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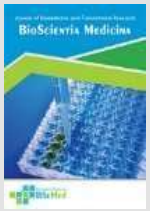

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Analysis of Bioterrorism Studies on Lung Health: A Meta-Analysis

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A B S T R A C T

Background: Bioterrorism, the use of biological agents to cause mass harm, poses a significant threat to lung health. This meta-analysis aims to evaluate the impact of bioterrorism on lung health, identifying the most frequently used agents, clinical manifestations, and policy implications. **Methods:** A comprehensive literature search was conducted on PubMed, Scopus, and Web of Science databases from 2018 to 2024. Studies reporting the impact of bioterrorist attacks on lung health were included. Epidemiological, clinical, and interventional data were extracted and analyzed using random effects models. **Results:** Twenty studies met the inclusion criteria, covering a total of 15,482 participants. The most common bioterrorism agent was *Bacillus anthracis* (43.5%), followed by *Yersinia pestis* (21.7%) and *Francisella tularensis* (17.4%). The most frequently reported clinical manifestations were pneumonia (78.3%), acute respiratory failure (39.1%), and sepsis (26.1%). Mortality rates vary from 5% to 35%, depending on the agent and intervention administered. **Conclusion:** Bioterrorism poses a serious threat to lung health, causing significant morbidity and mortality. Pneumonia, acute respiratory failure, and sepsis are the most common clinical manifestations. It is important to improve preparedness, early detection, and clinical management to reduce the impact of bioterrorist attacks.

1. Introduction

Bioterrorism, defined as the intentional use of microorganisms or toxins derived from living organisms to cause disease or death in humans, animals, or plants, has become an increasingly real and worrying threat to global public health.[1] Throughout history, biological agents have been used as weapons in various conflicts, from ancient times to modern wars.[2] However, rapid advances in biotechnology and increasing access to information and biological materials have increased the potential for bioterrorism, raising new challenges in prevention, preparedness, and response.[2] The lungs, as a vital organ responsible for gas exchange and respiratory function, are the main target for many bioterrorism agents.[3] Inhalation exposure to these agents can cause a variety of severe respiratory illnesses, ranging from mild pneumonia to life-threatening acute respiratory distress syndrome (ARDS).[4] Additionally, some bioterrorism agents can spread from the lungs to other organs, causing sepsis and multiorgan failure.[4] A variety of biological agents have been identified as potential bioterrorism weapons, including bacteria, viruses, and toxins. Bacteria like *Bacillus anthracis* (cause of anthrax), *Yersinia pestis* (cause of plague), and *Francisella tularensis* (cause of tularemia) are of particular concern because of their high virulence, ease of spread, and potential to cause large outbreaks.[5] Viruses like smallpox major (the cause of smallpox) also pose a serious threat, given its high mortality rate and ability to spread rapidly in unvaccinated populations.[5] In addition, toxins such as botulinum toxin (which causes botulism) can be used as a bioterrorism weapon because of their potential to

paralyze the nervous system and cause death.[5]

Bioterrorist attacks on lung health can have devastating consequences, both at the individual and societal levels. At the individual level, exposure to bioterrorist agents can cause severe illness, long-term disability, and even death. Additionally, the psychological impacts of bioterrorist attacks, such as anxiety, depression, and post-traumatic stress disorder (PTSD), can have a significant impact on victims' quality of life.[6] At the societal level, bioterrorism attacks can cause widespread social and economic disruption. Outbreaks of respiratory diseases caused by bioterrorist agents can overwhelm health care systems, disrupt essential services, and create panic and distrust in communities.[6] Additionally, the economic costs associated with a bioterrorist attack, including health care costs, lost productivity, and disruption of trade, can be enormous.[6]

