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Mini-Narrative Review

Anthrax: A narrative review

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ABSTRACT

Bacillus anthracis is a zoonotic bacterium, majorly responsible for causing human anthrax and the possibility of the outbreak spreading globally. Herbivorous animals serve as the inherent reservoir for the disease, whereas all endothermic species are vulnerable. Humans contract the disease inadvertently by contact with diseased animals or animal products or through the consumption or handling of infected flesh. There is no such reported data indicating the transmission of anthrax from human to human, which further does not guarantee the bacterium's mutations and new transmission route. Nevertheless, it can lead to various infections, including endophthalmitis, bacteremia, cutaneous infection, central nervous system infection, and pneumonia. Therefore, it is crucial to examine the present epidemiological situation of human anthrax in densely populated nations, including the altered symptoms, indications in people, and the method of transmission. This article highlights the current diagnostic methods for human anthrax, further examines the available therapy options and future perspectives in treatment protocol. This narrative review resulted from a simple search strategy on "PubMed", "ScienceDirect", "ClinicalTrials.gov" and web reports using "AND" as Boolean operator with search keywords, i.e., "Anthrax" AND "Infection", "Anthrax" AND "Pandemic", "Anthrax" AND "Infectious disease", "Anthrax" AND "Vaccine", "Anthrax" AND "Diagnosis" shows minimal narrative literature in between 2024 and 2005. Furthermore, this narrative review highlights the potential approaches for detecting anthrax infection, establishing suitable protocols for prevention, and focusing on the current epidemiology and available therapeutics, vaccine and its future developmental strategies for the prevention of infectious disorder.

1. Introduction and background

Anthrax is a zoonotic illness caused by the bacteria called *Bacillus anthracis* (*B. anthracis)*. This organism is a gram-positive capsulated bacterium that can survive in the presence or absence of oxygen and can develop spores when exposed to the environment through various body fluids of a deceased animal, allowing it to survive for extended periods [1,2]. The term "anthrax" originates from the Greek word "anthrakites," which means coal-like and describes the characteristic black eschar observed in the cutaneous manifestation of the disease [1]. This disease impacts both domestic animals and wild animals, and on rare occasions, it can also affect humans, leading to a global spread of the outbreak. Sheep have a higher infection rate compared to goats, horses, and other farm animals, especially cattle. However, the dwarf pig and Algerian

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sheep species show comparatively higher resistance to infection [2–4]. Herbivorous animals serve as the inherent reservoir for the disease, whereas all endothermic species are vulnerable. Humans contract the disease inadvertently by contact with diseased animals or animal products or through the consumption or handling of infected animal's flesh [5–7]. Anthrax can be transmitted through inter-animal or zoonotic transmission [8–10]. There is no recorded evidence of transmission in humans. Anthrax endospores exhibit resistance to desiccation, high temperatures, Ultraviolet (UV) radiation, gamma rays, and numerous disinfectants [8,9]. *B. anthracis* possesses two main factors that contribute to its ability to cause disease, i.e., tripartite toxin, and antiphagocytic polypeptide capsule [10–12], further summarized the life cycle of *B. anthracis* in Fig. 1. The genes responsible for these factors are located on two plasmids known as pX01 (182 kb) and pX02 (95 kb), respectively [13,14]. The organism's pathogenicity diminishes when one of these plasmids is lost. The tripartite toxin consists of three components, i.e., protective antigen, lethal factor (LF), and edema factor (EF). The primary function of PA is to facilitate the internal transportation of LF and EF within target cells, enabling their interaction with crucial cellular pathways [10,15–17]. The toxins are released during the proliferation of the vegetative *B. anthracis* and are accountable for the distinctive symptoms of anthrax [12,18,19].

The global warming may have significant impact on several infective agents including anthrax [20]. This is because an overall increase in the temperature of the planet has led to melting of permafrost which may allow anthrax spores to become active leading to increased risk of exposure to humans as well animals. Global warming may have an impact on the broader spectrum of disease vectors, changing their distribution and behavior. Insects and other arthropods are among these carriers. The changes in these species' distribution and behavior can indirectly affect the ecological dynamics of anthrax, even if vectors are not the primary means of transmission [21]. It has been demonstrated that rising temperatures and the stress they cause to livestock and wildlife can impair immune systems, leaving them more vulnerable to illnesses like anthrax. Anthrax outbreaks can occur more frequently and with greater severity when animals are under stress, especially in areas where climate change is having an immediate effect. The host-pathogen relationship is impacted by global warming, which creates favorable conditions for the persistence and spread of anthrax. For example, changes in animal densities, travel patterns, and habits brought on by climate change may make it more likely for naive populations to come into contact with *B. anthracis* spores, which could facilitate outbreaks [22].

A one health approach would be crucial at mitigating risks such as these outbreaks. To effectively control zoonotic illnesses like anthrax, a multidisciplinary strategy known as the One Health approach integrates the health of humans, animals, and the environment. Human health initiatives prioritize targeted immunization for at-risk persons together with early identification, quick diagnosis, and prompt therapeutic interventions. Simultaneously, animal health protocols emphasize routine monitoring, vaccinating livestock, and promptly notifying and eliminating afflicted animals to prevent epidemics. Controlling spore contamination through decontamination procedures and appropriate land management techniques is the focus of environmental health measures [23]. Most importantly, interdisciplinary cooperation makes it easier to share data and create coordinated reaction plans, which guarantees a coordinated and successful response across all sectors. Community involvement is crucial for spreading information about the risks of anthrax and preventive actions. This can be achieved through public awareness campaigns and local leaders' involvement. The sustained control and prevention of anthrax epidemics depend on an integrative approach that emphasizes the interdependence of environmental, animal, and human health in preserving public health [24].

Therefore, it is crucial to comprehend the existing epidemiological situation of human anthrax in developed or densely populated nations, including the altered symptoms, indications in people, and the method of transmission. This narrative review resulted from a simple search strategy on "PubMed", "ScienceDirect", "ClinicalTrials.gov" and web reports using "AND" as Boolean operator with search keywords, i.e., "Anthrax" AND "Infection", "Anthrax" AND "Pandemic", "Anthrax" AND "Infectious disease", "Anthrax" AND "Vaccine", "Anthrax" AND "Diagnosis" shows minimal narrative literature in between 2024 and 2005.

