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REVIEW ON BIOLOGICAL WARFARE

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ABSTRACT

Biological warfare comprise of any intentional means to spread disease to humans, animals or plants. It includes a complex cluster of potentially deadly pathogens, genetically-engineered strain of highly infectious disease and toxins which can be delivered by variety of methods. Biological agents are easy to develop, more toxic than chemical weapons, less expensive and more difficult to detect than nuclear weapons. Disease or epidemics caused by biowarfare agents are not only a public problem but also breach of nation's safety. In 2001 there were deadly anthrax attacks in the U.S mail and also the documents seized from Afghanistan by U.S. military force showing Al Qaeda's interest in biological warfare in 2002, have served to enhance the concern about bioterrorism. It is vital to develop information and recognition of the dangers without unnecessarily boosting public anxiety and fear. This review tries to summarize the history and advances in biological warfare.

KEYWORDS: Biological warfare, Disease, Toxic, Anthrax.

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INTRODUCTION

Biological warfare comprise of any intentional means to spread disease to humans, animals or plants. It includes a complex cluster of potentially deadly pathogens, genetically-engineered strain of highly infectious disease and toxins which can be delivered by variety of methods [1]. In modern day people are increasingly worried about the use of biological weapon, the so called "poor man's nuclear bomb" [2]. Biological warfare is a silent and invisible threat when compared with other warfare. Bioterrorism has now been defined as the "intentional use of a pathogen or biological product to cause harm to a human, animal, plant or other living organisms to influence the conduct of government or to intimidate or coerce a civilian population [3]. Biological agents are easy to develop, are more toxic than chemical weapons, are less expensive and more difficult to detect than nuclear weapons [4]. Disease or epidemics caused by biowarefare agents are not only public problem but also breach of nation's safety. Biological weapons may be living organisms or toxins that can cause diseases in humans. The biological agents are odorless and tasteless and they have no typical symptoms. It is usually confused with a naturally occurring disease or outbreak of a disease. Many of the initial manifestation will be similar to several other types of disease, which again impedes recognition, identification, and treatment. The broad range of potential biological weapons presents a massive threat to the world. Currently the rapid developments in the field of genetic engineering and thousands of scientists, technicians are working in large number of labs developing drugs and vaccines with the aim of upgrading crops, curing disease and developing new commercial products. Parallel studies and analysis are used for both legitimate public health and illicit weapons applications. In this swiftly developing and progressing field, there are no regulations to oversee the safety and security of deadly pathogens. The deadly anthrax attacks in the U.S. mail in the fall of 2001, [5] as well as documents seized by U.S. military forces in 2002 from Afghanistan showing Al Qaeda's interest in biological weapons, have served to enhance the concern about bioterrorism [6]. With this in mind, it is vital to develop information and recognition of the dangers without unnecessarily boosting public anxiety and fear.

History of Biological Weapons

Attempts to use biological weapons date back to antiquity. In 600 BC, the Assyrians used rye ergot to poison the wells of their enemies. The Scythians warriors in 400 BC dipped their arrows into decomposed bodies or in blood mixed with feces from diseased persons [7]. During 300-100 BC Romans used bees and hornets as weapons by throwing them at their enemies. In the Battle of Eurymedon, in 190 BC, Hannibal tossed pottery jars containing poisonous snakes onto the enemy's ships and had a naval victory [8]. During the Battle of Tortonain in 1155 AD, in Italy the Roman Emperor Frederick Barbarossa contaminated the enemy's wells using dead bodies [9]. In 1346 in Russia, Khan Janibeg, the commander in the siege of Kaffa, initiated an epidemic by throwing corpses of men who had died of plague. In 1495 in Italy, the Spanish provided their French enemies with wine contaminated with the blood of lepers [10]. During the conquest of the Incan Empire in Peru in 1528, Pizarro gave South American natives clothing contaminated with smallpox [11]. In 1710, Russian attackers threw plague cadavers into the city of Reval, Estonia [12]. In 1797 Napoleon, attempted to infect the residents of Mantua, Italy with Swamp fever [13]. In 1863, Dr. Luke Blackburn arranged the sale of smallpox-contaminated clothing to unsuspecting Union officers [14]. In the 20th century, bacteriological warfare became more skeptical, as the causative agents of many diseases were identified and many of these organisms were grown and studied in laboratories. The scientific knowledge, research and equipments needed to develop