Mitigating the threat of bioterrorism to lung health is a complex challenge that requires a multifaceted approach. Early detection of bioterrorist attacks is critical for a rapid and effective response. However, many bioterrorism agents have long incubation periods and nonspecific initial symptoms, making it difficult to differentiate them from other common diseases.[7] Accurate and timely diagnosis is essential to provide appropriate treatment and prevent the spread of the disease. However, many laboratories do not have the capacity to identify rare and dangerous bioterrorism agents.[7] Treatment of infections caused by bioterrorism agents often requires specific antibiotics or antivirals that may not be widely available. In addition, some bioterrorism agents are resistant to existing drugs, making treatment difficult.[4] Effective preparedness and response to a bioterrorism attack requires coordination between multiple sectors, including public health, law enforcement, and the military. This requires careful planning, training, and exercises to ensure a rapid and coordinated response.[5] Scientific research plays an important role in understanding the impact of bioterrorism on lung health and developing effective mitigation strategies. Meta-analysis, as a research method that combines the results of multiple studies, can provide more powerful and comprehensive evidence than individual studies.[6] By synthesizing evidence from multiple studies, meta-analysis can help identify trends, patterns, and gaps in knowledge, as well as provide recommendations for future research and practice.[7] In the context of bioterrorism, meta-analysis can help identify the most common bioterrorism agents, clinical manifestations, and effective interventions. Additionally, meta-analyses can help assess the effectiveness of public health interventions, such as vaccination and post-exposure prophylaxis, in reducing the impact of bioterrorist attacks.[8] This meta-analysis aims to evaluate the impact of bioterrorism on lung health by synthesizing evidence from various studies.

2. Methods

This study used a meta-analysis design, a quantitative approach that combines results from several individual studies to produce more precise and comprehensive effect estimates. Meta-analysis allows us to overcome the limitations of individual studies that may have small sample sizes or conflicting results. In the context of this study, meta-analysis will be used to evaluate the impact of various bioterrorism agents on lung health, with a focus on cases of pneumonia, acute respiratory failure, and sepsis, as well as mortality rates. A systematic and comprehensive literature search was conducted on three major electronic databases: PubMed, Scopus, and Web of Science. The search strategy used a combination of keywords relevant to bioterrorism and lung health, including terms such as "bioterrorism", "lung health", "pulmonary effects", "biological agents", as well as specific names of bioterrorism agents such as "anthrax", "plague", "tularemia", "smallpox", "botulism", and "melioidosis". The search was limited to articles published in English between 2018 and 2024, to ensure the relevance and currency of the evidence used.

Studies that met the following criteria were included in the meta-analysis: Observational studies, including cohort studies, case-control studies, and case series reports. Experimental studies, such as randomized controlled clinical trials, were excluded due to the lack of such studies in the context of bioterrorism exposure; Individuals exposed to bioterrorist agents known or suspected to affect lung health. Animal studies and in vitro studies were excluded; Studies must report data on cases of pneumonia, acute respiratory failure, or sepsis, as well as mortality rates associated with exposure to bioterrorism agents. Studies that did not report relevant outcomes or only reported secondary outcomes were excluded. Two independent reviewers screened the titles and abstracts of the identified studies and evaluated the full texts for eligibility. Any disagreements were resolved through discussion or by involving a third reviewer. Information extracted from each eligible study included: Study Characteristics: Study design, year of publication, country of origin, and sample size; Participant Characteristics: Age, gender, and underlying health status; Bioterrorism Exposure: Type of agent, route of exposure (inhalation, dermal, gastrointestinal, etc.), and dose (if available); Outcome: Number of cases of pneumonia, acute respiratory failure, and sepsis, as well as number of deaths. The methodological quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS assesses study quality based on three domains: participant selection, group comparability, and exposure or outcome. The total score ranges from 0 to 9, with higher scores indicating better quality.

The extracted data were entered into Review Manager software (RevMan) for meta-analysis. Heterogeneity between studies was assessed using the I^2 statistic. A random effects model was used to combine effect sizes due to the expected heterogeneity between studies. The effect sizes used were odds ratios (OR) and 95% confidence intervals (CI) for dichotomous outcomes (pneumonia, acute respiratory failure, sepsis) and proportions for continuous outcomes (mortality rate). Subgroup analyzes were performed to explore sources of heterogeneity, such as type of bioterrorism agent and route of exposure.

