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Bacillus anthracis: A Bioterrorism Agent

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INTRODUCTION

Bioterrorism broadly describes the use of biowarfare agent (chemicals, bacteria, and viruses) to induce disease in people or even kill them and may damage crops and livestock. It is the intentional use of a pathogen or chemical to destroy the economy of a country and also affects the social life of people (De Felice et al. 2008). Bioterrorism earned great attention during the first decade of the 21st century. Definitions of bioterrorism may vary by source and have evolved over time. According to Spencer, "the use of microorganisms as weapons with devastating effects, which can be described serious physical, psychological, or economic harm to a nation" (Rose and Larrimore 2002). It highlights some important points including the broad spectrum of microbes must be considered along with their physical, psychological and economic impact. In addition, Spencer describes the term agroterrorism: " any agent which is vulnerable to livestock and crops" (Tegnell et al. 2003). Various types of biological agents include viruses, bacteria, toxins and chemical agents (Fig. 1). Broadly biological agents have been grouped into three categories as represented in Fig. 2 (Jernigan et al. 2001).

Epidemiology of Bioterrorism

Unexceptional disease outbreaks may indicate a bioterrorism attack including exotic diseases i.e. plague, inhalation anthrax, typhoid tularemia, smallpox, hemorrhagic fever, and typhoid fever suggest the intentional dissemination (Mayer et al. 2001). Bioterrorism disease has relatively nonspecific characteristics, therefore, epidemiologists try to understand the cause of the disease. Unexpected regional or transient patterns are sign that disease outbreaks are not occurring naturally. For example, all cases of anthrax around Sverdlovsk were found active within 4 km of the military headquarters, indicating military territory was the target site or source of the outbreak. All cases were reported during the same era, suggesting the uncommon outbreak of a single biological agent (Bush et al. 2001). Atypical clinical symptoms may indicate an abnormal route of infection i.e., inhalation of anthrax. Unusually high incidence rates may occur in people exposed to a particular area or if people are living in protected areas, especially if multiple dotted source outbreaks occur at the same time (Bravata et al. 2004). If it occurs, it may indicate an intentional infection. A very high number of cases, and failure to identify a single source of infection, divert the scientists' intentions to associations with food contamination (Mondy et al. 2003).

History of Biological Agents

As early as 600 BC, infectious diseases were believed to have the potential to harm both civilians and armies. The opponent was utterly destroyed by the crude use of filth, animal carcasses, and pathogens (Nofal et al. 2021). Through the various European wars, the American Civil War, and even into the 20th century, the way of poisoning the opponent army's wells and other water sources remained continued. Even Middle Ages military leaders found that victims of infectious diseases may turn into weapons. A brief history of the use of biological agents is shown in Fig. 3 (Lashley 2004).

Bacillus anthracis: A Biological Agent

Introduction

A German physician Robert Koch discovered *Bacillus anthracis* (*B. anthracis*) in 1876. *B. anthracis* is an etiological

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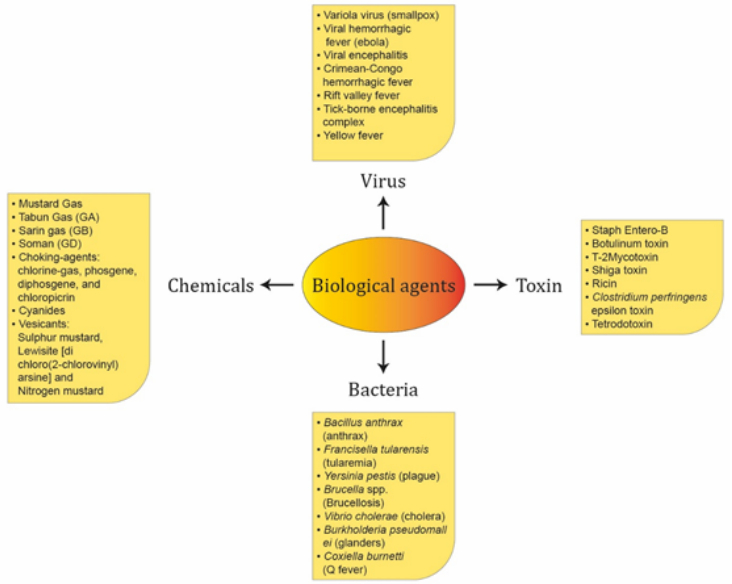

