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Biothreats - Bacterial Warfare Agents

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Abstract

Terrorism refers to the use or threat of force or violence against people or their property. The challenges of countering biological threats faced by the international community in the twenty-first century are broader and deeper in purpose the incidents connected with this series of events reveals certain important challenges and obstacles for the coordination and communication of public and private sector emergency responses to the possible terrorist bioweapon attacks. They do not only refer potential threat of States developing biological weapons but also to prevent the pathogens released into the environment and the accidental infection to the laboratory workers.

Keywords: Biowarfare; Biothreats; Bioterrorism; Anthrax; Bacterial warfare agents; Zoonotic agents.

Abbreviations: JEV: Japanese Encephalitis Virus; NAS: National Academy of Sciences; BW: Biowarfare; ABW: Advanced Biological Warfare; ELISA: Enzyme Linked ImmunoSorbent Assay; TBE: Tick-borne encephalitis; TLR: Toll like receptors.

Introduction

Bioterrorism is a planned and deliberate use of pathogenic strains of microorganisms such as bacteria, viruses or their toxins to spread life-threatening diseases on a mass scale in order to devastate the population of an area. The September 11, 2001 hijacking of four U.S. airliners and the subsequent striking of three of them into the two towers of the World Trade Center and the Pentagon was the worst mass casualty terrorist attack [1,2] in U.S. history. Approximately 3,000 people from over 80 countries lost their lives at the World Trade Center in New York. By addressing the broad spectrum of biological threats through a rather heterogeneous system of legally- or politically-binding agreements and practices among diverse stakeholders, the Biological Weapons Convention (BWC) and the United Nations Security Council Resolution 1540 (UNSCR 1540) effectively belong in a unique category of international regimes aimed at biological risk management [3]. A bioterrorist attack releases viruses, bacteria, or other germs to cause illness or death. These biological agents are typically found in nature. But they can sometimes be made more harmful by increasing their ability to cause or spread disease, or to resist medical treatment. These viruses and bacteria is considered a potential biothreat agent not only due to potential threats to human health and also because of agricultural concerns and ecotoxicological hazards [4] for example Japanese encephalitis virus can affect pig, cattle and horse populations. There is evidence that both the former Soviet Union and Japan evaluated the use of JEV as a bioweapon [5]. The terrorist use of airliners as missiles, the United States was faced with a series of anthrax attacks delivered to victims and target offices through the U.S. mail system. There was a series of anthrax attacks during 2001 via U.S. Postal Service fulfilled the warnings of those who had warned of the inevitability of future bioterrorist events. The anthrax attacks of 2001 in the United States validated the previous warnings by some experts concerning bioterrorism that it was not a question of "if"; it was a question of "when." Now such bioterrorism is a historical fact, not just a prediction of the future [6].

Terrorists may find biological agents to be an attractive alternative to conventional weapons because of their relatively low costs, their relative accessibility, and the relative ease in which they could be produced, delivered, and avoids detection. Their use, or even threatened use, is potentially capable of producing widespread social disruption. Biological agents such as *Bacillus anthracis, Yersinia pestis, Brucella Suis* and viruses such as Ebola, Variola virus, or Marburg Virus could be used as agents for bioterrorism. Research into the use of *Bacillus anthracis* as a bioweapon is at least 80 years old and several nations are believed to have weaponized anthrax [7,8].Some bioterrorism agents like smallpox virus, can be spread from person to person and some, like anthrax cannot [9].

Earlier in September 2008 the FBI issued a formal request to the National Academy of Sciences (NAS) to conduct an independent review of the scientific approaches used during the anthrax investigation. Before that review had been completed, the FBI formally concluded its investigation and released an "Amerithrax Investigative Summary" on February 19, 2010. The NAS committee issued its Report on February, 2011, after two delays and an additional meeting at the FBI's request. When the NAS Report came out the FBI released some10, 000 pages of scientific documents, much of which consisted of plans and reports of laboratory work on unidentified, coded materials. By agreement, all the information that had been available to the NAS committee is now in the public domain. The major finding of the committee, which had no access to classified information, was it is not possible to reach a definitive conclusion about the origins of the *B. anthracis* in the mailings based on the available scientific evidence. Perhaps their most celebrated finding is that "the scientific link between the letter material and flask number RMR-1029 (located in BruceIvins laboratory at USAMRIID) is not as conclusive as stated in the DOJ Investigative Summary" [10].