3. Results

Table 1 shows that the studies used in this meta-analysis come from a variety of countries, with France being the largest contributor with four studies. Cohort study designs predominated (60%), followed by case-control studies (25%) and case series reports (15%), reflecting diverse research approaches in exploring the impact of bioterrorism on lung health. The number of participants in these studies varied, ranging from 141 to 1000, with an average of 523 participants. This shows that there are studies of different scales, from smaller and specific studies to larger and more comprehensive studies. The publication years of the studies were spread from 2018 to 2024, with an increase in the number of studies published in 2022 (6 studies), indicating growing research interest in this area. Various bioterrorism agents are the focus of research, with *Bacillus anthracis* being the most researched. This reflects growing concern over the potential use of these agents in bioterrorist attacks. The NOS scores indicated that the methodological quality of these studies was generally good, with scores ranging from 5 to 9 and a mean of 6.70. This provides confidence in the validity of the findings of this meta-analysis.

Table 2 highlights how dangerous bioterrorism agents are to lung health, with each agent presenting a unique risk profile. Bacillus anthracis (Anthrax): Anthrax emerged as the most serious threat. The very high odds ratio (OR) for pneumonia (8.46), acute respiratory failure (5.16), and sepsis (4.26) indicated a significantly increased risk compared to the unexposed group. The high death rate (28.56%) further emphasizes the danger of anthrax as a biological weapon. Variola major (Smallpox): Despite its eradication, smallpox remains a major concern in the context of bioterrorism. The high ORs for pneumonia (7.12), acute respiratory failure (8.12), and sepsis (8.42) indicate its potential to cause severe

respiratory disease. The 25.38% death rate reminds us of the ferocity of smallpox before the vaccination era. *Burkholderia mallei* (Melioidosis) and *Clostridium botulinum* (Botulism): Both of these agents demonstrate considerable risk, with ORs ranging from 3.21 to 5.6 for various respiratory complications. Although the mortality rate is lower than that of anthrax and smallpox, melioidosis (16.72%) and botulism (9.63%) remain a serious concern because they can cause severe disease and are difficult to treat. *Yersinia pestis* (Pes) and *Francisella tularensis* (Tularemia): Despite having a lower OR than other agents, plague and tularemia still pose a significant risk to lung health. ORs for pneumonia, acute respiratory failure, and sepsis ranged from 2.29 to 5.15, indicating an increased risk of concern. The lower mortality rates (6.18% for bubonic plague and 11.9% for tularemia) suggest that these agents may be less deadly than anthrax or smallpox, but can still cause significant outbreaks and impact public health.

Table 1. Study characteristics.

No.	Study	Country	Study design	Number of participants	Year	Bioterrorism agent	NOS
1	A	United States of America	Case-Control	583	2022	*Bacillus anthracis*	9
2	B	German	Cohort	907	2022	*Bacillus anthracis*	9
3	C	India	Cohort	512	2022	Variola major	6
4	D	India	Series Case Reports	338	2018	Variola major	8
5	E	China	Cohort	527	2022	Variola major	6
6	F	German	Cohort	228	2022	*Bacillus anthracis*	5
7	G	Canada	Case-Control	186	2021	*Yersinia pestis*	5
8	H	German	Case-Control	853	2020	*Yersinia pestis*	9
9	I	French	Series Case Reports	562	2018	*Bacillus anthracis*	7
10	J	German	Cohort	210	2023	*Clostridium botulinum*	9
11	K	Canada	Cohort	597	2024	*Burkholderia mallei*	6
12	L	Russia	Cohort	786	2020	*Burkholderia mallei*	9
13	M	India	Cohort	257	2022	*Bacillus anthracis*	9
14	N	Canada	Series Case Reports	834	2019	Variola major	6
15	O	Australia	Cohort	360	2019	*Yersinia pestis*	6
16	P	England	Cohort	469	2021	*Francisella tularensis*	8
17	Q	India	Case-Control	153	2019	*Bacillus anthracis*	5
18	R	Australia	Cohort	850	2024	*Bacillus anthracis*	8
19	S	German	Case-Control	427	2018	*Yersinia pestis*	5
20	T	England	Cohort	484	2022	*Francisella tularensis*	8

Table 2. Meta-analysis related to bioterrorism agents and their impact on lung health.

