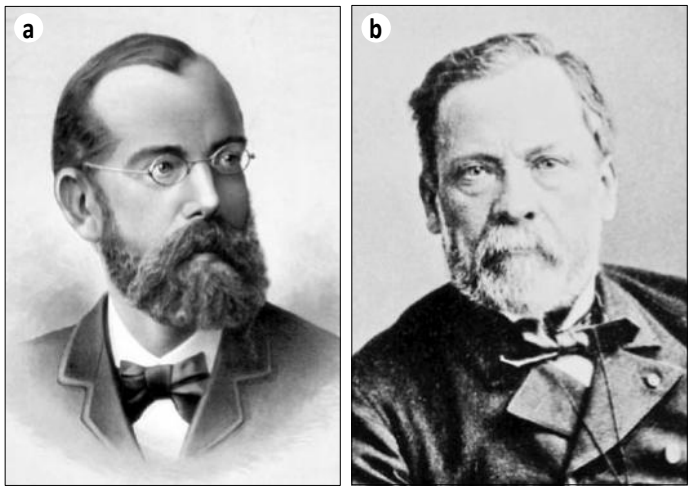


Figure 1. (a) Robert Koch and **(b)** Louis Pasteur. Courtesy of the Images from the **History of Medicine database of the National Library of Medicine.**

In the latter decades of the 20th century, the number of cases significantly decreased thanks to advances in industrial hygiene procedures and limitations on the importation of animal products. However, when anthrax was inhaled, fatality rates remained high (>85%). Improvements in animal husbandry and the processing of animal products, along with vaccinations for humans and animals, were thought to be responsible for the decline in anthrax among farmers and workers in the animal-processing industry (9, 12). The US Army Chemical Corps produced a human anthrax vaccination in the 1950s. In 1970, following over 20 years of usage, a new, enhanced, and approved vaccination was introduced (13). All active and reserve members of the US military forces were required to get vaccinated beginning in 1997.Although the number of instances of naturally occurring human anthrax have considerably dropped over the past century, it is still rather widespread, especially in Asia and Africa, with 20,000 to 100,000 cases per year being reported during the first half of the 20th century. Additionally, significant anthrax epidemics are occasionally reported in Africa, Asia, and South America. Animal anthrax is still widespread among herbivores globally. 1 million

sheep perished in an extensive epidemic in Iran in 1945 (15). With an estimated 2000 cases reported each year, cutaneous anthrax in humans is the most prevalent type of anthrax in the world (16). Between 1945 and 1994, 224 occurrences of cutaneous anthrax were documented in the USA (17). Between 1979 and 1985, Zimbabwe saw the largest documented outbreak, which was exclusively cutaneous.Only a few cases of gastrointestinal anthrax in humans have been documented globally (16, 18, 19), making it a very uncommon type of the illness. However, outbreaks have occasionally been detected in Asia and Africa (20–23). Typically, eating contaminated meat that hasn't been fully cooked leads to gastrointestinal anthrax. A rural area in northern Thailand reported 24 cases of oropharyngeal anthrax in 1982; the outbreak was brought on by the ingestion of tainted buffalo meat (20). Northern Thailand (22) reported 14 cases of gastrointestinal and oropharyngeal anthrax in 1987. As previously indicated, in the second half of the 20th century, the incidence of inhalational anthrax substantially decreased.

A review of inhalational anthrax was published in 1980 by Philip Brachman of the CDC (7). Between 1900 and 1978, there were only 18 cases reported in the USA, with the bulk of those cases happening in certain risk groups, such as workers in goat hair or goatskin mills, as well as in the wool and tannery industries. 16 of these cases resulted in death, and two of these cases were lab-related mishaps (7). As was the accepted view in the western medical establishment, Brachman concluded that inhalational anthrax was "now primarily of historical interest." Subsequent occurrences did not support this. The advent of modern microbiology and the formulation of Koch's postulates throughout the 19th century allowed for the manufacturing of stocks of certain viruses, and various nations tried to create these weapons of biological warfare (1).suggests that during World War I, Germany, England, and France all had extensive biological warfare programs. According to reports, these projects featured covert operations utilizing B. anthracis (anthrax) and Pseudomonas pseudomallei (glanders) as agents (1, 24, 25). Some of the aforementioned nations, along with others like Russia and Japan, started biological weapons research programs during World War II. The events that took place during and after World War II were muddled by numerous accusations and denials. Up until the conclusion of World War II, Japan performed biological weapons research in Manchuria under occupation (1). Once more, B. anthracis was one of the species that was studied and employed the most. Medical researchers infected prisoners even though the German biowarfare effort during World War II was modest in comparison to that of other nations.

A German offensive biological weapons program was never fully realized despite these efforts, which were obviously behind those of other nations.

German officials, on the other side, asserted that the Allies had utilized biological weapons. Given that the British were testing at least one biological weapon—B. anthracis—some of these claims were plausible. In the 1940s, Dr. Paul Fildes oversaw the British effort at Porton Down. By November 1940, he had concluded that dispersing an aerosol of particles that could be maintained in the lungs was the most efficient technique to employ a biological warfare agent.In order for everyone in the target region to inhale effective concentrations of bacteria, it seemed that bursting ammunition filled with a liquid suspension of bacteria was the most successful dissemination mechanism (27, 28). The focus of the British biological warfare program was B. anthracis, and trials using weaponized B. anthracis spores were carried out on Gruinard Island, which is close to Scotland's northwest coast (29). 106 unique bomblets containing anthrax spores made up the so-called N bomb. Due to these studies, the island was heavily contaminated with persistent, live spores. Plans to implement these efforts were surpassed by events near the end of World War II. Gruinard Island was ultimately cleaned up in 1986 with the help of formaldehyde and seawater.