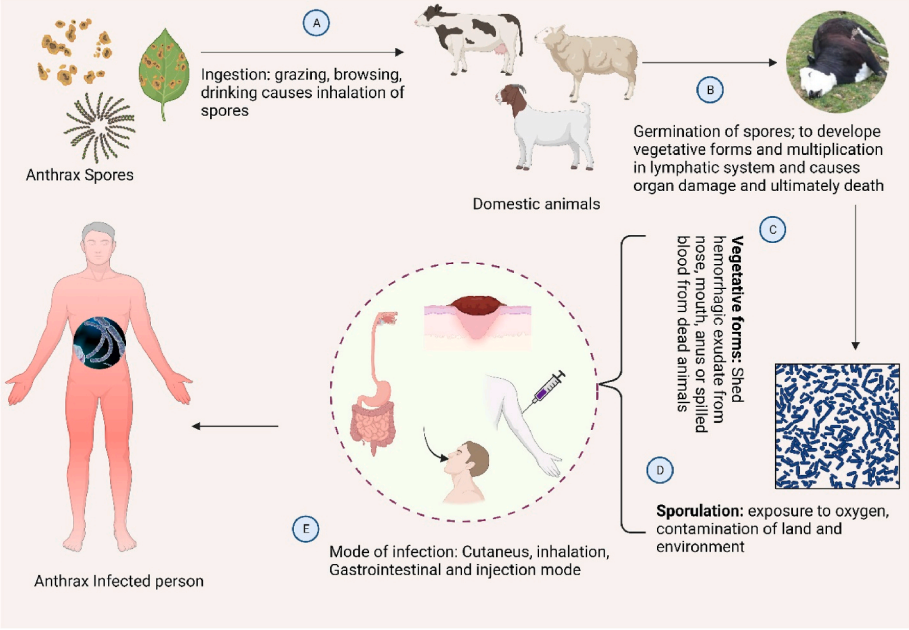

Fig. 1. Depicted the process of *B. anthracis* infection from anthrax spores to infection subjects. The soil serves as the primary reservoir for the virus, which becomes contaminated through the release of spores from the carcasses of sick animals. This leads to a new cycle of infection, death, and the production of spores, further contact with the humans via infected animals or animal products.

2. Epidemiology and recent outbreak in Zambia

The bacteria responsible for anthrax was identified by Pierre Raver and Casimir Joseph Davaine in 1850. Robert Koch initially documented the whole life cycle of the anthrax bacillus in 1876. In 1881, Louis Pasteur pioneered the creation of the initial animal vaccination that consisted of weakened living germs. The licensure of the human anthrax vaccination occurred in 1970 [1,25,26]. Anthrax maintained a global presence, with an annual frequency of 20,000–100,000 cases in the first half of the 20th century. However, the number of cases decreased to around 2000 per year in the second half of the 20th century. Most of these instances were of cutaneous anthrax [1,27]. The initial incidence of anthrax in humans was officially documented on June 16, 2023, as announced by the Lusaka Central Veterinary Research Institute (CVRI) [28]. On November 20, 2023, there were 684 suspected cases of humans contracting the disease, with 4 fatalities reported over 116 districts in nine out of Zambia's ten provinces. The Sinazongwe district had the most impact, accounting for 42 % of the total 684 cases (287 cases) and 50 % of the total four deaths (two deaths) [28,29]. Some of the major provinces that have been impacted include Southern, Western, Lusaka, Eastern, and Muchinga [29]. In 2011, Zambia saw a second outbreak, which resulted in a total of 511 suspected cases [29]. Zambia recently experienced an anthrax outbreak from September 2022 to January 2023. During this period, 42 probable cases of anthrax were reported at the Dengeza Health Post [28]. During the beginning of June 2023, the Kanchindu and Siameja veterinary camps documented occurrences of anthrax in both humans and animals. Anthrax infection spread to animals and humans in the Southern, Northwestern, and Western regions from July 2023 to November 2023. The increased danger at the regional level is due to the frequent movement of both animals and humans between Zambia and its neighboring countries, namely Angola, Botswana, Democratic Republic of the Congo, Malawi, Mozambique, Namibia, Tanzania, Uganda, and Zimbabwe [28,29]. In addition, a recent study conducted a comprehensive analysis of anthrax distribution [30] in 70 countries and revealed that around 1.83 billion individuals reside in areas globally that are at risk of anthrax. These regions are primarily located in rural rainfed systems in arid and temperate lands across Asia, southern Europe, sub-Sahelian Africa, North America, and certain parts of Australia. India is an endemic nation for animal anthrax infection, boasting the world's greatest cattle population. Consequently, there are intermittent and seasonal outbreaks of the disease in humans [31,32].

The disease manifests in cutaneous, inhalational, and gastrointestinal forms, develops due to endospores penetration into the body through skin wounds, inhalation, or ingestion, respectively. The majority, around 95 %, of anthrax infections in humans manifest as cutaneous or skin-related, whereas the remaining 5 % are inhalational. Gastrointestinal anthrax is an exceptionally uncommon occurrence, accounting for fewer than 1 % of all documented cases [33,34]. Anthrax meningitis is an uncommon occurrence that can arise as a consequence of any of the other three variants of the disease [1,35]. In Victorian England, inhalational anthrax was commonly referred to as woolsorters' sickness. This was due to the high incidence of infection among mill workers who were exposed to animal fibers that were contaminated with *B. anthracis* spores [25,35]. Furthermore, throughout antiquity, anthrax has resulted in significant economic losses in both domesticated and wild animals. However, since the development of the vaccine, its occurrence has been greatly diminished. Over the past 30 years, the incidence of sporadic cases has decreased in most locations where routine immunization programs for farm animals are carried out. Its zoonotic significance and potential as a bioweapon are causing widespread concern [36].

3. Clinical illness, and types of anthrax infection

3.1. Pathophysiology and symptoms

The bacteria (*B. anthracis*) generate significant potent toxins, which are responsible for the symptoms, leading to a high lethality rate in the pulmonary form [19]. Humans are being infected by infected animals or by using contaminated animal products. This gram-positive bacterium, which has a rod-shaped morphology, produces three exotoxins that are encoded by plasmids. These exotoxins include the edema factor, which is calmodulin-dependent adenylate cyclase and is responsible for the edema observed in *B. anthracis* infections. Additionally, it produces a fatal toxin that causes tissue necrosis, as well as a protective antigen [19,37]. Fig. 2 further summarizes the pathophysiology of anthrax infection in human or host bodies via inhalation of spores. Anthrax spores can enter the body by infected animal products, inhalation, or through cuts or abrasions. Once inside, the spores germinate, multiply, and produce poisons [19,38]. The presence of uncared-for carcasses of wild animals drifting on rivers raises the likelihood of diseases and infections spreading internationally to neighboring countries. These carcasses can carry bacteria and pathogens, posing a risk of transmission to other regions, including nearby nations. Additionally, other animals consuming these carcasses may contribute to the further propagation of the spread [8,12,37].