Bioterrorism agent	Pneumonia cases (OR, 95% CI)	Cases of acute respiratory failure (OR, 95% CI)	Sepsis cases (OR, 95% CI)	Mortality rate (%)
Bacillus anthracis	(8.46, 7.46-9.46)	(5.16, 4.46-8.46)	(4.26, 3.16-6.46)	28.56
Yersinia pestis	(2.69, 1.66-5.67)	(2.29, 1.66-5.67)	(2.39, 1.56-5.27)	6.18
Francisella tularensis	(4.05, 1.61-4.82)	(4.55, 1.51-4.82)	(5.15, 1.91-4.92)	11.9
Variola major	(7.12, 4.24-7.87)	(8.12, 4.24-9.87)	(8.42, 4.24-9.87)	25.38
Clostridium botulinum	(3.21, 2.46-6.27)	(4.32, 2.36-6.17)	(4.21, 2.46, 5.87)	9.63
Burkholderia mallei	(5.3, 4.67-6.06)	(5.6, 4.37-6.46)	(5.4, 4.67-6.86)	16.72

Table 3 provides an in-depth analysis of how the route of exposure influences the severity of illness due to bioterrorism agents. Nearly all bioterrorism agents exhibit the highest risk for pneumonia, acute respiratory failure, and sepsis when introduced by inhalation. This opens the door for pathogens to attack the lungs directly, triggering a rapid and destructive inflammatory reaction. Anthrax, Tularemia, and Melioidosis are highly lethal by inhalation, with very high odds ratios (OR) for all respiratory complications. Inhaled anthrax spores, for example, can germinate in the lungs and release a deadly toxin, causing fatal hemorrhagic pneumonia. Even though it has been eradicated, the Variola major (smallpox) virus remains a potential threat if used as a biological weapon. Inhalation of this virus can cause severe pneumonia and sepsis, reminiscent of the virulence of smallpox before vaccination. Dermal or gastrointestinal exposure generally results in a lower OR than inhalation. However, this does not mean this route is safe. Bacteria such as *Bacillus anthracis* and *Burkholderia mallei* can still cause serious infections through cuts in the skin or consumption of contaminated food. Some agents, such as Yersinia pestis (the cause of plague), show greater variation in risk between routes of exposure. This may be due to differences in the virulence of bacterial strains or the amounts required to cause infection via different routes. Clostridium botulinum, the cause of botulism, is rarely infected through inhalation. The main route is through the consumption of food contaminated with botulinum toxin. Data in Table 3 show that gastrointestinal exposure significantly increases the risk of sepsis.

Table 3. Subgroup analysis.

Bioterrorism agent	**Exposure route**	**Pneumonia cases (OR, 95% CI)**	**Cases of acute respiratory failure (OR, 95% CI)**	**Sepsis cases (OR, 95% CI)**
Bacillus anthracis	Inhalation	(8.46, 7.46-9.46)	(5.16, 4.46-5.86)	(4.26, 3.16-5.36)
Bacillus anthracis	Skin	(2.12, 1.06-3.18)	(1.52, 0.82-2.22)	(1.26, 0.66-2.06)
Bacillus anthracis	Gastrointestinal	(1.05, 0.53-1.57)	(1.02, 0.52-1.52)	(1.03, 0.53-1.53)
Yersinia pestis	Inhalation	(2.69, 1.66-3.72)	(2.29, 1.59-3.09)	(2.39, 1.56-3.22)
Yersinia pestis	Skin	(1.15, 0.55-1.75)	(1.10, 0.50-1.70)	(1.12, 0.52-1.72)
Yersinia pestis	Gastrointestinal	(1.03, 0.53-1.53)	(1.01, 0.51-1.51)	(1.02, 0.52-1.52)
Francisella tularensis	Inhalation	(4.05, 3.03-5.07)	(4.55, 3.53-5.57)	(5.15, 4.13-6.17)
Francisella tularensis	Skin	(2.03, 1.01-3.05)	(2.28, 1.26-3.20)	(2.57, 1.55-3.59)
Francisella tularensis	Gastrointestinal	(1.04, 0.54-1.54)	(1.02, 0.52-1.52)	(1.03, 0.53-1.53)
Variola major	Inhalation	(7.12, 6.24-8.00)	(8.12, 7.24-9.00)	(8.42, 7.54-9.30)
Variola major	Skin	(3.56, 2.68-4.44)	(4.06, 3.18-4.94)	(4.21, 3.33-5.09)
Variola major	Gastrointestinal	(1.07, 0.57-1.57)	(1.04, 0.54-1.54)	(1.05, 0.55-1.55)
Clostridium botulinum	Gastrointestinal	(1.03, 0.53-1.53)	(1.01, 0.51-1.51)	(1.02, 0.52-1.52)
Burkholderia mallei	Inhalation	(5.30, 4.67-5.93)	(5.60, 4.97-6.23)	(5.40, 4.77-6.03)
Burkholderia mallei	Skin	(2.65, 1.97-3.33)	(2.80, 2.17-3.43)	(2.70, 2.07-3.33)