Even though residual contamination of the ground might happen, anthrax is unlikely to seriously affect military activities (19). The studies

conducted on Gruinard Island have demonstrated this. Anthrax thus poses a greater threat to the whole populace. An expert committee of the World Health Organization (WHO) estimated in 1970 that an aircraft release of 50 kg of anthrax over a developed, urban population of 5 million people would result in 250,000 casualties, of which 95,000 would be expected to die without treatment and an additional 125,000 would be severely disabled (30). A situation like this would put a significant amount of strain on medical resources, necessitating the placement of 95,000 dead individuals, antibiotics for 125,000 people for 60 days, and the need for 13,000 people to stay in hospitals. The upshot was unquestionably a complete breakdown of civilian infrastructures and medical supplies. The initial WHO findings were validated by more recent analyses, such as those conducted by the US Congress Office of Technology Assessment in 1993 (31). An economic model created by the CDC (32) suggests that the price per 100,000 people exposed to an anthrax bioweapon strike would be $26.2 billion. Only one incidence of inhalational anthrax has been documented in the USA in the 20th century prior to the bioterrorism-related incident in 2001 (33). Additionally, the FSU experienced the only significant (inhalational) anthrax outbreak of the 20th century. On April 2, 1979, residents of Sverdlovsk, a 1.2-million-person metropolis 1400 kilometers east of Moscow, experienced an anthrax pandemic. The pandemic affected people who resided and/or worked in a constrained downwind area of Compound 19, a Soviet military laboratory for the study of microorganisms. A significant amount of cattle also perished from anthrax in the same region, up to a 50 km distance away (1, 34).

A Russian-language publication linked to the Soviet émigré community in Frankfurt, West Germany, published the first reports of the outbreak in October 1979. It aired a brief piece about a serious germ incident in Russia that caused thousands of deaths, according to estimates (35). Early US and European intelligence believed that this facility was engaged in biological warfare research at the same time and suspected accidental anthrax spore release as the cause of the pandemic. Later, in early February 1980, the highly read German tabloid Bild Zeitung published a tale about an accident that had led to an anthrax cloud at a Soviet military settlement near Sverdlovsk (36). After then, major western publications and magazines started to show interest in the Sverdlovsk anthrax outbreak. Soviet authorities first reported the disease epidemic in Sverdlovsk in 1980, attributing it to cutaneous and gastrointestinal anthrax brought on by eating tainted meat. Later that year, a number of publications about an anthrax outbreak in animals appeared in Soviet medical, veterinary, and legal periodicals.

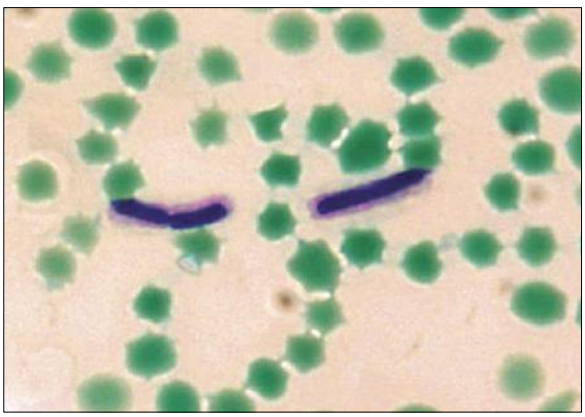
Little more information was made public until 1986, when Matthew Meselson (Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA) reiteratively asked Soviet officials to send outside scientists to Sverdlovsk to look into the occurrence after his initial requests had been denied (1, 36). Eventually, four Soviet doctors who had traveled to Sverdlovsk to deal with the outbreak responded to his request by inviting him to come to Moscow to talk about the occurrence. They came to the conclusion that more research into the epidemiologic and pathoanatomical data was required. Two of these Soviet doctors agreed to travel to the USA in 1988 after being invited to do so in order to continue discussing the incident with both public and private experts. According to these two Soviet scientists, an epizootic south of the city's contaminated animals and meat caused 96 cases of human anthrax, contradicting Soviet Union claims that the anthrax outbreak was brought on by consumption of meat bought illegally. Of these instances, 64 deaths were reported in the first group and none in the second, with 79 cases being reported as gastrointestinal and 17 as cutaneous (36).

The Russian president at the time, Boris Yeltsin, instructed his advisor on environment and health to identify the cause of the pandemic in Sverdlovsk after the dissolution of the Soviet Union. Meselson and his team went back to Russia in 1994 to support these inquiries (1, 36).

They looked through the pathologists' research at a nearby hospital in Sverdlovsk. Dr. Faina Abramova, one of the lead authors, made her private records from a series of 42 autopsies, which represented the majority of the fatalities from the outbreak, available to the public (37). Data on demographics, the environment, and the atmosphere were also examined. The pattern of these 42 fatal cases of anthrax bacteremia and toxemia was determined to be typical to inhalational anthrax as found in nonhuman primates that were experimentally infected. In conclusion, the outbreak was caused by an aerosol that began at Compound 19 based on the small area of human and animal anthrax infections that extended downwind from there (36, 37). Numerous high-ranking members of the FSU military and Biopreparat had fled to western nations at the time of these inquiries. Ken Alibek, a former chief deputy director of Biopreparat, provided a thorough description of the FSU bioweapons program in his account of the Sverdlovsk anthrax outbreak, corroborating earlier studies by US scientists and doctors (38).

The FSU maintained their anthrax research after the Sverdlovsk event at a distant military location in Stepnogorsk, Kazakhstan (1, 38, 39). A novel strain of anthrax was created in both powdered and liquid form as a result of the increased anthrax research. Penicillin and streptomycin were just two of the regularly used medications this strain was resistant to (38). These facts make it abundantly evident that the FSU had the capacity to conduct biological warfare on a scale unmatched by any other country in recorded history. Few of the Biopreparat stations were subject to international disarmament processes after the FSU's eventual collapse and the rearrangement of its provinces and states. Some of the knowledge and research are yet unknown.