The concept of using biological agents in warfare is not new. Microbial population is a highly diverse and a ubiquitous group among the living world [11]. There are many examples throughout recorded

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history- even as early as the 6th century BC when the Assyrians reportedly poisoned wells of their enemies with the fungus rye ergot. In the 1700s during the French-Indian War, it is suspected that the British gave blankets that had been used by smallpox victims to the Native Americans, resulting in decimation of the native population. More recently, in 1984, followers of the Bhagwan Shree Rajneesh contaminated salad bars in Oregon with *Salmonella* in an attempt to influence a local election (although hundreds were sickened, this attack did not impact the election). However, as our knowledge of infectious disease agents increases, and the technology to design and produce these agents improves, there is an elevated risk that biological agents could used as weapons of mass destruction in the future [7].

The evolution of chemical and biological weapons is broadly categorized into four phases. World War I saw the introduction of the first phase, in which gaseous chemicals like chlorine and phosgene were used in Y pres .The second phase ushered in the era of the use of nerve agents e.g. tabun, a cholinesterase inhibitor, and the beginnings of the anthrax and the plague bombs in World War II. The Vietnam War in 1970 constituted the third phase which was characterized by the use of lethal chemical agents e.g. Agent Orange, a mix of herbicides. Stimulation of hormonal function results in defoliation and crop destruction. This phase included also the use of the new group of *Novichok* and mid-spectrum agents that possess the characteristics of chemical and biological agents such as auxins, bioregulators, and physiologically active compounds. Concern has been expressed in regard to the handling and disposal of these mid-spectrum agents by "chemobio "experts rather than by biologists [12].

Biological agents in warfare

Historically, Biological Warfare (BW) agents of concern have included a relatively select group of pathogens and toxins, referred to as traditional BW agents. Traditional biological warfare agents are all naturally occurring organisms or their toxic products. From the perspective of biological warfare scientists, traditional BW agents have serendipitously evolved a select group of traits: toxicity, stability, and ease of production. However, until recent decades, the serendipity that aided researchers in choosing select organisms also limited BW applications to the characteristics of available agents. For example, environmental stability, infectious dose, time to effect, clinical progression, and lethality are all properties intrinsic to candidate traditional agents that may limit their utility for biological warfare. Technologies developed across multiple disciplines and as a result there is a potential to revolutionize biological warfare by facilitating an entirely new class of fully engineered agents referred to as Advanced Biological Warfare (ABW) agents [13].

BW agents (Table 1-3) will be able to target specific biological systems, such as the cardiovascular, immunological, neurological, and gastrointestinal systems and can also produce a wide range of effects including death, incapacitation, or neurological impairment. The advances in biotechnology facilitate novel agents engineered to attack human systems [14].

Toxins	Disease	Symptoms
Clostridium botulinum	Botulism	Blurred vision, dilated pupils, photo-phobia, difficulty with speaking/swal-lowing, (severe) muscle paralysis
Staphylococcal-Toxin	SEB-Intoxication	Sudden onset of fever, chills, cough, vomiting, diarrhea. Higher exposure: septic shock
Ricin	Ricin-Intoxication	Fever, chest tightness, nausea, gastrointestinal ailment, resp. failure, pulmonary edema

Table 1: Types of Toxins Biological Warfare Agents.

Viral Pathogens	Disease	Symptoms
Variola virus	Smallpox	Acute: malaise, fever, headache, vomiting. Erythematous rash spread centrally to the trunk, quickly progresses to papules/pustular vesicles (centrifugal distribution). Pustules → scabs after 8 - 14 days
H1N1 Virus[17,18]	Swine flu	fever cough, fatigue, headache, nausea, vomiting, diarrhea. If the viral infection persists, and some can develop seizures.
Ebolavirus [19-21]	hemorrhagic fever [22]	Hemorrhagic Fever with a fatality rate of 50-90%.Sore throat, Weakness, Severe headache, Joint and muscle aches, Diarrhea, Vomiting Dehydration, Dry, hacking, cough, and Stomach pain.
Marburg-Virus	Marburg-Fever (Viral Hemorrhage. Fever)	Myalgia, fever, headache, flushing of the face and chest, conjunctival/ cutaneous bleedings, dizziness, hypotension, renal insufficiency, shock, death
VEE-Virus	Venet. Equine Encephalitis	Acute: febrile illness with severe headache, fatigue, photophobia, nausea, vomiting, rigors.etc

Table 2: Types of viral Biological Warfare Agents.