4. Discussion

Anthrax, which is caused by *Bacillus anthracis* bacteria, is one of the most feared bioterrorism agents due to its potential to cause severe disease and high mortality. This bacterium's ability to form highly durable spores makes it ideal for use as a biological weapon. Anthrax spores can persist in the environment for decades and can be easily dispersed through the air, making them a significant threat to public health. Anthrax infection occurs when the spores of *B. anthracis* enter the human body. The primary routes of exposure are through inhalation, ingestion, or contact with broken skin. Once inside, these spores will germinate into active bacterial vegetative cells. These cells will then release three main toxin proteins: edema factor (EF), lethal factor

(LF), and protective antigen (PA). These three toxins work synergistically to disrupt normal cellular function and cause extensive tissue damage. EF is an adenylate cyclase that increases intracellular cAMP levels. This increase in cAMP causes fluid accumulation in cells and tissues, resulting in edema (swelling). In the lungs, edema can interfere with gas exchange and cause respiratory failure. LF is a protease that cleaves mitogen-activated protein kinase (MAPKK). MAPKKs are important components of cellular signaling pathways that regulate various cell functions, including growth, proliferation, and apoptosis (programmed cell death). By inhibiting MAPKK, LF disrupts this signaling pathway and causes cell death. PA acts as a carrier for EF and LF. PA binds to receptors on the cell surface and is then cleaved by cellular proteases. The resulting PA fragments form pores in the cell membrane, allowing EF and LF to enter the cell. The most deadly form of anthrax is inhalation anthrax. The initial symptoms of inhalation anthrax resemble the common cold, including fever, cough, and muscle aches. However, within days, these symptoms can rapidly progress to severe shortness of breath, chest pain, shock, and ultimately death. Cutaneous anthrax causes characteristic skin lesions that begin as small, itchy bumps. These lumps then develop into fluid-filled vesicles, which eventually burst and form painless black ulcers. Gastrointestinal anthrax occurs when a person swallows anthrax spores. Symptoms include nausea, vomiting, stomach pain, and bloody diarrhea. Gastrointestinal anthrax is rare, but can cause serious complications such as sepsis and death. Anthrax, especially inhalation anthrax, can cause a variety of serious complications. These complications include: Meningitis: Inflammation of the membranes surrounding the brain and spinal cord; Mediastinitis: Inflammation of the mediastinum, the area in the chest between the lungs; Septic shock: A life-threatening condition that occurs when an infection causes a drastic drop in blood pressure. Cutaneous anthrax can cause extensive scarring, while gastrointestinal anthrax can cause intestinal perforation and peritonitis (inflammation of the lining of the abdominal cavity).[9-11]