The last instance of inhalational anthrax in the USA was in 1976 before October 2001 (33). The first confirmed case connected with the deliberate dissemination of the bacterium was discovered in a journalist in Florida on October 4, 2001 (40-42). Postal workers who had handled tainted mail were responsible for the subsequent 10 instances of cutaneous and inhalational anthrax. In March 2002, a laboratory worker handling *B. anthracis* samples for the CDC inquiry into the aforementioned instances was diagnosed with cutaneous anthrax (9, 10). A detailed investigation into these occurrences led to the hypothesis that the Ames strain of *B. anthracis* may be used for domestic bioterrorism. The case study analysis also improved knowledge of the pathophysiology and diverse clinical manifestations of inhalational anthrax. The cases in 2001 demonstrated that survival can be significantly increased by early diagnosis, enhanced intensive care, and combination antibiotic therapy (10), in contrast to earlier research that indicated a death rate of more than 90%. To better define the antimicrobial regimens and investigate the use of adjuvant treatment modalities including immunoglobulin, antitoxin, corticosteroids, and other toxin inhibitors, more research will be required.



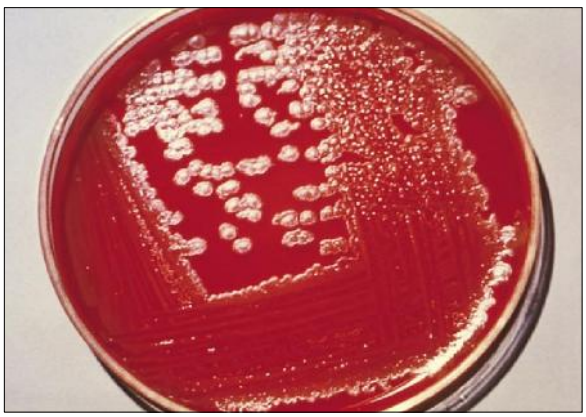


Figure 3& 4. McFadyean capsule stain of *Bacillus anthracis,* grown at 35ºC in defibrinated horse blood. Courtesy of CDC/Larry Stauffer/Public Health Image Library.

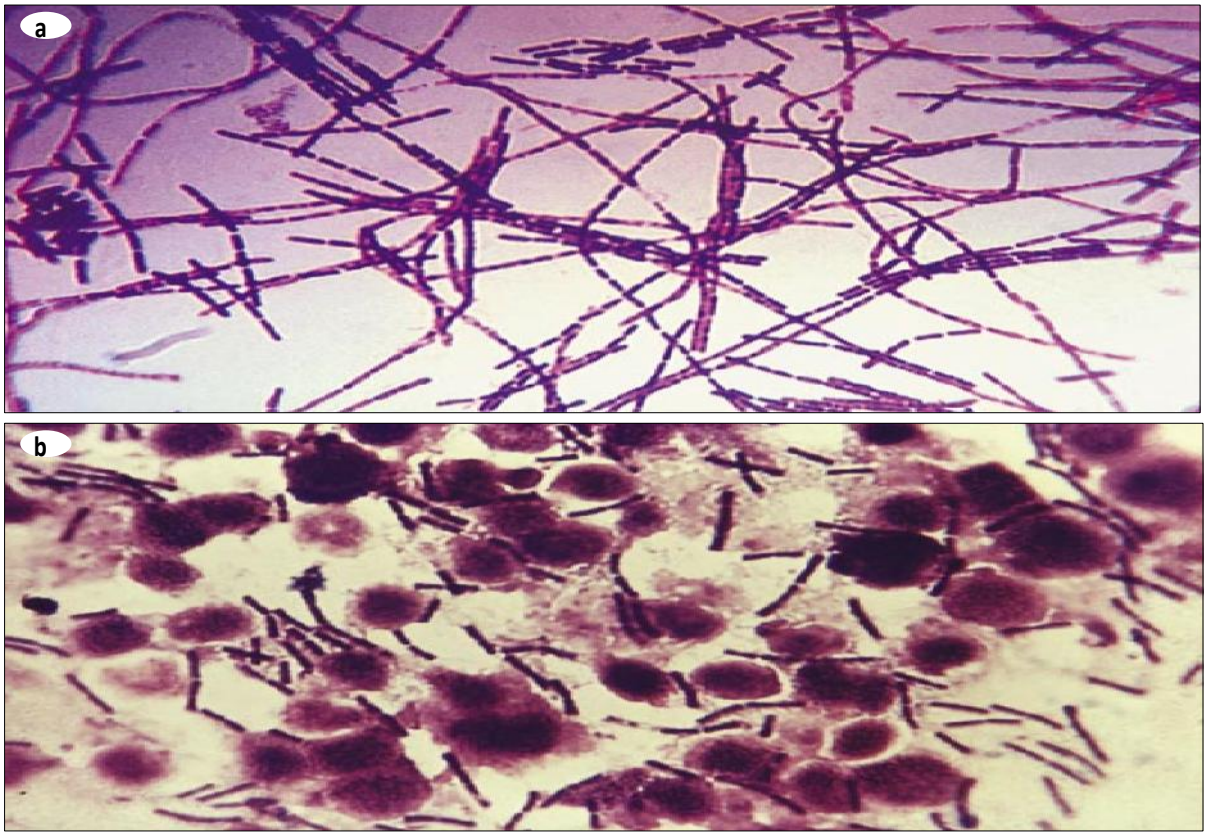


Figure 2. Gram stain of *Bacillus anthracis:* **(a)** from culture; **(b)** from infected tissue. Courtesy of CDC/Public Health Image Library.