Fig. 1: Types of biological agents

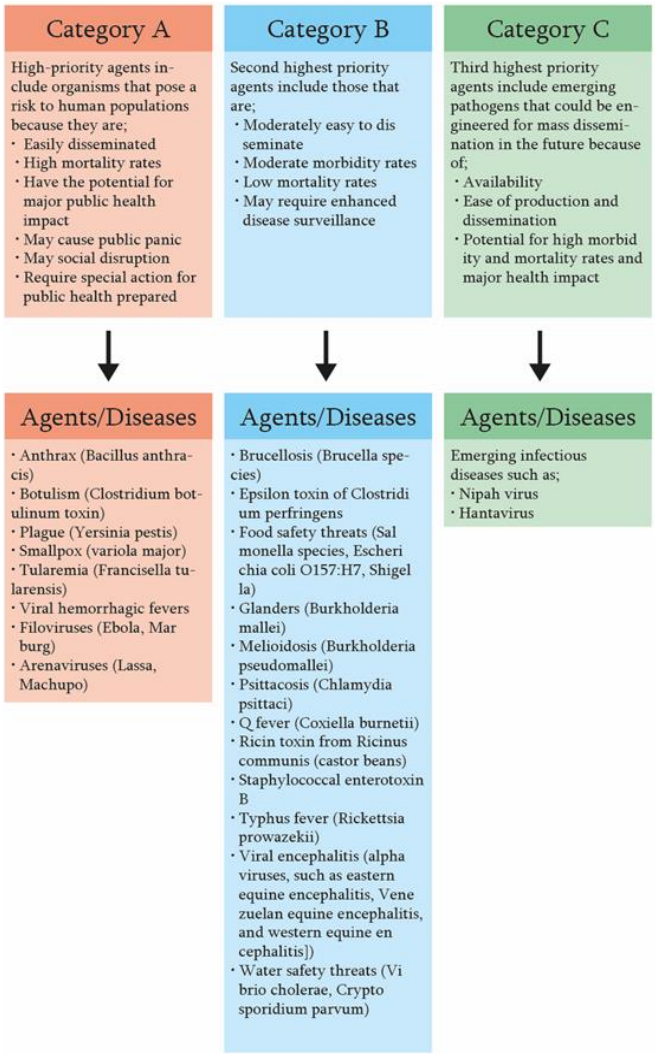

Fig. 2: Categories of biological agents.

agent of a zoonotic disease called anthrax that occurs in herbivores and other animals and it is important for both public health and biodefence protection (Mukarati et al. 2020). The word anthrax originates from the Greek letter, "*anthracite* "which signifies Black Coal. *B. anthracis* is a gram-positive, non-motile and spore-forming bacterium. In favorable conditions, its spores can survive for up to ten years (Hueffer et al. 2020). In addition, spores have high resistivity to natural condition so it is supposed to be the most potent biological weapon agent. Biological agents are considered to be the most potent weapon used in bioterrorism since they are often inexpensive and have a broader impact than physical damage (Chateau et al. 2020). Countries with agriculture as a main source of income are more vulnerable to the attack of anthrax. The spores of *B. anthracis* enter the body through skin lesions, gastrointestinal routes and lungs. Once spores enter the body, they can replicate in the blood, can travel to lymph nodes, and can produce toxins that may even cause death. Symptoms include flu-like infection, shock, acute respiratory distress and ultimately death (Hoffmaster et al. 2006).

This bacterium has two large plasmids pXO1and pXO2, both necessary for toxicity. Plasmid pXO1 harbor the structural genes for anthrax toxin proteins and pXO2 carries genes for capsular synthesis. Even though *B. anthracis* forms a strongly monomorphic phylogeny with the *B. cereus* complex; *B. thuringiensis* and *B. cereus* strains that are genetically related to the *B. anthracis* cluster (Carlson et al. 2019). This bacterium can infect humans in three ways including cutaneous, respiratory tract and gastrointestinal tract. A most recent study also describes another way of infection which is injectable anthrax. The most severe and fatal types of the disease are gastrointestinal and inhalational anthrax. The virulence mechanism of anthrax allows the bacterium to spread to the lymph nodes and subsequently to the bloodstream leading to internal infection. In the host, *B. anthracis* has two forms i.e., vegetative and spores (Inglesby et al. 2002; Kamal et al. 2011).