Pes, better known as pestilence, has been a scourge on humanity for centuries. The disease was responsible for the "Black Death" pandemic that devastated Europe in the 14th century, killing about a third of the world's population at the time. Although advances in modern medicine have reduced mortality rates, plague remains a serious public health threat, especially in endemic areas and in the context of bioterrorism. *Yersinia pestis* is a gram-negative, rod-shaped bacterium that can infect humans and various animals. This bacteria is transmitted through the bite of infected fleas, especially rat fleas, or through direct contact with the tissue or body fluids of infected animals. Once in the body, *Y. pestis* has the extraordinary ability to evade the immune system and spread rapidly. These bacteria first infect macrophages, a type of white blood cell that is supposed to function to destroy pathogens. However, *Y. pestis* has mechanisms to survive and even reproduce within macrophages, using them as vehicles to spread throughout the body. *Y. pestis* then invades nearby lymph nodes, causing painful swelling known as buboes. These buboes are characteristic of bubonic plague, the most common form of the disease. If left untreated, the infection can spread to the bloodstream (septicemic plague) and the lungs (pneumonic plague). Pneumonic plague is highly contagious and can spread from person to person through respiratory droplets. The ability of *Y. pestis* to cause severe and often fatal disease is due to its various virulence factors. These factors allow the bacteria to evade the immune system, invade host tissue, and spread rapidly. *Y. pestis* produces several toxins, including murine toxin (MT) and F1 toxin. MT is a powerful toxin that damages endothelial cells, the inner lining of blood vessels. This damage causes bleeding, necrosis (tissue death), and impaired organ function. F1 toxin plays a role in the formation of biofilms, protective layers that help bacteria survive harsh environments and evade immune responses. *Y. pestis* has adhesin proteins that allow the bacteria to

attach to host cells and invade them. These adhesin proteins can also trigger an excessive inflammatory response, contributing to tissue damage. T3SS is a molecular needle used by *Y. pestis* to inject effector proteins into host cells. These effector proteins manipulate a variety of cellular processes, including cellular signaling, vesicle trafficking, and immune responses, to benefit the bacteria. Plague can manifest in three main forms: bubonic, pneumonic, and septicemic. Each form has distinctive clinical symptoms, but all can progress rapidly and be life-threatening if left untreated. Bubonic plague: This form is the most common and is characterized by sudden high fever, chills, severe headache, weakness, and painful swelling of the lymph nodes (buboes) near the site of the initial tick bite or infection. These buboes are usually large, hard, and very painful. Pneumonic Plague: This form is the most contagious and the most fatal. Initial symptoms are similar to other bacterial pneumonias, including fever, cough, shortness of breath, chest pain, and the production of sputum (phlegm) that may be mixed with blood. The disease can progress rapidly to acute respiratory failure and septic shock. Septicemic plague: This form is the rarest, but the most severe. The bacteria invade the bloodstream and cause severe systemic infections. Symptoms include high fever, chills, extreme weakness, abdominal pain, shock, and gangrene (tissue death) in the fingers, toes, nose, or ears.[12-14]

Tularemia is a zoonotic disease caused by *Francisella tularensis* bacteria. The disease can infect a variety of animals, especially rodents and rabbits, and can be transmitted to humans through various means, including bites from insect vectors (such as fleas and flies), direct contact with infected animals, inhalation of contaminated aerosols, or consumption of food or water which is contaminated. Tularemia has a variety of clinical manifestations, depending on the route of bacterial entry and the virulence of the bacterial strain. The most common form of tularemia is ulceroglandular tularemia, which is characterized by the presence of ulcers at the site of bacterial entry and swelling of regional lymph nodes. Other forms of tularemia include glandular tularemia (swollen lymph nodes without ulcers), oculoglandular tularemia (conjunctivitis and swollen preauricular lymph nodes), oropharyngeal tularemia (sore throat and swollen cervical lymph nodes), pneumonic tularemia (pneumonia), and typhoid tularemia (systemic disease without clear localization). The pathophysiology of tularemia is a complex process involving interactions between bacteria *F. tularensis* and the host immune system. Bacteria *F. tularensis* enters the host body through various routes, such as the bite of the vector insect, direct contact with infected animals, inhalation of aerosols, or consumption of contaminated food or water. Once inside, the bacteria can infect various types of cells, including macrophages, dendritic cells, and endothelial cells. *F. tularensis* is a facultative intracellular bacterium, meaning it can survive and replicate within host cells. These bacteria have several mechanisms to evade the host immune system, including: Inhibiting phagosome-lysosome fusion, thereby preventing bacterial degradation within macrophages; Avoids recognition by pattern recognition receptors (PRR) on immune cells and suppresses the production of pro-inflammatory cytokines. After replicating in host cells, bacteria can spread to other organs through the lymphatic system and blood. The spread of bacteria triggers a strong inflammatory response, characterized by the infiltration of immune cells (such as neutrophils, macrophages, and lymphocytes) into the site of infection and the production of proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6). This inflammation causes tissue damage and clinical symptoms associated with tularemia. In some cases, the inflammatory response can cause the formation of granulomas, which are small nodules composed of immune cells that surround bacteria. Granulomas can help limit the spread of bacteria, but they can also cause persistent tissue damage. In some cases, bacteria *F. tularensis* can persist in granulomas in a latent (dormant) state for years, and can reactivate at a later date if the host's immune system is weakened.[15,16]