Microbiology

There are 70 different species in the Bacillus genus, including *B. cereus*, *B. subtilis*, *B. anthracis*, and *B. thuringiensis*. New Bacillus species that have been proposed have resulted in the extinction of several species. *B. anthracis*, *B. cereus*, and *B. thuringiensis* are all pathovars of the same species, which makes them members of the B. cereus group (43). It is more practical to include *B. anthracis* with the B. cereus group, which according to phenotypic includes *B. cereus*, *B. anthracis*, *B. thuringiensis*, and *B. mycoides* (44).Large, aerobic, gram-positive, spore-forming, and nonmotile, *B. anthracis* is a bacillus (Figure 2). The only obligatory pathogen in the genus is the nonflagellated vegetative bacillus, which measures 1-1.5 by 3-10 m (43, 45). When stained with polychrome methylene blue (McFadyean stain; Figure 3) or highlighted with India ink, the polypeptide capsule that surrounds the bacilli in infected blood or tissues can be seen under a microscope. However, no capsule can be found in stained smears from anthrax colonies grown on plates unless the medium contains 0.7% bicarbonate or 5% serum and the plates are incubated in an environment with a carbon dioxide concentration of 5% to 10% (46).

By using multiple-locus variable-number tandem repeat analysis and amplified fragment-length polymorphism, it is possible to identify between *B. anthracis* and other species of the B. cereus group, but not between species of the B. cereus group as a whole (47, 48). One of the most monomorphic known bacteria at the molecular level is *B. anthracis*. However, all known *B. anthracis* strains can be divided into five groups for geographical identification based on the varying numbers of tandem repeats in the area of the VrrA gene (49).

On sheep blood agar, B. anthracis is nonmotile and nonhemolytic, in contrast to other members of the B. cereus group. It quickly establishes typical white-gray colonies with an oval, slightly granular appearance on a range of laboratory media at a temperature of 37°C. When compared to other species in the B. cereus group, B. anthracis colonies have a diameter of roughly 2 mm and are somewhat smaller (Figure 4). Colony morphology, susceptibility to the diagnostic gamma phage (Figure 5), and the capacity to generate the distinctive capsule as seen by the McFadyean stain make it relatively simple to separate the virulent B. anthracis from members of the B. cereus group.

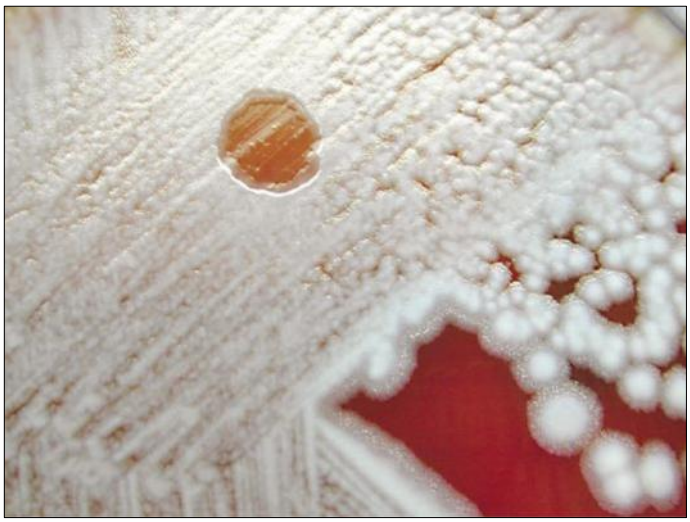


Figure 5. Gamma phage lysis of *Bacillus anthracis* on sheep blood agar. Courtesy of CDC/Larry Stauffer/Public Health Image Library.

When the environment's supply of specific nutrients is depleted or when bodily fluids contaminated with anthrax are exposed to outdoor air, bacilli will produce spores (47). But when conditions are right, anthrax spores grow and quickly proliferate into vegetative anthrax bacilli. Vegetative bacilli have a dismal prognosis for survival outside of an animal or human host; 24 hours after water inoculation, colony counts rapidly drop to undetectable levels. This stands in stark contrast to the *B. anthracis* spore's ability to endure in harsh environments for long periods of time (3, 43, 50).

Pathogenesis

The pXO1 and pXO2 plasmids responsible for the anthrax toxins have been sequenced to date (51, 52) following the recent analysis of the B. anthracis (Ames strain) genome. According to experts at the Center for Biological Defense College of Public Health at the University of South Florida, similar plasmids have also been found in non-Bacillus cereus species and can be transferred across these species of Bacillus. Since current and upcoming research for the development of new treatment options and vaccines will focus on these virulence factors, the primary virulence factors and their involvement in the pathogenesis of anthrax will be briefly described. The bacilli must have three plasmid-encoded toxin components as well as an antiphagocytic capsule in order to be fully virulent. The pXO2 plasmid (51) encodes the high-molecular-weight polypeptide (poly-D-glutamic acid) that makes up the capsule. The three genes capB, capC, and capA are encoded by this little plasmid (95.3 kilobase pairs). The capsule prevents the vegetative form of B. anthracis from being phagocytosed by the host (47). The 184.5 kilobase pair-long plasmid pXO1 encodes three toxins: the 83-kd fatal factor,

the 89-kd edema factor (cadherin-dependent adenylate cyclase), and the 85-kd protective antigen (52–54).While acting in binary combinations, these proteins, which individually are not toxic, cause the host organism to exhibit two separate harmful reactions: edema and cell death (55). When the protective antigen binds to a receptor on the host cells, the hazardous complexes begin to assemble. The membrane-bound protective antigen is then partially endocytosed after being cleaved by a furin class protease. This procedure also makes it easier for the deadly and edema factors to enter the host cell. The fatal toxin is created when the endocytosed portion of the protective antigen mixes with the lethal factor (56). The edema factor limits neutrophil phagocytosis and the oxidative process.The deadly toxin, which is composed of a lethal factor and a protective antigen, is cytolytic for macrophages and results in the production of interleukin-1 and tumor necrosis factor. Endothelial cells are harmed by interleukin-1 and tumor necrosis factor.