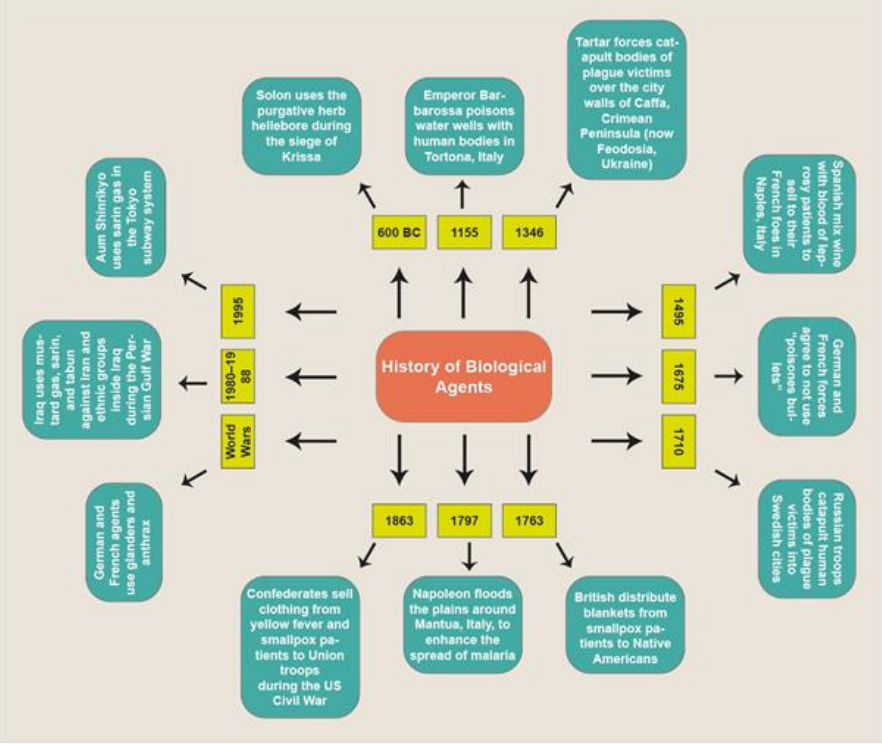

Fig. 3: History of use of biological agents (Lashley 2014).

This bacterium is commonly present in the soil, in the form of endospores, which can survive for many years. *B. anthracis* is categorized into pathogenic and non-pathogenic species. In addition, *B. anthracis* has two virulence factors, acid poly-γ-D-glutamic acid capsules and tri-partite toxin (Hoffmann et al. 2017). It has long been suspected of being used as a bioterrorist agent because it produces spores that can be aerosolized and proliferate the disease. During the Cold War Era and afterward as a bioterror agent, *B. anthracis* was regarded as a potential biowarfare agent (Leendertz et al. 2004). After September-October 2001 Anthrax Terrorist Attacks in the US, The U.S. Postal Service, spread spores that killed 5 people and infected 17, which lead to the identification of anthrax as a disease in 2001. As a result of these incidents, the number of scientific studies on *B. anthracis* has dramatically increased. Due to its highly pathogenic nature, spore-forming ability and high mortality rate, *B. anthracis* is known to be high-rank biological weapon (Antonation et al. 2016).

Microbiology of *B. anthracis*

B. anthracis produces large gram-positive bacilli (1-1.5 mm x 4-10 mm). This facultative anaerobe has nonmotile, encapsulated cells that are organized in chains. Swabs from infected tissue typically show evidence of encapsulation, however, this is not the case when the organism is grown in conventional laboratory culture media where it produces spores (Sharma et al. 2020). After 24 hours of incubation at 35°C, *B. anthracis* produces spherical, flat or slightly convex non-hemolytic colonies with a diameter of 2–5 mm on sheep blood agar plates (Missiakas and Schneewind 2017).

Strains of *B. anthracis*

There are three strains of *B. anthracis* namely Ames, Stern, and Vollum. Ames is a frequently examined and highly virulent strain that contains the two plasmids: pXO1 and pXO2. It was originally isolated from a dead cow in Texas in 1981. Whereas, its geographical regions are US and UK (Norris et al. 2020). First isolate of Ames strain was reported in Florida in 2001 from a victim of an anthrax attack. Stern is a toxin-producing but non-virulent strain because it carries the anthrax toxin plasmid pXO1 but lacks the encapsulated plasmid pXO2. This strain is often used in the development of animal vaccines (Pilo and Frey 2018). Vollum is a low-virulence strain used in research studies and has been found in the UK, Payne, and Zimbabwe. This strain is also used in the development of animal vaccines. Moreover, the V770 strain has also been used in the production of toxins and in various research-related studies (D'Agnillo et al. 2020).