Bacterial Pathogens	Disease	Symptoms
Yersinia pestis	Pneumonic Plague	Acute: high fever, headache, productive cough blood-tinged sputum, vomiting. Hematogenous dissemination: sepsis, shock, meningitis
Bacillus anthracis	Inhalation Anthrax	Nonspecific symptoms of fatigue, myalgia, fever, nonproductive cough, followed by chest pain, respiratory distress, high fever, pneumonia. Other forms: Intest/ Cutan Anthrax (not as BW-Agents)
Brucella suis	Brucellosis	Nonspecific: Fever, malaise, body aches, sweats, muscle and joint aches. Hepato-/ splenomegaly
Francisella tularensis	Tularemia (Rabbit Fever)	Fever, chills, headache, myalgia, abdominal pain vomiting, diarrhea. Chest pain, pneumonia, cutaneous ulcer. Enlarged lymph nodes.
Coxiella burnetii	Q-Fever	Extremely infectious, no characteristic illness: severe headache, back pain, fatigue, weight loss
Burkholderia mallei *Burkholderia pseudomallei*	Glanders melioidosis	Severe sickness, fever, rigors, pulmonary distress abscesses of internal organs (e.g. liver and spleen)

Table 3: Types of Bacterial Biological Warfare Agents.

One possible way for Advanced Biological Warfare is through aerosols. This can be ineffective as the materials often get clogged when spraying. Biological agents distributed by air may also be destroyed by UV light [15] or rain may wash them away. Another method of distribution may be to attach the toxins to a bomb so that they may be released upon explosion. The problem with this is that the microbes will most likely be destroyed by the explosion as well [16].

The virus family Paramyxoviridae, consisting of viruses possessing non-segmented, single stranded negative sense RNA genomes can be used as BW agent, this is the source of several highly contagious pathogens such as measles virus and mumps virus in humans and canine distemper virus in dogs [23,24]. Measles virus is most closely related to the etiologic agent of "cattle plague", rinderpest virus, and is thought to have been acquired from this species at the time of domestication of cattle, possibly around the 11th to 12th century [25]. Influenza A virus [26] causes regular epidemics and periodic pandemics [27]. These later events include the catastrophic H1N1Spanish influenza of 1918, which killed more than 50 million people worldwide [28], the H2N2 Asian flu of 1957, which caused more than 1 million deaths, and the H3N2Hong Kong flu of 1968, which caused 0.5 million deaths [17]. New highly fatal diseases have emerged or reappeared during the last 4 decades such as severe acute respiratory syndrome (SARS) *Legionella*, Hantavirus pulmonary syndrome (Sin Nombre virus) Nipah virus encephalitis, avian influenza, West Nile encephalitis, tick-borne encephalitis (TBE) sero complex of flaviviruses [29] and Rift Valley fever with adverse global or regional public health and economic impact [30]. These viruses have been proven to be highly infectious by the aerosol route [31]. Serological detection and identification of virus was carried out by following Enzyme Linked ImmunoSorbent Assay (ELISA) [32,33].

Bacterial warfare agents

***Bacillus anthracis*:** Anthrax is a zoonotic disease (Zoonotic diseases are diseases that can be transmitted from animals to humans and from humans to animals) that is transmissible through handling or consumption of contaminated animal products [34]. The etiologic agent of anthrax, *Bacillus anthracis*, is a spore forming gram-positive bacillus. Areas currently listed as high risk are South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East [35]. In late 2001, a deliberate dissemination of *Bacillus anthracis* spores via letters sent through the U.S. Postal Service resulted in 12cases of cutaneous anthrax and 11 cases of inhalation anthrax Humans can become infected with *B. anthracis* by handling products or consuming under cooked meat from infected animals [36]. Infection may also result from inhalation of B.anthracis spores from contaminated animal products such as wool or the intentional release of spores during a bioterrorist attack. Cutaneous infections occurs when the bacterium or spore enters a cut or abrasion on the skin, such as when handling contaminated wool, hides, leather or hair products (especially goat hair) from infected animals. Approximately 20% of untreated cases of cutaneous anthrax result in death. Cutaneous anthrax usually appears in the form of a localized, painless, central black eschar with surrounding oedema [37].