Anthrax infection happens when spores enter the body through a skin break (cutaneous anthrax) or the mucosa (gastrointestinal anthrax). At the port of entry, macrophages consume spores, which results in germination of the vegetative phase and fast bacilli multiplication. Lethal toxin and edema factor synthesis occur simultaneously with rapid extracellular expansion. Spores (diameter: 1-2 m) are inhaled and lodged in the alveoli in inhalational anthrax.

They are then moved to the mediastinal lymph nodes and nearby lymphatics, where they germinate and result in hemorrhagic lymphadenitis. Septicemia is then brought on by the subsequent spread of vegetative bacilli through the lymphatic and blood systems.

The host organism rapidly declined and manifested symptoms as a result of the high levels of toxin the bacilli produced, which were combined with the host reaction (production of tumor necrosis factor and interleukin-1) to cause these symptoms. Patients pass away within a few days if untreated. In fact, the Sverdlovsk incident in 1979 shown that sickness and mortality happen six weeks after anthrax spores are unintentionally released. Research on rhesus monkeys, a useful model for studying inhalational anthrax, has revealed that germination can take place up to 60 days after exposure and that infected animals pass away within a week of developing complete symptoms (57). These findings serve as the rationale for the 60-day antibiotic prophylactic recommendation in response to inhalation exposure.

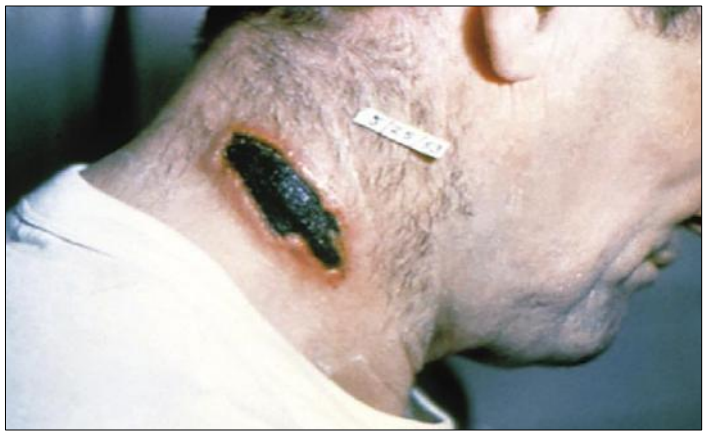


Figure 6. The eschar of cutaneous anthrax. Courtesy of CDC/Public Health Image Library.

Clinical manifestations and pathologic characteristics of anthrax

The most prevalent type of anthrax in humans, accounting for 90% or more of all occurrences globally, is cutaneous illness. Arms, hands, faces, and necks with exposed skin are more frequently afflicted. There is little evidence to support a lengthy latency period for the emergence of cutaneous anthrax following exposure. In Sverdlovsk, cutaneous anthrax patients didn't start showing up until 12 days after the occurrence (36). Incubation times as low as 12 hours and as long as 19 days have been documented in the literature (58). Following spore germination in skin and soft tissues, toxin production causes localized edema and the formation of a ring of vesicles.Most often, these symptoms develop over the course of a day. The central papule first develops edema and vesicle development, then it

ulcerates and dries to form the well-known black eschar (Figure 6). Within the subsequent 1 to 2 weeks, the eschar dries, becomes loose, and eventually falls off, leading to complete healing with little to no scarring. Despite treatment, cutaneous lesions frequently disappear (59). Lymphangitis and painful lymphadenopathy are frequently the initial indications of a systemic disease. 20% of cases of cutaneous anthrax that go untreated Patients have septicemia and pass away. However, the mortality rate is only 1% when the right antibiotics are used (60).

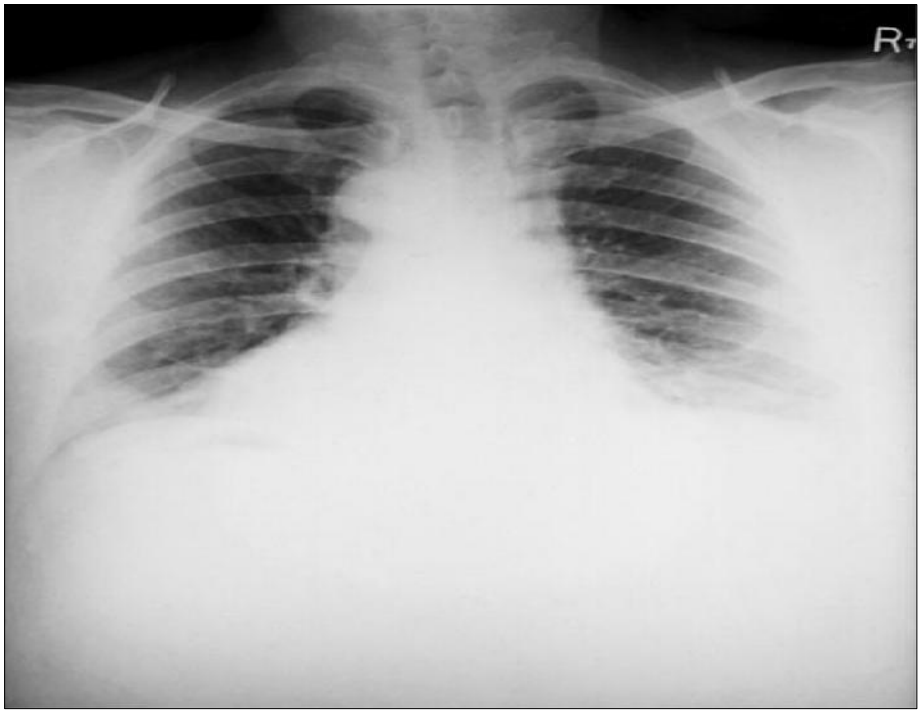


Figure 7. A posteroanterior chest radiograph taken shortly after onset of inhalational anthrax in a 46-year-old man who contracted the disease from working in a goat hair processing mill. The radiograph reveals bilateral pulmonary effusion and a widened mediastinum, which are hallmarks of the disease process. Courtesy of CDC/Arthur E. Kaye/Public Health Image Library.