Virulence Factors and Toxins

Toxins and autophagic capsular polypeptides, including D-glutamic acid, constitute the anthrax virulence factor. The

genes for these virulence factors are on different plasmids. Anthrax toxin is composed of three proteins: EF (edema factor), PA (protective antigen) and LF (lethal factor) (Enosi Tuipulotu et al. 2021). All three parts have been studied for purification, characterization, and structural gene sequencing. On the surface of host cells, PA fragments can bind to specific receptors. Cellular proteases cleave part of the molecule to generate PA fragments that act as specific receptors for EF or LF. Host cells absorb toxins through a process known as receptor-mediated endocytosis (Aoyagi et al. 2020).

Life Cycle of *B. anthracis*

Animals become affected when they ingest anthrax endospores found in agricultural areas. Endospores find favorable conditions inside the mammalian host, such as an aqueous environment with enough nutrition, and begin to germinate. An important phase in the pathogenesis of anthrax is the transition of the spore into a vegetative cell since only the vegetative form of the bacterium can produce virulent components, such as the capsule and tripartite toxin (Antonation et al. 2016). The peptidoglycan layer and S-layers surround the poly-D glutamic acid capsule, which creates a complicated surface for *B. anthracis*. The capsule is essential for bacterial survival as it circumvents the immune system of the host. After death, the bacteria are enclosed and spread through natural orifices with blood dissemination (Hu et al. 2020). When the vegetative bacteria come into contact with oxygen, they transform into spores and re-infest the agricultural fields, where grazing animals can ingest/contact the lethal spores ultimately resulting in anthrax infection (Fig. 4).

Clinical Types of Anthrax

Depending upon the route of infection, there are three clinical types of anthrax: cutaneous (skin), gastrointestinal (ingestion), and pulmonary (inhalation of spores) (Thappa 2019). A different strain namely "injectional anthrax" has recently been discovered among European heroin injectors. Some cases of anthrax have been associated with insect bites, as some insects may spread the disease after biting an anthrax-infected animal (Berger et al. 2014).

Spores do not appear to develop in the host as the oxygen tension of the dying host is too low for sporulation or the virulence gene regulator *AtxA* inhibits sporulation (Shearer 2016). Within 3 hours of germination, spores infiltrate macrophages at the point of entry, develop into vegetative cells, propagate into tissues and begin to produce anthrax toxin (Fig. 5) (Zhang et al. 2022).

Cutaneous Anthrax

An irritating papule that looks like an insect bite is the first sign of cutaneous anthrax infection. This papule grows within a day or two and develops into ulcer with a raised, circular margin and a necrotic center (Nayak et al. 2019). Such sores often develop within 2–5 days after the spores enter the skin. After 7–10 days, a black eschar with edema surrounding it forms, leaving a scar formation after anthrax treatment. There may be swelling and enlargement of the local lymph nodes (Kasradze et al. 2018). The majorities of cutaneous anthrax infections are painless and only affect the dermis. However, when bacteria enter the bloodstream and cause bacteremia, it can spread throughout the body. However, on skin, hemorrhagic lesions may be formed (Tekin et al. 2015).

Gastrointestinal Anthrax

Gastrointestinal (GI) anthrax occurs by eating or ingesting food contaminated with anthrax spores. After intake, spores germinate and can leave sores across the body of host (Nakanwagi et al. 2020). Typically, the incubation phase lasts 3 to 7 days. Abdominal and oropharyngeal anthrax are the two forms of GI anthrax that can be identified by the lesions. In abdominal GI anthrax, lesions predominantly develop in the ileum and cecum (Owen et al. 2015).

Symptoms of abdominal gastrointestinal anthrax include nausea, bloody vomiting, diarrhea, abdominal pain, headache, loss of appetite, and severe ascites. Oropharyngeal anthrax is another type of intestinal anthrax whose lesions occur primarily in the oral cavity and resemble cutaneous anthrax. Symptoms include sore throat, difficulty in swallowing, cervical lymphadenopathy and swelling of the throat due to inflammation (Goel 2015).