Anthrax is transmitted in several ways among humans and animals. Cutaneous anthrax is generally transmitted through contact of *B. anthracis* spores with broken part of the skin, or mucous membranes of the host's body, or direct contact with animals. Similarly, inhalation anthrax is caused when a person inhales anthrax spores and is also associated with animal handling. Eating under cooked food may lead to transmission of gastrointestinal anthrax. The injection anthrax as the name suggests may be transmitted through injected through used needles with anthrax spores attached to it [39]. The transmission between animals takes place by inhalation or ingestion of spores from contaminated soil or water also contact with carcasses infected with the anthrax spores may lead to transmission. Human to human transmission although rare, may be possible if direct contact with skin lesions of a person with cutaneous anthrax.

The symptoms of anthrax typically depend on the type of infection the person is suffering from Ref. [12], further summarized in Fig. 3. Most of the symptomatic cases were epidemiologically associated with the confirmed cases and not tested [40]. Depending on the route of bacterial entry anthrax infection is classified into 4 categories and each category shows different or sometimes similar symptoms which are- (a) cutaneous anthrax shows small blisters or bumps that causes itching and inflammation around the sore. Mainly this painless black type sore often occurs onto the face, arms, and necks. (b) Patients with gastrointestinal anthrax primarily show sign like food poisoning but later they can feel swelling of neck or neck glands, flushing (red face), red eyes, stomach pain, sore throat and bloody diarrhea. (c) Inhalation anthrax shows symptoms like chest discomfort, shortness of breath, extreme tiredness, body aches and dizziness etc. (d) Pulmonary anthrax, is the most critical condition followed by common cold and rapidly introduces breathing complication, fever, chills, abscesses deep under the skin or in the muscle [12,40,41], further summarized in Fig. 3.

3.2. Types of anthrax infections

The categorization of human anthrax mostly relies on the pathway by which the germs infiltrate the host. Anthrax is categorized into four distinct classifications [42]. Cutaneous anthrax is the predominant form of anthrax infection (near about 95 %) [43], resulting from the entry of anthrax spores into the skin through a cut or abrasion. The individuals contract this type of infection through direct contact with diseased animals or through handling contaminated goods such as wool, skins, or hair [42–44]. Cutaneous infection primarily disseminates on the head,

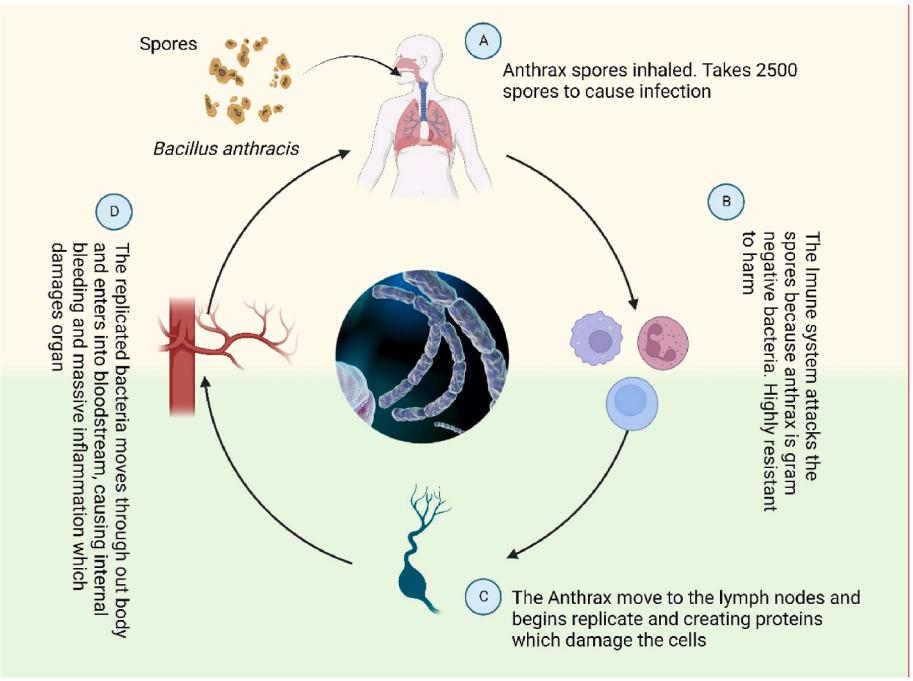

Fig. 2. Pathophysiology of anthrax infection in human or host bodies via inhalation of spores and disease progression.

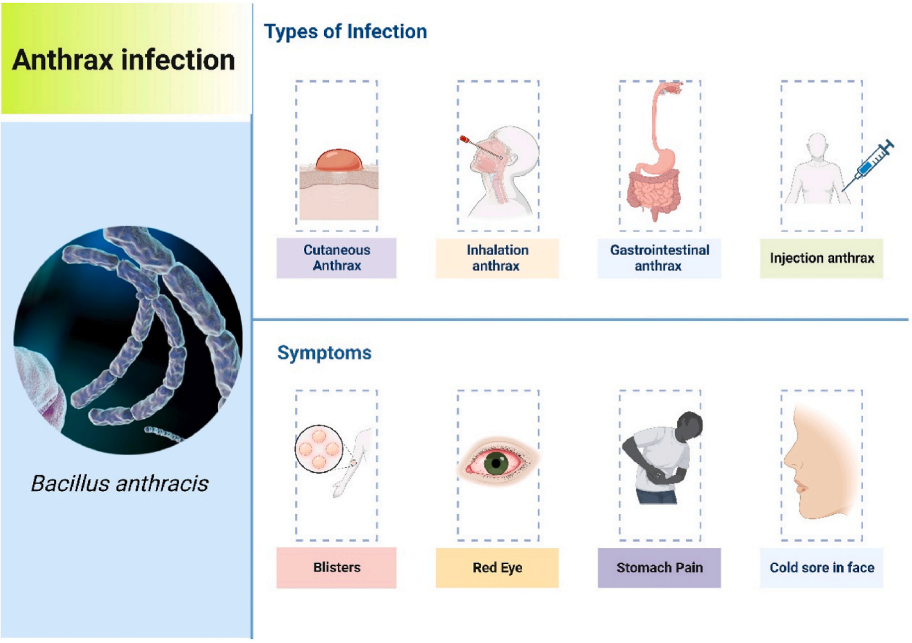

Fig. 3. Understanding of possible sign, and symptoms of anthrax infection in human due to *B. anthracis* bacterium.

neck, forearms, and hands, resulting in harm to the skin and surrounding tissue in the affected region. The onset of this infection often occurs within 1 week following exposure to anthrax [42–44]. The second variant is inhalation anthrax, which poses the highest level of risk. It occurs when individuals contract the infection by exposure to spores in wool mills, slaughterhouses, and tanneries. Initially, the symptoms manifest in the lymph nodes in the chest before disseminating throughout the entire body [42,44]. Gastrointestinal anthrax arises from the ingestion of raw or undercooked meat obtained from animals that are infected. Mainly, this type of infection disseminates to the throat, esophagus, stomach, and intestines [42,43]. Injection anthrax, a recently discovered form of the disease, has been detected in heroin users who inject drugs throughout northern Europe. Primarily, the infection disseminates within the subcutaneous tissue following the administration of the medicine [42–44]. The various ranges of percentage (%) of mortality have been further summarized in Fig. 4.