Following the depositing and subsequent germination of spores in the upper or lower gastrointestinal tract, gastrointestinal anthrax develops. Consuming raw meat from animals that have been exposed to anthrax is frequently linked to the illness. Oral or pharyngeal ulcers, localized lymphadenopathy, edema, and sepsis are the hallmarks of the oropharyngeal type of the illness (20, 22). Although the cecum, colon, stomach, and duodenum can also be affected, the wall of the terminal ileum typically develops ulcers and eschars in the abdominal form of the disease. The symptoms that are currently present are anorexia, fever, nausea, and vomiting. Hematemesis, bloody diarrhea, severe abdominal pain, and death are all symptoms of advanced illness (47). These symptoms are caused by the first eschar's extensive and widespread necrosis as well as the intestines' and mesentery's noticeable edema. An important condition is lymphadenopathy. Patients can be treated and cured if the diagnosis can be made early on. However, early detection of gastrointestinal anthrax is challenging due to the disease's initially vague symptoms, which ultimately leads to a high death rate.

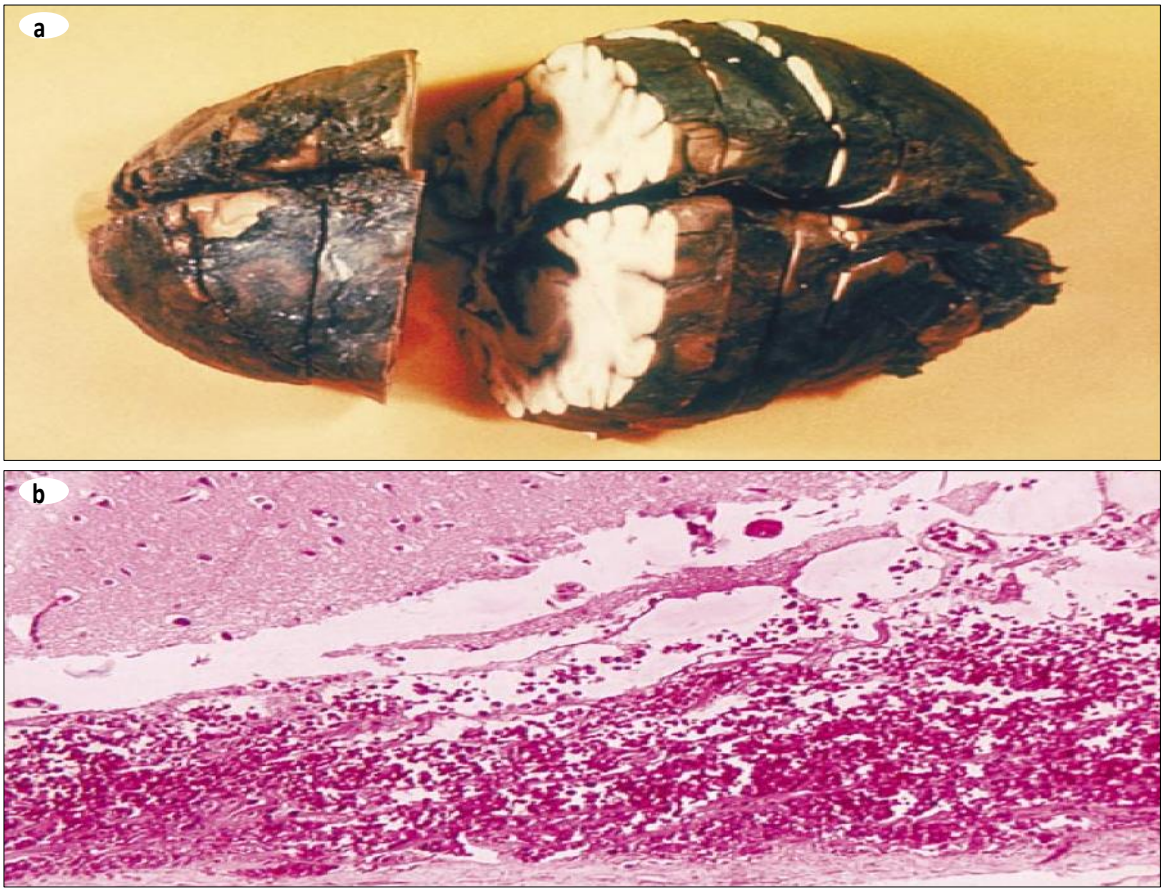


Figure 8. Hemorrhagic meningitis due to inhalational anthrax. **(a)** Gross pathology of a formalin-fixed and cut brain. Courtesy of CDC/Public Health Image Library. **(b)** Photomicrograph of meninges, ×125. Courtesy of CDC/Dr. LaForce/Public Health Image Library