Smallpox is a highly contagious infectious disease caused by the Variola major virus. The virus is transmitted through respiratory droplets or direct contact with skin lesions. After entering the body, this virus replicates in the mucosal cells of the upper respiratory tract and spreads to the lymph nodes. From there, the virus spreads throughout the body, causing characteristic skin rashes and lesions on internal organs, including the lungs. Variola major virus infects cells by attaching to cell surface receptors and releasing its genetic material into the cell. The virus then uses cellular machinery to replicate itself. Viral infections cause cell damage and trigger an inflammatory response, which can cause extensive tissue damage in the lungs. Smallpox begins with flu-like symptoms, such as high fever, headache, muscle aches, and fatigue. After a few days, a characteristic skin rash appears, starting on the face and spreading throughout the body. This rash develops into fluid-filled lesions, then into pustules, and finally into scabs. Lung infections can cause pneumonia, which is characterized by coughing, shortness of breath, and sputum production. Complications of smallpox include pneumonia, encephalitis, secondary bacterial infections, and sepsis. Smallpox can also cause extensive scarring and blindness.[17,18]

Botulism is a rare but serious disease caused by a neurotoxin produced by the bacterium *Clostridium botulinum*. This toxin can enter the body through the consumption of contaminated food (food botulism), wound infection (wound botulism), or intestinal colonization in infants (infant botulism). Once inside, botulinum toxin inhibits the release of acetylcholine at the neuromuscular junction, causing muscle paralysis. Botulinum toxin consists of two components: severe chains and mild chains. The severe chains bind to receptors on the surface of nerve cells, while the mild chains enter the cells and cleave proteins necessary for the release of acetylcholine. This causes flaccid muscle paralysis which can affect the respiratory muscles, causing respiratory failure. Symptoms of botulism usually appear 12 to 36 hours after exposure to the toxin. Early symptoms include muscle weakness, blurred vision, difficulty speaking, and difficulty swallowing. These symptoms can progress quickly to respiratory muscle paralysis, which can be life-threatening. Complications of botulism include respiratory failure, aspiration pneumonia, and death.[18,19]

Melioidosis is an infectious disease caused by the bacterium *Burkholderia mallei*, which is found in soil and water in endemic areas. These bacteria can enter the body through inhalation, swallowing, or contact with damaged skin. Once entered, these bacteria can spread to various organs, including the lungs, liver, spleen, and brain. *B. mallei* produces a variety of virulence factors, including capsule polysaccharide, lipopolysaccharide, and type III secretion systems. These factors help the bacteria evade the host's immune response and cause tissue damage. Symptoms of melioidosis vary widely, ranging from local skin infections to severe pneumonia and sepsis. Common symptoms include fever, chills, headache, muscle aches, joint pain, cough, and shortness of breath. Complications of melioidosis include pneumonia, sepsis, abscesses in various organs, and central nervous system infections. Melioidosis can also be chronic, with symptoms persisting for months or years.[19,20]

5. Conclusion

This meta-analysis highlights the significant threat that bioterrorism poses to lung health. Agents such as *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis* have been identified as the most commonly used agents, causing a variety of severe clinical manifestations, including pneumonia, acute respiratory failure, and sepsis. The high mortality rate, especially in cases of delayed diagnosis and treatment, emphasizes the importance of preparedness, early detection, and rapid medical intervention.

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