3.2.1. *Cutaneous anthrax*

Cutaneous anthrax is transmitted through contact with contaminated animal products particularly if it comes in contact with exposed wounds. Cases of cutaneous anthrax spreading from human to human are quite scarce. The symptoms of cutaneous anthrax usually include itchy sores resembling that of an insect bite, followed by blister formation which ultimately evolves into a painless ulcer with a black center

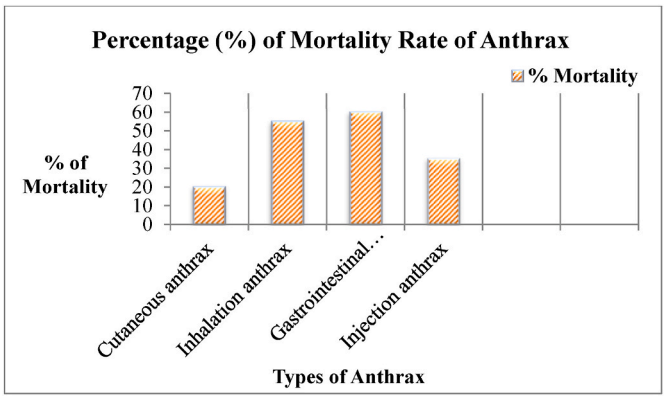

Fig. 4. Graphical understanding of % of mortality rate of several types of anthrax infection in human, relies on the pathway by which the germs infiltrate the host.

known as eschar [45]. Cutaneous anthrax is generally cured using antibiotics such as ciprofloxacin or doxycycline. Ciprofloxacin belongs to the quinolone group of antibiotics which inhibits the activity of DNA gyrase and topoisomerase IV [46]. On the other hand, doxycycline belongs to the tetracycline group of antibiotics which allosterically binds to the 30S subunit of prokaryotic ribosome, inhibiting protein synthesis [47]. These antibiotics are given intravenously in case of severe systemic symptoms. About 20 % of the cases, may cause death in the absence of proper treatment. Some ways to avoid cutaneous anthrax infections include, wearing gloves while handling animals/animal products, and ensuring proper sterilization of the areas where animals are bred or kept in bulk. The vaccination of animals for high-risk populations is also an important step forward.

3.2.2. *Gastrointestinal anthrax*

Gastrointestinal anthrax is a rare type of anthrax caused by the ingestion of *B. anthracis* spores through contaminated, uncooked, or raw food. One of the most common sources is meat from herbivorous animals such as cattle and sheep. Symptoms include vomiting, nausea, diarrhea, abdominal pain, and loss of appetite [48]. Diagnosis includes serological assays as well as laboratory testing of stool samples, and microbiological and biochemical analysis [49]. The treatment regimen includes conventional antibiotics such as doxycycline and ciprofloxacin or penicillin derivatives. This form of anthrax has a far worse prognosis than that of the cutaneous anthrax, about 50 % of the patients may die if proper treatment is not given [50]. GI anthrax infections can be avoided by proper handling and cooking of meat, education, and surveillance on proper disposal of animal carcasses.

3.2.3. *Pulmonary/inhalation anthrax*

Pulmonary anthrax is a potentially fatal form of anthrax infection which is mainly caused by inhalation of *B. anthracis* spores. Aerosolized spores found in animal and textile industries are the major driving force of the infection. Once the spores are inhaled, they germinate in the alveoli of the lungs. Symptoms of this infection include high fever, chills, sore throat, and mild cough i.e. dry cough. These conditions may be followed by chest pains, shortness of breath, and dizziness. Pulmonary anthrax can be diagnosed by clinical evaluation, computed topography (CT)/X-ray imaging of the lungs, typically showing widened mediastinum, or laboratory testing of sputum samples. Medications include ciprofloxacin and doxycycline as the first line of treatment along with certain antitoxins such as raxibacumab and Obiltoxaximab. The prognosis of this form of anthrax is one of the worst ranging up to 100 % mortality if not treated in time and with proper medication, with timely intervention 55 % of the patients will survive [51].

4. Diagnosis

Physicians typically rely on the patient's medical history, standard diagnostics, and microbial culture to diagnose *B. anthracis*. As per the criteria outlined by the World Health Organization (WHO), it is recommended to assess an individual's travel history, occupation with animals, and contact with infected or deceased animals. In order to verify the diagnosis of this infection, microbiological testing is conducted to detect the presence of antibodies or any toxin in the blood, as well as to identify *B. anthracis* samples from blood, spinal fluid, skin lesion swabs, and respiratory secretions. *B. anthracis* is a bacterium that has a rod-shaped structure that stains purple when subjected to the Gramme staining method. The capsule of the bacteria exhibits a striking pink color when treated with polychrome methylene blue. Blood agar is the medium employed for cultivating microorganisms present in the bloodstream. Selective media such as PLET (polymyxin-lysozyme-EDTA-thallous acetate) agar [52], and TSPBA more efficacious for *B. anthracis* culture than blood agar. Also, leukocyte count is an effective method to understand whether a person is infected or not. Another selective approach is Anthrax Blood Agar (ABA), which includes cycloheximide, polymyxin B, trimethoprim, and sulfamethoxazole. When grown on this medium, the organism forms white or grey colonies that do not cause hemolysis. Another alternative is the utilization of R&F Anthrax Chromogenic Agar (ChrA), which includes cycloheximide, polymyxin B, and X-indoxyl-choline phosphate (X-CP). X-CP serves the purpose of identifying the existence of the phosphatidylcholine phospholipase C enzyme, which *B. anthracis*, *B. cereus*, and *B. thuringiensis* secrete. After incubating for 24 h, colonies of *B. anthracis* exhibit a frosted glass-like appearance and are cream to faded blue. After a further 24 h of incubation, white margins start to emerge. Chromogenic *B. cereus* Agar and Cereus Ident Agar can serve as selective media. The media contain a chromogenic substrate called 5-bromo-4-chloro-3-indolyl-ß-glucopyranoside. This substrate is broken down by the β-glucosidase enzyme, which is produced by the majority of Bacillus species. *B. anthracis* colonies exhibit a white-creamy hue on these substrates [12]. Modern approaches such as BD™, and BACTEC™ FX40 Automated Blood Culture System are used which are capable of growth and detection of blood-borne pathogens are also used for the detection of *B. anthracis* [53]. *B. anthracis* is susceptible to gamma phage infection [54], penicillin G [55], further exhibited the catalase activity [56], and non-hemolytic on blood agar [57]. All these properties can be exploited for diagnosis and detection of this pathogen.