Respiratory or Inhalation Anthrax

Respiratory anthrax occurs when spores of anthrax are inhaled into the lungs (also known as pulmonary anthrax). This is the most dangerous type of anthrax. The spores are taken up by alveolar macrophages and transported to the mediastinal lymph nodes. Symptoms of anthrax inhalation are similar to those of a cold or flu, initially with mild chest pain, shortness of breath, nausea, and finally fatal respiratory collapse (Azarkar and Zare Bidaki 2016). Hemorrhagic mediastinitis and pulmonary enema, unlike pneumonia, are caused by anthrax (Asgharian et al. 2016).

Injectable Anthrax

The symptoms of anthrax from injection are the same as for cutaneous anthrax, although the infection may be under the skin or deep into the muscle where the drug was injected. Sometimes the injection site may be red (Hu et al. 2020). Injectable anthrax can be difficult to diagnose because a variety of other common bacteria can infect the skin and injection site, and difficult to treat because it spreads quickly throughout the body (Fig. 5) (Mukarati et al. 2020).

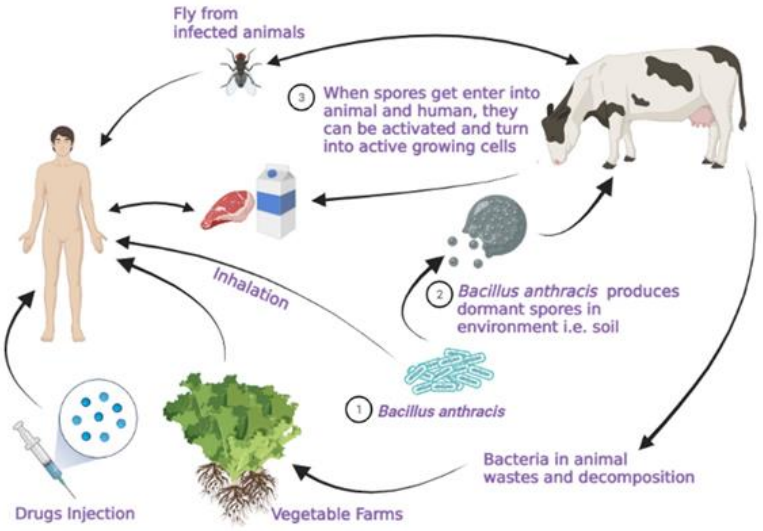

Fig. 4: Life cycle of *B. anthracis*

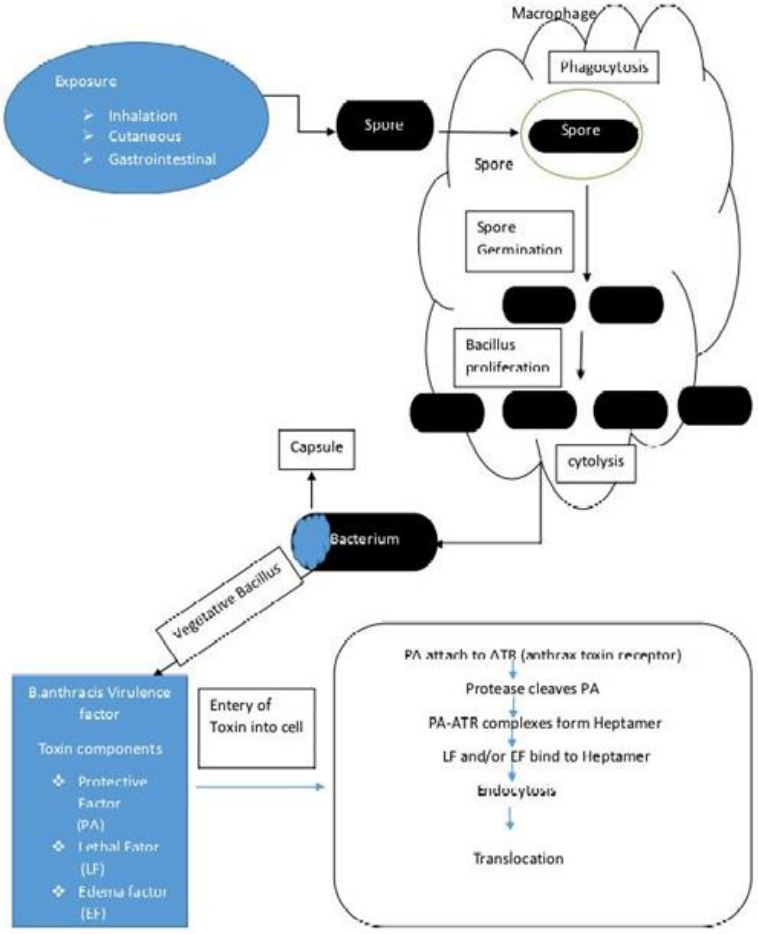

Fig. 5: Pathogenesis of *B. anthracis*

Potency of *B. anthrax* as a Bioterrorist Agent

Due to its extremely pathogenic potential and sporulation, anthrax is a top candidate for use in bioterrorist attacks. In 1970, the World Health Organization estimated that between 130,000 and 3 million individuals may die following the introduction of 100 kg of *B. anthracis* in 1993. This is just as deadly as an hydrogen bomb (Ehling-Schulz et al. 2019). According to research from animals, the human LD50 (a dose that kills 50% of infected people) is estimated to be between

2,500 and 55,000 inhaled spores. The WHO also predicted that if 50 kg of *B. anthracis* were spread over a 5-million-person urban population in 1970, it would infect 250,000 people and kill 100,000 (Berger et al. 2014). Therefore, if properly dispersed, an envelope containing 2g of powder (equal to 200 billion spores), like the one mailed to Senator Dasher in 2001, will kill thousands of individuals. From fermented cultures, it is possible to create highly pathogenic spores that, after going through a series of procedures, can be dispersed via aerosol delivery technology over a large region by an airplane (Antonation et al. 2016). Anthrax was primarily found in animals before being reported in humans. The increased significance of identifying infected individuals presents a significant challenge to public health concern. According to CDC guidelines, *B. anthracis* is enlisted in Category A high-priority diseases (Kasradze et al. 2018).

History of *Bacillus anthracis* in Different Biological Warfare