The gastrointestinal form of anthrax may follow the consumption of contaminated meat from infected animals and is characterized by an acute inflammation of the intestinal tract. Many factors secreted by monocytes and macrophages contribute to chronic inflammation [38]. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea. The mortality rate is difficult to determine for gastro intestinal anthrax but is estimated to be 25%-60%.Inhalation anthrax is a form of anthrax results from inhaling *B. anthracis* spores [10] and is most likely following an intentional aerosol release of *B. anthracis*. Fever, malaise, and fatigue may be present initially, sometimes in association with a nonproductive cough and mild chest discomfort. Severe respiratory distress with dyspnea (labored breathing), diaphoresis (perspiration), stridor (high-pitched whistling respiration), and cyanosis (bluish skin color) *B. anthracis* is considered a potential biological warfare threat agent. The U.S. Department of Defense recommends anthrax vaccination of all U.S. active duty military personnel. The vaccine is a cell-free filtrate that contains protective antigen and alum. The vaccine is reported to be93% effective in protecting against cutaneous anthrax [35].

Yersinia pestis: Plague, one of the most devastating diseases of human history, is caused by *Yersinia pestis*. *Y. pestis* is primarily a disease of rodents or other wild mammals that usually is transmitted by fleas and often is fatal. *Y. pestis* has been subdivided into three biovars (Antiqua, Medievalis, and Orientalis). *Y. pestis* causes fatal bubonic plague and is transmitted by flea bites [39]. During the first week of November 2002, *Yersinia pestis*, the causative agent of bubonic plague, made headline news when two New Mexico residents visited New York City and were diagnosed with the infection, causing many to wonder at the time if this was a second biologic attack. There are fewer than 10 cases of plague a year in the United States, usually occurring in rural areas of western states. However, over the course of history, epidemics of plague have killed hundreds of thousands of people and devastated cities and countries. The destructive potential of the plague is best evidenced by its presentation in the 14th century as the Black Death, which killed one third of the Western European population. Overall, *Y. pestis* is estimated to have killed 100 to 200 million individuals throughout history, making it one of the leading infectious disease killers of humans. The clinical symptoms of bubonic plague include fever, chills, weakness, headache, and swollen, tender lymph nodes (buboes) secondary plague septicemia is a frequent occurrence and the fatality rate is higher in patients with higher colony counts. Primary pneumonic plague is uncommon and results from inhalation of organisms, usually via respiratory droplets from infected individuals or animals or, in rare circumstances. *Y. pestis* can be identified in the laboratory by both bacteriologic and serologic methods. Cases of plague resulting from a terrorist attack would have clinical manifestations different from naturally occurring cases. The most likely method of terrorist release would be aerosolized *Y. pestis*, which would result in primary pneumonic plague thus would be a sudden outbreak of severe pneumonia and possibly sepsis [40].

Brucella Suis: Brucellosis is an important but neglected disease caused by *Brucella Suis* [41]. This zoonotic disease is present in all livestock systems and increased demand for dairy products accompanied with changing and intensified farming practices has raised the concern for increased spread and intensified transmission of this infection to the human population with increased risk of disease. The general symptoms are Fever, malaise, body aches, sweats, muscle, joint aches, hepato or splenomegaly [14]. Brucellosiscan be controlled by mass vaccination of livestock. Brucellosis is present in different species of mammalian farm animals including cattle, goats, buffalo, yaks, camel, horses and pigs [42, 43]. Brucellosis is caused by members of the bacterial genus Brucella. These are facultative intracellular Gram-negative pathogens. Mass vaccination is crucial for the control and eradication of bovine, ovine and caprine brucellosis. The intermittent or remittent fever maybe accompanied by malaise, anorexia and prostration [41]. *Brucellosis* also occurs in Respiratory forms (bioterrorist threat) from inhalation of aerosols or dust that contains organisms [44].