However, microbiological testing can give ambiguous results, hence more specific and efficient testing technologies have been implemented in recent times. Diagnosis of anthrax infection can be done with the help of polymerase chain reaction (PCR) via targeting anthrax-specific gene segments such as *capB, capA, pagA*, etc. [58]. The isothermal DNA amplification was carried out by Zasada AA et al. for 3 different pathogens, i.e., *B. anthracis, Yersinia pestis,* and *Francisella tularensis.* Three methods were used to do so, loop-mediated isothermal amplification, *thermophilic* helicase-dependent isothermal DNA amplification and recombinase polymerase. Three different approaches were shown to have low specificity for *B. anthracis*, medium specificity for *Y. pestis*, and high specificity for *F. tularensis*. For each approach, the detection limit and sensitivity were similar and high. they came to the conclusion that the lateral flow dipsticks, which allow viewing the results without the need for any equipment, have been a very helpful instrument for product identification of the isothermal amplification method [58].

ELISA is another important technique which can be used to detect the presence of anthrax infection, however one major limitation to this technique lies in the structure of the surface antigens of *B. anthracis* surface antigens. The surface antigens of *B. cereus* endospore and that of *B. anthracis* endospore are similar in structure. The only difference being a presence of tetra saccharide containing monosaccharide on the surface of *B. anthracis* surface antigen, known as anthrose. In addition, Tamborrini M et al. demonstrated that production of Anti-tetra saccharide and anti-anthrose-rhamnose disaccharide monoclonal antibodies and

performing sandwich ELISA was an effective method for detection. The problem of *B. cereus* cross reactivity was minimized and conclusive detection of *B. anthracis* was possible. This test was followed by a Luminex assay. The Anti-tetra saccharide and anti-anthrose-rhamnose disaccharide monoclonal antibodies were used in this assay as well. The Luminex technology is based on color-coded fluorescent beads. A reagent designed specifically for a given analyte can be applied to each bead subset, enabling the analyte to be captured and detected from a complicated sample. Lasers activate internal dyes in the BioPlex analyzer to identify individual bead particles and any reporter dye that may have been caught during the experiment. The Luminex assay exhibited a sensitivity that was ten to one hundred times greater than an equivalent antigen capture ELISA, no cross reactivities were observed. Hence, Luminex assay was established as an important rapid detection technique for *B. anthracis* spores [59]. ELISA against Protective antigens of *B. anthracis* was found to have a minimum detection limit of around 0.06 μg/mL with a lower limit of 0.09 μg/mL. The sensitivity of diagnosis was around 97.8 % with specificity of 94.2 %. To enhance this specificity competitive ELISA could be performed which would increase the specificity to 100 %. This has been found to serve as an extremely sensitive and specific method for the identification of inhalational anthrax as well as cutaneous anthrax. This technique was developed by the Centers for Disease Control and Prevention developed after the 2001 human anthrax epidemic [60].

An immunoprecipitation-based approach was elucidated by Barr JR et al., revolved around quantification of Protective Antigen-LF also known as lethal toxin or LTx via anti-PA IgG magnetic immunoprecipitation. The study exhibited 100 % specificity and sensitivity in animal (*Rhesus macaques*) and 27 clinical trials. Ltx was detected even after exposure to antibiotics and 36 h post exposure, Ltx levels increased gradually towards the late stages of anthrax in animal model. This establishes LTx based immunoprecipitation as one of the most efficacious and rapid tests for the accurate detection of anthrax [61].

The United States Food and Drug Administration has also released special kits for anthrax detection known as anthrax-PA kits which basically detects the presence of anthrax protective antigen. Biosensors such as Genosensors and immunosensors are also effective and rapid detection technologies with high efficiency [9]. Geno sensors work on the principle of nucleic acid hybridization wherein, pathogen specific DNA-probes are designed in order to bind to pathogenic DNA segments/genes (e.g. *pagA)*, subsequently confirming the presence of the pathogen [9]. Using cyclic voltammetry (CV) redox peaks, Raveendran and his colleagues invented the first DNA biosensor, utilizing mercaptohexanol (MCH) and a thiol-linked pagA-specific probe forming a self-assembled layer on a gold electrode. Through the process of hybridization, the immobilization of this probe onto the electrode enabled the detection of target DNA, resulting in detectable changes in peak current and potential in the cyclic voltammetry study [62].

A quartz crystal microbalance (QCM) biosensor was used by Hao et al. to find pagA and BA813 chromosomal markers. A DNA probe that has been thiol-modified is attached to the QCM's gold surface as part of the biosensor [63]. A similar alternative is use of Immunosensors, which uses antibody probes which bind to pathogenic epitopes [64]. Lead magnesium niobate-lead titanate/tin (PMN-PT/Sn) piezoelectric microcantilever sensors (PEMS) were developed specifically for the detection of *B. anthracis* spores, and a novel application was shown by McGovern et al. The process entails immobilizing certain antibodies on the platinum electrode that is part of the PMN-PT layer. Based on the piezoelectric effect, this novel sensor device measures changes in electrical characteristics due to mechanical stress caused by *B. anthracis* spores adhering to immobilized antibodies. An inventive amperometric immunoassay was developed by Waller et al. to identify *B. anthracis* spores. The immunomagnetic separation is an assay technique that effectively extracts spores from a given sample. By using magnetic beads conjugated with antibodies that bind to *B. anthracis* spores selectively, this approach improves specificity [65]. Amperometric measurements are used to precisely quantify the spores after they are captured. Amperometry is a dependable method of detection that measures the electric current produced during an electrochemical process. Immunomagnetic separation in conjunction with amperometric measurement guarantees a sensitive and specific assay for *B. anthracis* spores, which is essential for the prompt and precise identification of this disease [66]. For cutaneous anthrax a swab-based protocol is followed. This method generally relies on the presence of viable cells of *B. anthracis* from the lesions. Three main types of swabs are may be used including rayon, polyester and flocked-nylon swabs. The RT-PCR was performed after extraction, and the extraction tube system yielded favorable results with high recovery of *B. anthracis* from swabs within day 1. As the number days increased, the reduced viability was observed leads to yielding non-viable cells by 28 days [67].