Japanese Army Units 731 and 100 purportedly experimented with the aerosolization of *B. anthracis* and the contamination of food and water supplies with enteric infections during World War II. In April 1979, a case of inhalation anthrax was recorded close to the Soviet Institute of Microbiology and Virology in Sverdlovsk, USSR, during the Cold War (Mukarati et al. 2020). The 77 confirmed cases—including 66 deaths—represent the largest known anthrax inhalation pandemic. According to more current estimates, there were 250 infected and 100 reported deaths as a result of the illegal spread. 21 cases of cutaneous anthrax from contaminated letters in 2001, 22 cases of inhalation anthrax, and 5 deaths due to anthrax in the US have been reported. Anthrax has a long history with human populations and was also popular in China and Europe (1190–1491 BC) (Goel 2015; Pilo and Frey 2018).

The fifth plague of Egypt, described in the book of Genesis (1491 BC) as an outbreak that ravaged ancient Egypt and wiped out all of the livestock, including cattle, sheep, goats, camels, horses, and donkeys may have been caused by anthrax. Anthrax in domestic and wild animals appears to be the disease that Virgil (29 BC) described in his third Georgics (collection of poems on agriculture and animal husbandry), as it was a significant agricultural disease in Europe from the 16th to the 18th centuries (Asgharian et al. 2016). In Japan, culturally identified anthrax in humans is on the national list of all reportable diseases, and medical officers must report all cases to the government. However, only 4 cases of *B. anthracis* were reported in Japan in 1990 (Takahashi et al. 2004). In August 1994, an event in Tokyo involved a man in his 80s from the Sumida district, which is adjacent to the Edo district (Kameido's site). However, there was no clear connection between this incident and that happened in July 1993. Between 1979 and 1985 more than 10,000 human cases were reported in Zimbabwe (Mayer et al. 2001). The US incident shows how human population can be affected from anthrax biological weapons (Nofal et al. 2021).

Conclusion

Anthrax has been a significant disease in the early days of microbiology, approximately 125 years ago, that halted domesticated animals and the farming industry. When this issue was identified, vaccinations were used as efficient preventative strategies. *B. anthracis* poses a major concern whether employed for terrorist or military purposes. Though treatments and preventative countermeasures are available, anthrax still poses a lethal impact on the human population. The critical steps in the present strategy are an accurate diagnosis, prompt identification, prophylactic measures, and appropriate treatment. The military and terrorist threat from anthrax inhalation is still present and may even be getting worse worldwide. Therefore, public health officials and medical professionals need to be aware of the different forms of anthrax. Pre and post exposure vaccination, and protective masks with 1 to 5 µm particle filters are important preventative measures. Though these precautionary measures may offer some protection against aerosolized *B. anthracis*, still morbidity and mortality rate are significant due to its potent bioterrorist attacks.

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