biological agents into weapons were at first expensive, and the use of biological weapons are limited. During the later part of 20th century, the use of biological weapons increased. During World War I (1914-1918), the biological weapons were primarily intended for animals. In 1915 a German-American, Dr. Anton Dilger, grew cultures of *Bacillus anthracis* and *Pseudomonas mallei* (Glanders), supplied by the German government, in his Washington D.C. home. The agents and an inoculation device were used to infect animals, destined for the Allied troops in Europe. Several hundred troops were additionally affected. The broad and most disgusting biological weapons research occurred in Manchuria from 1932 until the end of the war [15]. This program, known as Unit 731 was located in Ping fan Manchuria. Unit 731 employed a staff of over 3,000 scientists and technicians. Experimentation on prisoners using *Shigella* spp, *Vibrio cholerae* and *Yersinia pestis* was part of the Unit 731 program and at least 10,000 prisoners had died. Most of them died from "experimental infection" and the remaining were executed after experiments for autopsy [16]. In October 1940, the Japanese filled paper bags with plague infested fleas and grain and dropped them over the cities of Ninbo, Quzhou and Zhejiang province. In 1941, the British experimented with anthrax off the Scottish coast. The United States started its own studies into use of and protection from biological agents.

Members of the right-wing "Order of the Rising Sun" were arrested in Chicago, in 1972 since they possessed 30-40 kg of typhoid cultures that were to be used to poison the water supply in Chicago, St. Louis, & other mid-west cities [17]. In1972, Biological Weapon convention was convened, and 103 nations signed it. In 1972, all US biological warfare agents were destroyed. The first example of state supported bioterrorism in recent history occurred in 1978 on September 7th, in Bulgaria when Bulgarian exile George Markov was injected in the leg with a steel ball soaked with Ricin by a specially constructed umbrella and by third day he had died [18]. In the city of Sverdlovsk, USSR, in April 1979, a detonation from Military complex 19 resulted in a toxic release. In the next few days, more than 40 people died of anthrax; local doctors announced an outbreak of inhalational anthrax, and the government blamed it was due to tainted beef [19]. The official cause is made known by the President Boris Yeltsin in 1992, that it was an unintentional release of anthrax spores in a biological warfare program [20]. In Oregon in 1984, Rajneeshee religious cultists had tainted restaurant salad bars with *Salmonella* Typhimurium to prevent town's people from participating in local elections. Over 750 were poisoned and 40 hospitalized [21].In the United States in 2001, from September to November, there were 23 confirmed cases of anthrax due to bioterrorism. The letters contaminated with anthrax were the source of infection to postal workers in New Jersey and Washington DC and the rest happened at media companies in Florida and New York.The hazard of biological agents used on resident population and armed forces staff is at present more plausible than at any point in the earlier history.

Biological warfare agents

Biological weapons or biological warfare agents include microorganisms or biological toxins that are used to produce death or disease in humans, animals, and plants.

Classification of Biological Warfare Agents (BWA)

The biological warfare agents can be classified as:

Bacteria: Anthrax, plague, brucellosis, cholera, *Clostridium perfringens* toxin, *Staphylococcus* enterotoxin B, melioidosis, tularemia.

Virus: Congo Crimen Hemorrhagic Fever, Ebola Hemorrhagic Fever, Small Pox, Rift Valley Fever, Venezuelan Equine Encephalitis

Fungus: Trichothecene Mycotoxin

Rickettsia: Q fever

Misc: Saxitoxin (derived from paralytic shellfish)
Ricin (cytotoxin derived from caster bean mesh)

Symptoms
Symptoms appear 1–2 weeks after exposure. It includes fever, headache, chills, and general pains, followed by a body rash, usually starting around the armpits or upper trunk and spreading outward. The rash typically does not appear on the face, the palms of the hands, or the soles of the feet.

Diagnosis: Typhus is diagnosed by a variety of blood tests.

a. Glanders
Glanders is a rare disease caused by the bacterium *Burkholderia mallei*. It mainly affects horses, mules, and donkeys, but can also infect humans.

Glanders as a weapon
The bacteria are highly lethal in aerosol form. Only a few particles of the bacteria can make someone sick. The Germans used glanders in World War I against attacking cavalry.
Symptoms: Symptoms include fever, headaches, muscle tightness, and chest pain, begins 1-4days of exposure. If infection occurs through a cut, a pustular lesion appears and in severe cases, pneumonia develops.
Diagnosis: Symptoms of glanders resemble those for a cold or the flu. There is no single test to confirm glanders.

b. Food Safety Threats
- There are varieties of bacteria that can affect food safety. The terrorists can poison the food supply with agents such as *E. coli* O157:H7, *Salmonella* spp., and *Shigella* spp., leading to illness and death. Most strains of *E. coli* are harmless and are found in healthy humans. *E. coli* O157:H7 is one of hundreds of strains of *E. coli* bacteria. It is the most toxic strains and can cause severe illness and, in some cases, death.