5. Prevention

The healthcare professionals are working to enhance the knowledge within communities and also positive efforts had been implemented event-based surveillance (EBS) and early detection mechanisms of anthrax infection [25,68,69]. Active surveillance has been started on Meat inspections in butcher shops. Several specific training sessions are conducted to boost the case management efficiency in the provinces. Various health promoting programme including social media campaigns, radio broadcasts, and the distribution of informative brochures and posters. The general public is advised to refrain from handling and consuming meat sourced from animals that have died suddenly, undergone emergency slaughter, or has an uncertain origin. Additionally, anthrax poses an occupational hazard for professionals such as veterinarians, agriculture and wildlife workers, as well as those involved in animal butchery or meat, hide, hair, and wool processing [25,68,69]. It is crucial for these workers to wear preventive clothing, gloves, or personal protective equipment (PPE) to minimize the risk of exposure [25,68,69]. It is also notable to improve the screening process of anthrax infection. When tending to patients with draining anthrax lesions, it is crucial to enforce contact precautions. This involves isolating the patient in a private room and utilizing personal protective equipment (PPE), such as examination gloves and a fluid-resistant gown. Additionally, dressings may be applied to manage drainage and minimize the risk of environmental contamination [25,68,69]. The proper disposal of these dressings as infectious waste is essential after use. The travelers heading to countries where anthrax is prevalent should be mindful of regulations pertaining to the importation of restricted animal products, trophies, and souvenirs. Anthrax is managed through initiatives such as animal vaccination programs, prompt detection and reporting, quarantine procedures, treatment of animals showing subclinical symptoms (post exposure prophylaxis), and the disposal of suspected or confirmed animal cases through burning or burial [25,68,69]. Centre for Disease Control and Prevention has established guidelines for prevention and control of anthrax. It recommends vaccination for individuals who are at high risk of infection such as people who are handling animals as well as people who are working with *B. anthracis* in lab settings. Anthrax vaccine absorbed (AVA) is one of the primary preventive measures for people at high risk. The public health officials also provided the impacted population, including children, a 10-day course of antibiotic (ciprofloxacin and doxycycline) prophylaxis within 48 h of suspected exposure. It might be advised to administer antibiotic PEP for an extra 50 days to individuals who have confirmed substantial exposure [70]. In cases of systemic anthrax, particularly those without meningitis, the CDC advises using a combination therapy strategy that combines several antimicrobials. When it comes to anthrax inhalation, which is linked to increased rates of morbidity and mortality, this approach has proven to be more effective than monotherapy. The goal of this combination therapy is to reduce the chance of experiencing serious side effects while increasing therapeutic efficacy against *B. anthracis* spores. The CDC's Cities Readiness Initiative (CRI) describes strategies for quickly

providing medical countermeasures to impacted populations in the widespread anthrax attack. The purpose of this project is to lessen the effects of a possible anthrax-related bioterrorism incident. Based on fresh findings and clinical information, the CDC continuously evaluates and revises its anthrax management guidelines [71]. These changes are based on recent research, which includes systematic evaluations of hospital treatment outcomes. This research also helps to improve recommendations for other interventions, i.e., antibiotic treatment.

6. Therapeutics

The therapeutic interventions for human anthrax involve addressing the challenges posed by *B. anthracis*, a bacterium causing both animal and human infections. Inhalational anthrax, a severe and potentially fatal form of the disease, necessitates effective treatment beyond conventional antibiotics. Raxibacumab, a fully-human monoclonal antibody targeting the protective antigen of *B. anthracis*, serves as an adjunct treatment by blocking toxin activity. Prophylactic and therapeutic efficacy has been demonstrated in animal models, with favorable safety profiles in humans [72]. In cases where anthrax meningitis is suspected or cannot be ruled out, empiric treatment should involve three antimicrobial drugs, including one with bactericidal activity, one acting as a protein synthesis inhibitor, and all with good central nervous system penetration [73]. Diagnosis relies on case history, disease epidemiology, clinical signs, and laboratory examinations. Swift identification and treatment of affected individuals, vaccination, quarantine, premises disinfection, and disposal of infected materials are recommended [74]. The emergence of antibiotic resistance in anthrax poses a significant public health concern. Overuse of antibiotics in animal husbandry and aquaculture contributes to antibiotic-resistant bacteria, including those responsible for anthrax. Several studies in China and Indonesia reveal instances of antibiotic resistance, emphasizing the potential transmission of resistant strains from animals to humans [75,76]. The infected person must be admitted to the hospital and can be treated by using antibiotics or by introducing antitoxin. Antibiotics, mainly penicillin G or amoxicillin are effective against all kinds of anthrax infection. In cases of cutaneous anthrax oral antibiotics such as doxycycline as well as ciprofloxacin are also used [77,78]. This calls for alternative treatments, such as tetracycline, and underscores the urgency of developing new vaccines, anthrax toxin inhibitors, and antibiotic therapeutics to combat resistance and enhance treatment options [76,79]. Neutralizing anthrax toxins is a key aspect of treatment, with raxibacumab and anthrax immune globulin being crucial antitoxins. Raxibacumab, a recombinant human monoclonal antibody, prevents the binding of anthrax toxin's protective antigen component, mitigating its harmful effects [72]. Anthrax immune globulin, containing neutralizing antibodies against protective antigen, improves hemodynamics and survival during toxin-induced shock, particularly when used alongside antibiotics [80,81]. These antitoxins, integral to anthrax management, are recommended in combination with antibiotics, with raxibacumab also advocated for use with anthrax vaccination in cases of suspected exposure [72]. The ongoing development of effective treatments, including vaccines, anthrax toxin inhibitors, and antibiotics, is crucial to address antibiotic resistance and enhance the overall management of anthrax infections [81].

6.1. Antibiotic treatment

In case of mild cutaneous anthrax, intramuscular procaine penicillin treatment is generally carried out. Approximately 500–600 mg needs to be injected every 12–24 h, for a span of 3–7 days. Other alternatives include amoxicillin as well as penicillin V treatment (orally given 500 mg every 6 h) [82]. In case of life-threatening cases of gastrointestinal or inhalation anthrax, the intravenous antibiotic therapy is preferred. For instance, Penicillin G is generally administered approximately 2400 mg ever 4–6 h via intravenous injections. Other drug choices include ciprofloxacin. Penicillin G is often supplemented with clarithromycin or aminoglycoside based on the types of anthrax. Gastrointestinal anthrax requires aminoglycoside group of antibiotics in conjunction with Penicillin G, on the other hand inhalation anthrax require clarithromycin or clindamycin [43]. On the other hand, levofloxacin is recommended for anthrax meningoencephalitis [83].