The disease caused by inhaling anthrax is typically described as having two stages. It starts off subtly with flu-like symptoms such a nonproductive cough, a low fever, lethargy, and malaise. About 2 to 5 days after the initial exposure, these symptoms (prodromal phase) start to appear and remain for about 48 hours. The prodromal phase then abruptly ends as a relatively acute sickness manifests itself with symptoms like severe and acute dyspnea, stridor, fever, and cyanosis. Massive lymphadenopathy and mediastinum enlargement are seen at this stage. During this stage, a chest radiograph most frequently reveals a wider mediastinum consistent with lymphadenopathy (Figure 7) (61).Fever, tachypnea, cyanosis, tachycardia, moist rales, and pleural effusion evidence are among the clinical symptoms. Without medical attention, the sickness advances quickly; in its latter stages, the pulse becomes feeble and highly rapid, and the symptoms of dyspnea and cyanosis intensify. Extreme disori-fluid are typically followed by death and unconsciousness (47). Patients with anthrax meningitis and inhalational anthrax have exceedingly bad prognoses. Hemorrhage and edema are the telltale signs of anthrax. These findings are only seen in tissue close to the inoculation site in cutaneous anthrax patients. The type and location of lesions associated with septicemic dissemination of anthrax are essentially the same regardless of the route of infection, with the exception of the site of initial entry and the mediastinal edema in patients with inhalational anthrax (36).

Toxins produced by bacilli at the site of introduction are what lead to the severe localized reaction. The bacteria have a propensity to quickly colonize the lungs and digestive system as they multiply. Preexisting lesions from different origins are frequently colonized.

Examples include neoplasms, sites of chronic active inflammation, and parasite nodules. The organisms spread through the bloodstream, and the local anthrax lesion looks like an abscess. Coma and death occur fast after severe septicemia that involves the brain, spleen, and entation (62, 63). With inhalational anthrax, up to 50% of patients experience hemorrhagic meningitis, along with meningismus, confusion, and obtundation. However, any of the three disease stages can become anthrax meningitis as a final stage. Within a few hours to days, clinical symptoms including the presence of blood in the cerebrospinal fluid, liver, and nearly every other organ will take place (37). The hemorrhagic meningitis, often known as the "cardinal's cap" (Figure 8), is striking (37).

Light microscopy reveals bleeding, edema, necrosis, fibrin deposition, and a varying degree of inflammatory cell infiltrate, primarily composed of neutrophils, in tissue from patients with disseminated anthrax (Figure 9). Lesions on the spleen exhibit fibrinopurulent necrosis and a loss of white pulp. Hemorrhage, fibrinopurulent inflammation, and a wide variety of bacilli in and near blood vessels are the hallmarks of hemorrhagic meningitis (37). Also possible are disseminated intravascular coagulation and necrotizing vasculitis. Touch preparations from tissue and blood smears also show a variety of gram-positive bacteria that are often "box car" shaped and encapsulated.

Category	Initial therapy (intravenous)	Follow-up therapy/duration
Adults (including pregnant women† and immunocompromised)	Ciprofloxacin 400 mg BID or doxycycline 100 mg BID and one or two additional antimicrobials	Switch to oral therapy when clinically appropriate: Ciprofloxacin 500 mg BID or doxycycline 100 mg BID Continue for 60 days (intravenous and oral combined)
Children (including immunocompromised)	Ciprofloxacin 10–15 mg/kg BID‡ or doxycycline: >8 y and >45 kg: 100 mg BID >8 y and ≤45 kg: 2.2 mg/kg BID ≤8 y: 2.2 mg/kg BID and one or two additional antimicrobials	Switch to oral therapy when clinically appropriate: Ciprofloxacin 10–15 mg/kg BID‡ or doxycycline: >8 y and >45 kg: 100 mg BID >8 y and ≤45 kg: 2.2 mg/kg BID ≤8 y: 2.2 mg/kg BID Continue for 60 days (intravenous and oral combined)

*Source: *MMWR* 2001; 50:909–919 (reference 41). Patient information sheets available at http://www.bt.cdc.gov.

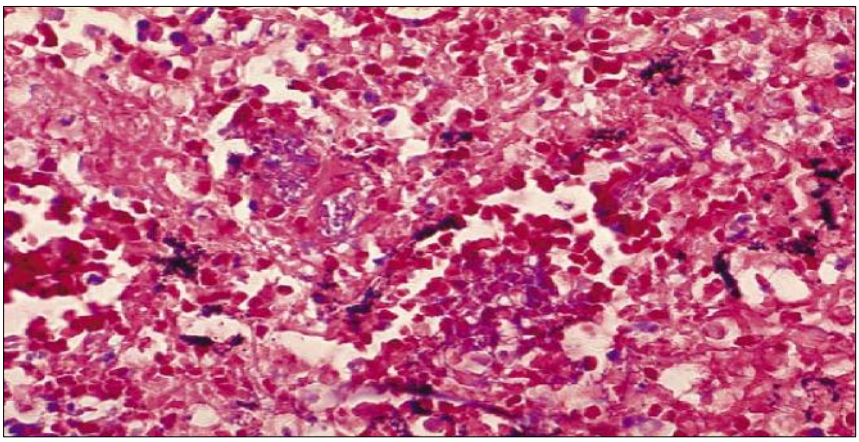


Figure 9. Histopathologic study of mediastinal lymph node in fatal human anthrax. Courtesy of CDC/Dr. Marshall Fox/Public Health Image Library.

The fatality rate from anthrax inhalation was once estimated to be greater than 95%. Before the utilization of critical care units and, in some cases, before the development of potent antibiotics, the majority of these cases were occupationally acquired (7). Out of the 79 documented cases of inhalational anthrax at Sverdlovsk, 68 people passed away. The validity of these data and diagnoses, however, is still debatable (36). According to reports, patients who were diagnosed 30 days or more after the organism was unintentionally released had a higher likelihood of survival than those who received their diagnosis or first signs of the disease sooner. Residents of the Sverdlovsk area were treated with antibiotics, antianthrax globulin, and vaccinations.