Coxiella burnetii: *Coxiella burnetii* is a Gram-negative, non-sporing short, rod-like, non-motile, aerobic microorganism that is the causal agent of Q fever, a zoonotic disease. *Coxiella* are capable of inducing acute infections in humans resulting in isolated bouts of fever, pneumonia, granulomatous hepatitis. This can then be transported to humans via inhalation or tick bite. Preliminary study suggests that, especially *Bartonella* spp., are prevalent causative organisms of blood culture–negative endocarditis. *Coxiella burnetii* is an infectious possible

biological weapons agent that in its spore-like form is resistant to heat, pressure, drying and certain antiseptics. Q fever would most likely be spread in an aerosolized cloud. Disinfection could be achieved with 0.05% hypochlorite solution (1 tbps. bleach per gallon of water). Q fever was developed as a biological agent by both US and Soviet biological arsenals [45].

Francisella tularensis: *Francisella tularensis* causes tularemia (Rabbit fever), with high fever, acute septicemia, toxemia and Oral infection causes typhoid. The bacterium *Francisella tularensis* poses a serious threat as an agent of bioterrorism. Historically, *Francisella tularensis* attracted attention as a biological weapon and was a subject of military research in the United States, the former Soviet Union, and Japan. In the post-Cold War era, however, Francisella tularensis is included among the top six agents showing potential for great adverse public health impact if used as a bioterrorism agent [46,47]. Considering that vaccines against infectious diseases such as francisella have been successful mainly in prophylactic settings rather than in therapeutic settings [48]. Role of toll like receptors [TLR] in innate immune system and their part in eventual stimulation of adaptive immunity is exploited to develop vaccines. Although the immune system has often been regarded as functioning independently in protecting the organism against foreign intruders [49]. TLR agonists in conjugation with vaccines are shown to increase therapeutic efficacy in some cases [50].

The organisms are small, nonmotile, Gram-negative coccobacilli. *Francisella* is nutritionally demanding. It is biochemically similar to the brucellae, but antigenically distinct. *Francisella* is primarily a pathogen of squirrels and rabbits; humans are infected by the bite of an infected deerfly or tick or by handling infected rabbit carcasses or eating undercooked meat. Blood smears can be stained with specific fluorescent antibody. Hemagglutinins appear in 10 to 12 days; a rising titer is diagnostic. A live attenuated vaccine is available killed *F tularensis* vaccines are not very effective, even when presented in adjuvant. *Francisella* is susceptible to streptomycin, tetracycline, and chloramphenicol [51].

Burkholderia pseudomallei & Burkholderia mallei: The *Burkholderia* are non spore-forming, Gram-negative bacteria. *Burkholderia* pseudomallei is a saprophytic bacillus and the causative agent of the emerging infection melioidosis, an endemic disease in southeast Asia and Northern Australia [52]. *Burkholderia mallei* is an obligate pathogen of solipeds and most cases occur in horses, mules or donkeys. Rarely, humans may become infected after handling infected animals [53]. It is the causative agent of glanders, a disease that is endemic in areas of Asia, the Middle East, Northern Africa and the Mediterranean [54]. Both *B. mallei* and *B. pseudomallei* have been classified as category B threat agents by the US Center for Disease Control and Prevention.

Glanders and melioidosis have both been studied for weaponisation in several countries in the past. Glanders was reported to have been used during both the first and second world wars [55,56]. During the First World War, it was used to infect large numbers of Russian horses and mules on the Eastern Front, affecting troop movements. During the Second World War, the Japanese deliberately infected animals and humans at the Pinfang Institute in China. *B. pseudomallei* was studied, but has never been used for biological warfare [57].

Conclusion

Because of the increased threat of terrorism and the risk posed by various microorganisms as biological weapons needs to be evaluated and the historical development and use of biological agents should be better understood. Biological warfare agents' in particular bacterial bio warfare agents may be more potent than conventional and chemical weapons. During the past century, the progress made in biotechnology and biochemistry has simplified the development and production of such weapons. In addition, genetic engineering holds perhaps the most dangerous potential of biothreat. Ease of production and the broad availability of biological agents have led to a further spread of biological weapons and an increased desire among developing countries to have them. This article explains the concepts of biological warfare particularly the bacterial agents used in biowarfare and their proliferation throughout history. The threat of bioterrorism is real and significant .It is neither in the realm of science fiction nor confined to a particular nation.

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