Another form of anthrax is systematic anthrax which has a considerably high mortality when compared to other forms of anthrax. A thorough strategy is emphasized in the current national guidelines for the individualized treatment of systemic anthrax, a potentially fatal infection. A minimum 2-week course of combination intravenous antibiotics is indicated as part of the recommended treatment strategy. These antibiotics have been carefully selected to meet the complexity of anthrax infection. Interestingly, in order to maximize treatment effectiveness, a combination of bactericidal and protein synthesis inhibitor antimicrobials is recommended for all instances of systemic anthrax. When anthrax affects the central nervous system, especially when anthrax meningitis occurs, the recommendations emphasize the need to use at least three antimicrobials with strong blood-brain barrier penetration. The goal of this multifaceted strategy is to effectively eradicate the anthrax bacteria from the central nervous system while optimizing the therapeutic effect. The guidelines emphasize treating each patient individually, taking into account their unique needs and the variety of obstacles this infectious disease presents. This reflects a nuanced understanding of the disease's many presentations. By supporting such a comprehensive and customized approach, the guidelines are in line with modern medical practices and concepts and seek to maximize results and reduce the dangers related to systemic anthrax. Compared to patients receiving no overlapping medication, those getting overlapping bactericidal and protein synthesis inhibitor therapy had a survival rate of 45 % and only 28 % in case of monotherapy [84].

6.2. Antibody/anti-toxin treatment

A study by Hull et al. demonstrated that a plant based monoclonal antibodies against protective antigen showed efficacious results against *B. anthracis* in primates. The monoclonal antibody was able to neutralize protective antigen of *B. anthracis* spores. A concentration of 50 mg/ml was able to neutralize the protective antigen, which resulted in survival of the cell. Monoclonal antibody injected mice were able to survive the injection of the spores of *B. anthracis* while control mice died within a span of 3 days. This shows that monoclonal antibodies targeting protective antigen could be an effective in prevention and treatment of anthrax [85]. Lethal toxin (LT) from anthrax is a key component of the pathogenicity of anthrax; multiple animal experiments have demonstrated that reducing toxin activity significantly reduces morbidity. Currently being investigated tactics include antibodies, which are the most sophisticated technique that is almost ready for product fruition, receptor decoys, inhibitors of dominant-negative translocation, inhibitors of small molecule, and substrate analogues. These many approaches highlight how antitoxin research is changing and show a deliberate attempt to develop effective countermeasures to the critical role that LT plays in anthrax pathogenesis. Antitoxins are used to treat the active spores present into the body. Raxibacumab and Obiltoxaximab are two monoclonal antibodies/antitoxins which has shown beneficial effects in animal models [86]. Raxibacumab is an IgG1 class of monoclonal antibody against the protective antigen of *B. anthracis.* In animal model it has shown efficacy against inhalation anthrax. It has already been approved by US in 2012 based on animal model and human volunteers. It has recommended dose of 40 mg/kg, and it is administered intravenously in subjects above the age of 40. On the other hand, Obiltoxaximab, is a human mouse chimeric monoclonal antibody, against the protective antigen of *B. anthracis*. Similar to Raxibacumab it is administered intravenously with a recommended dose of 16 mg/kg. Both treatments could be supplemented with anti-histamines to avoid allergic response/hypersensitivities [87].

Table 1
Summarizations of various clinical trials on vaccines for the treatment of anthrax infection in the past years, summarized from ClinicalTrials.gov.

NCT Number	Study Title	Interventions	Sponsor	Completion Date	Reference
NCT03877926	VELOCITY: An Anthrax Vaccine Clinical Study	AV7909, BioThrax	Emergent BioSolutions	06-08-2020	[110]
NCT03518125	BARDA Securing Anthrax Immunity For the Elderly	BioThrax, AV7909, Sodium chloride injection USP, 0.9 % (placebo)	Biomedical Advanced Research and Development Authority	09-12-2019	[111]
NCT01770743	A Phase 2 Safety and Immunogenicity Study for an Anthrax Vaccine Using 3 Schedules and Two Dose Levels	AV7909, BioThrax	Emergent BioSolutions	2014–12	[112]
NCT04067011	Velocity 2: An Anthrax Vaccine and Antibiotics Clinical Study	Ciprofloxacin 500 mg Tablet, Doxycycline 100 mg Tablet, AV7909	Emergent BioSolutions	19-03-2020	[113]
NCT01491607	Immunogenicity and Safety Study of a Three-Dose BioThraxÂ® Regimen for Post-Exposure Prophylaxis in Healthy Adults	BioThrax	Emergent BioSolutions	2012–05	[114]
NCT01753115	Ciprofloxacin BioThrax Co-Administration Study	BioThrax, Ciprofloxacin	Emergent BioSolutions	2013–08	[115]
NCT01263691	Safety, Tolerability and Immunogenicity Study of AV7909 Anthrax Vaccine in Healthy Adults	BioThrax, AV7909 Formulation 1, AV7909 Formulation 2, AV7909 Formulation 3, AV7909 Formulation 4	Emergent BioSolutions	2012–06	[116]
NCT01641991	Assessment of the Immunogenicity and Safety of a Dose-Sparing BioThraxÂ® AVA Schedule	BioThraxÂ®, BioThraxÂ®	National Institute of Allergy and Infectious Diseases (NIAID)	2013–06	[117]
NCT00119067	Anthrax Vaccine Clinical Trial to Assess Dose Reduction and Route Change	Anthrax Vaccine Adsorbed, Saline injection	Centers for Disease Control and Prevention	2010–02	[118]
NCT02339155	Effect of Raxibacumab on Immunogenicity of Anthrax Vaccine Adsorbed	AVA, Diphenhydramine	Emergent BioSolutions	06-06-2017	[119]

7. Vaccinations

Vaccines are also available for livestock and humans in limited supply. Human vaccines are limited to those with possible occupational exposure. Veterinary vaccines are used for control of anthrax in livestock. Vaccination protocols for livestock should be strictly followed to curb anthrax spread. Preventing the disease in animals will protect human health. Human vaccines have been developed against protective antigen, and has been licensed by UK and US. Protective immunity has been found against primates. *B. anthracis* strain V770-NP1-R was used to formulate the US licensed vaccine, it requires six doses followed by booster doses yearly. *B. anthracis* Sterne strain 34F2 was used for the UK vaccine it requires four doses followed by yearly booster doses. Second-generation protein-based vaccinations are a significant advancement due to their precisely defined composition, lack of side effects, and use of animal-free media. The aim of these vaccines is to enable self-administration, so removing the requirement for needles and enabling broader vaccination campaigns. The optimal composition simplifies logistical issues by allowing for large-scale manufacture and room temperature storage in addition to providing efficient protection with low dosage. Strict safety, effectiveness, and clinical trial protocols highlight the dedication to guaranteeing the dependability and appropriateness of these cutting-edge vaccinations for widespread distribution, signaling a significant transition towards safer, easier-to-acquire, and more effective immunization approaches. The Avecia vaccine, developed by the Defence Science Technology Laboratory at Porton Down uses an optimized version of the Protective Antigen (PA) gene based on nucleotide codons. This gene can produce significant amounts of recombinant PA (rPA) in grammes per litre when produced by *Escherichia coli* (*E. coli*). In order to obtain large yields of rPA, the cooperation makes use of knowledge in genetic optimization and *E. coli* expression systems, highlighting the vaccine's creative approach to the goal of effective and scalable production. This novel fusion of microbial expression and genetic engineering represents a major breakthrough in the creation of vaccines [88]. Third generation vaccines include vaccines which are user friendly and can be easily administered. Live attenuated vaccine and edible antigens are currently two frontiers in anthrax vaccine research.