Data on patients who had received such interventions, hospital records, and comprehensive data from these treatments are not available, albeit (36). According to accounts, the average time between the beginning of symptoms and death in many of the fatal instances was three days.

On the other hand, six of the patients of the 11 cases that have been identified so far in the USA survived, giving a death rate of 45%. This reduced number may demonstrate the efficacy of prompt diagnosis, prompt and appropriate antibiotic therapy, and complete critical care support.

Treatment and prophylaxis

For the treatment of (cutaneous) anthrax, penicillin has long been the preferred medication, and only very rarely has penicillin. These suggestions take into account the trends of antibiotic resistance as well as the potential need to treat numerous casualties. Early antibiotic therapy is crucial due to the quick onset and frequently lethal course of inhalational anthrax. The 10 most recent cases of inhalational anthrax in the USA have also demonstrated that this strategy is effective. The treatment of systemic anthrax with penicillin or amoxicillin alone is no longer advised because the Ames strain responsible for these recent infections has demonstrated the presence of constitutive and inducible -lactamase.

Use of ciprofloxacin (500 mg twice daily), doxycycline (100 mg twice daily), or amoxicillin (500 mg three times daily) is advised in moderate instances of cutaneous anthrax (3). With variations in the way these antibiotics are administered, recommendations were produced for scenarios with contained and mass casualties. Antibiotic treatment in laboratory animals stopped the emergence of a sufficient immune response (57). The results of these trials indicate that there is a significant chance of disease recurrence for at least 60 days, even when the right antibiotics are given. It has been suggested that dormant spore germination could happen up to 60 days following infection. Therefore, the Working Group on Civilian Biodefense suggested that an antibiotic course last at least 60 days (3) (Table 1). The majority of specialists concur that anyone or any party without access to advanced biotechnology laboratories is unable to produce and employ a fatal anthrax aerosol. However, following the September 11, 2001 attacks on the World Trade Center, 10 examples of resistance to naturally occurring *B. anthracis* strains were discovered. Penicillins, fluoroquinolones, tetracyclines, chloramphenicol, aminoglycosides, macrolides, imipenem, rifampicin, and vancomycin have all been shown to be effective against B. anthracis in in vitro tests. Cephalosporins, trimethoprim, and sulfonamides are typically ineffective against the organism (47).

Based on a small number of investigations in experimental animals and the lessons learned from the Sverdlovsk event, the earliest recommendations for the management of (inhalational) anthrax in the context of a bioterrorist attack were developed (3). In contrast, therapy for cases of spontaneously occurring (cutaneous) anthrax lasts 7 to 10 days. The best practices for postexposure prophylaxis are still being debated and are not yet finalized. Unless public health or police authorities deem the exposure significant and a significant risk for the development of disease symptoms occurs, such

prophylaxis is currently not advised for asymptomatic people (3, 47). Again, due to the likelihood of delayed germination of inhaled anthrax spores, a 60-day timeframe is advised for prophylaxis.

Naturally, vaccination appears to be the best method of widespread defense. The first anthrax animal vaccine was created by Pasteur in 1881, but human vaccinations did not appear until the middle of the 20th century (47). The protective antigen is the main antigen involved in the induction of immunity (16, 19). The inactivated cell-free product (Sterne 34F2) used in the US anthrax vaccine for animals has shown to be incredibly secure and efficient. The Food and Drug Administration approved a vaccination for human use in 1970. This vaccine's foundation was a culture in a synthetic medium, formerly known as "528 medium." An alhydrogel-absorbed, cell-free culture filtrate of the anthrax civilian population was modified, and today's US vaccine is employed.If dried anthrax were to be released in the form of aerosolized particles over major cities, the WHO's report from 1970 offered a bleak prognosis on the expected casualties (1).

Concerns have been voiced that these assaults are the start of terrorism rather than its conclusion due to the events in Sverdlovsk and the uncovering of bioweapons research in various nations (such as the FSU and Iraq). Although there have been advances in treatment, anthrax remains a deadly infection. Primary prevention relies on establishing a strong global norm that forbids the development of such weapons, while secondary prevention calls for early detection and prompt treatment of disease. Unfortunately, the tools of primary and secondary prevention are insufficient.All active-duty and reserve members of the US military must now receive the vaccination, which is administered in a 6-dose course over a period of 18 months (64). No significant adverse events were documented from the vaccine's usage in the military, despite modest side effects (3). In addition, research on monkeys who received the vaccine revealed that at 8 and 38 weeks and at 100 weeks after vaccination, the vaccine was 100% protective against an aerosol challenge of anthrax spores (65). Humans are vaccinated with live spores in the FSU and China either through scarification or subcutaneous injection (65). The FSU also employs a strain (ST-1) that is comparable to the Sterne 34F2 animal vaccination used in the US. In the West, attenuated vaccinations are not thought to be appropriate for human usage.

There has been a lot of work done recently to create novel, safer anthrax vaccines that would satisfy the licensing requirements in place and provide enhanced efficacy (65, 66). The majority of recent research has been directed toward subunit vaccines with whole length recombinant protective antigen as the active component. Such novel vaccines would ideally be administered orally or intranasally and offer protection after just one dosage.

Summary

Despite its terrifying potential as a biological weapon, anthrax has long been a common natural illness in all parts of the world. Anthrax was a significant disease in the early days of microbiology, roughly 125 years ago, as it was devastating to domestic animals and the farming industry. Vaccine development and use were among the suitable countermeasures that were implemented after the issue was revealed. The development of multidrug-resistant strains and the ease of bioweapon dispersion were the main goals of anthrax research and development in the first half of the 20th century. It became increasingly obvious that anthrax would not likely seriously impair military operations.

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