Anthrax vaccines are actively undergoing clinical development to address research gaps in the field [89]. Two evaluated vaccines, BioThrax and AV7909, have been studied in adults aged 66 years and older [90]. The Guinea Pig Inhalational Anthrax Model has been established to assess post-exposure prophylaxis efficacy [91]. Simultaneous administration of foot-and-mouth disease (FMD) and anthrax vaccines in sheep has shown no hindrance to FMD vaccine response and may even enhance early antibody response [92]. Development of more effective veterinary vaccines, not containing the pathogen, is crucial [93]. Various types of anthrax vaccines exist, categorized by nature and bacterial strain. These include inactivated, live attenuated, toxoid, subunit, conjugate, DNA, and edible vaccines [94,95]. Each type has distinct advantages and disadvantages, requiring consideration of factors like bacterial strain, desired immune response, and administration route. Research indicates the timing, number of doses, and antibiotic combination for anthrax vaccination depend on the specific vaccine and exposure scenario. Both pre- and post-exposure vaccination can reduce casualties in large-scale attacks [96]. The number of doses varies, such as the two-dose regimen for Px563L, a recombinant vaccine candidate [97]. Combining antibiotics with vaccination, especially in post-exposure prophylaxis, is crucial [96]. Effectiveness and limitations of anthrax vaccination involve studies on acellular protein vaccines, with partial protection in guinea pigs, and identified side effects like injection site reactions [98,99]. A combination of vaccination and sanitation is effective in controlling anthrax transmission in animals [100]. An oral vaccination method has been developed, potentially simplifying mass campaigns [101]. Immune response and protection levels vary based on vaccine type and individual characteristics. Live anthrax vaccines and certain adjuvants can elicit durable immune responses [102,103]. Recombinant chimeric proteins and DNA vaccines show promise in inducing strong immune responses in animal studies [104,105]. Future directions in anthrax vaccine development include stable modified recombinant antigens, bicistronic secretory anti-anthrax DNA vaccines, and comparative studies identifying promising components [106–109]. These advancements aim to enhance stability, immune responses, and protection against virulent strains of *B. anthracis*. Table 1 further summarizes the various clinical trials on vaccine for the treatment of anthrax infections in past few years.

8. Conclusions

The current outbreak of anthrax in Zambia, caused by *B. anthracis*, has prompted significant public health concerns. The persistence of this zoonotic disease can be attributed to societal norms, community resistance, lack of awareness, the socioeconomic crisis, and inadequate medical resources. The COVID-19 pandemic underscores the imperative for collaborative endeavors in disease monitoring and prevention across neighboring nations. The heightened danger at the regional level is due to the frequent movement of animals and people across borders. The identification of anthrax infection promptly is challenging since it presents with diverse symptoms, i.e., cutaneous, gastrointestinal, inhalation, and pulmonary manifestations. Although traditional microbiological testing remains essential, recent advancements in diagnostic technology, i.e., PCR and ELISA, offer more precise and efficient methods for identifying microorganisms. The main objectives of preventive measures encompass enhancing community knowledge, implementing active surveillance, and promoting safe meat handling practices. The healthcare professionals endorse animal vaccination programs and emphasize the importance of implementing preventive measures for individuals vulnerable to workplace injuries. To reduce the case-fatality rate, it is crucial to implement the novel therapeutic interventions, i.e., administering antitoxins, antibiotics, and development of immunological products. There is no direct correlation or known interaction between COVID-19 and anthrax. However, a patient with compromised immunity due to COVID-19 could theoretically be more vulnerable to secondary infections, including anthrax if exposed. However, such cases would be extremely rare given the differing transmission pathways. In order to mitigate the impact of anthrax outbreaks and safeguard the well-being of both humans and animals, it is crucial to implement a holistic approach that includes enhanced diagnostic methods, proactive preventive measures, and increased public knowledge. Furthermore, the understanding and preventive measures of such infectious diseases should be taken into considerations by the human subjects those who are at higher risk of exposure or directly involved with such jobs or activities.

CRediT authorship contribution statement

Sumel Ashique: Writing – review & editing, Writing – original draft, Resources, Formal analysis, Data curation, Conceptualization. **Aritra Biswas:** Writing – original draft, Formal analysis, Data curation. **Sourav Mohanto:** Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Shriyansh Srivastava:** Writing – original draft, Resources. **Md Sadique Hussain:** Writing – review & editing, Resources. **Mohammed Gulzar Ahmed:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Vetriselvan Subramaniyan:** Writing – review & editing, Project administration, Funding acquisition, Data curation.

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Declaration of competing interest

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List of abbreviations:

B. anthracis: *Bacillus* anthracis; **UV**- Ultraviolet; **PA**- Protective antigen; **LF**- Lethal factor; **EF**- Edema factor; **PLET**- Polymyxin-lysozyme-EDTA-thallous acetate; **TSPBA**- Trimethoprim sulfamethoxazole polymyxin blood agar; **EDTA**- Ethylenediaminetetraacetic acid; **ABA**- Anthrax Blood Agar; **ChrA**- Chromogenic Agar; **X-CP**- X-indoxyl-choline phosphate; **PCR**- Polymerase chain reaction; **ELISA**- Enzyme linked immunosorbent assay; **CV**- Cyclic voltammetry; **DNA**- Deoxyribonucleic acid; **MCH**- Mercaptohexanol; **QCM**- Quartz crystal microbalance; **PMN-PT/Sn**- Lead magnesium niobate-lead titanate/tin; **PEMS**- Piezoelectric microcantilever sensors; **EBS**- Event-based surveillance; **PPE**- Personal protective equipment; **LT**- Lethal toxin; **IgG1**- Immunoglobulin G1; **UK**- United Kingdom; **USA**- United States of America; **rPA**- Recombinant protective antigen; **FMD**- Foot-and-mouth disease.

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