Exposure
Eating raw or undercooked meat, especially ground beef, contaminated raw vegetables, unpasteurized milk and juice, and swimming in or drinking sewage-contaminated water can infect a person. *E. coli* O157:H7 can spread if an infected person does not wash his or her hands properly.
Symptoms: It appears from hours to days after contact. The infection causes severe bloody diarrhea and abdominal cramps. A slight fever may be present. In young children under age 5 and the elderly, severe cases of O157:H7 may result in kidney failure.
Diagnosis: *E. coli* O157:H7 diagnosed by testing a stool sample.

c. Salmonellosis
There are different serovars of *Salmonella* causing salmonellosis.

Salmonellosis as a Weapon
An attack can be triggered by polluting the food supply. An attack would be identifiable if large numbers of people get sick.

Exposure
Salmonellosis spread to humans by eating foods contaminated with animal feces that contain the bacteria. Contaminated food is often meat, such as beef and poultry, or milk or eggs, but any food can be contaminated.
Symptoms: It usually develops 12–72 hours after illness. Symptoms include diarrhea, fever, and abdominal cramps.
Diagnosis: A stool sample test can be used to detect salmonellosis.Once the test confirms salmonellosis; another test should be conducted to identify the type of salmonellosis.

d. Shigellosis
It is an infection caused by the bacteria *Shigella* spp. It is present in the diarrheal stools of infected persons.

Shigella as a weapon
The bacteria would be used to infect food or water.

Exposure
Most *Shigella* spp. infections are the result of the bacterium passing from stools or soiled fingers of one person to the mouth of another person. Flies breed on infected feces and cause food contamination. People swimming in water polluted by sewage overflow or by a sick person can be exposed to the bacteria.

Shigella spp. can also enter the body through an open wound.

Symptoms: Symptoms usually occur 1–2 days after exposure. It includes bloody diarrhea, fever, and stomach cramps. Some infected person may experience no symptoms but can still spread the infection to others

Diagnosis: A stool sample test can detect the presence of the bacteria and identify the type of strain so appropriate medication can be prescribed**.**

e. Ricin toxin

Ricinus communis is a biological toxin. Ricin can be made from the waste left over from processing castor beans. It can take powder, mist, or pellet form, or it can be dissolved in water. Ricin has some potential medical uses, such as in bone marrow transplants and cancer treatment. The illness resulting from ricin poisoning is not contagious.

Note: Ricin is classified by CDC as both a chemical and a biological agent because it is a chemical toxin but has a biological source (unlike other chemical agents, such as sarin).

Ricin Toxin as a Weapon

Ricin can be processed into a powder and used as an aerosol. People would become sick after breathing in the substance. Pellets of ricin dissolved in a liquid can be injected into people's bodies. Ricin can also contaminate water or food and then be swallowed.

Ricin Toxin Illness

Ricin works by preventing the cells from making the proteins they need. Without the proteins, cells die. Eventually this is harmful to the whole body, and death may occur.

Exposure: Ricin can be inhaled, ingested, or injected.

Symptoms

Inhalation: Initial symptom arises within 8 hours of exposure and includes difficulty breathing, fever, cough, nausea, and tightness in the chest. Later they will have severe sweating and dyspnoea and the skin might turn blue. Hypotension and respiratory failure lead to death.

Ingestion: Initial symptoms occur within 6 hours and comprise vomiting and bloody diarrhea. Severe dehydration may result, followed by hypotension. It is followed by hallucinations, seizures, and blood in the urine. Several days later, liver, spleen, and kidneys might stop working, and the person might die.

Injection: A tiny amount of ricin (the size of a pinhead) is enough to cause death, such as in the 1978 case in London in which ricin was used on the tip of an umbrella to assassinate a Bulgarian exile. Ricin immediately kills the muscles and lymph nodes near the site of the injection. Failure of the major organs and death usually follow within 4 days.

Diagnosis: No reliable test exists to confirm the ricin exposure. Tracking symptoms of those suspected of being exposed could lead to a diagnosis. An X-ray could confirm fluid in the lungs.

f. Botulinum toxin

The toxin, or poison, is produced by the bacterium *Clostridium botulinum*. Botulinum toxin is the most poisonous substance known to science. Botulism is a muscle-paralyzing disease that develops after a person is poisoned with botulinum toxin. The toxin is colorless, odorless, and tasteless. *Clostridium botulinum* exists naturally in the environment, and the toxin can cause two types of illness:

- Food borne botulism/ Infant botulism
- Wound botulism

Inhalation botulism is caused by breathing botulinum toxin. It does not occur naturally but could happen because of deliberate dissemination of the toxin in the air, by a technologically refined terrorist or as a laboratory accident. However, botulism is not contagious.

Botulinum Toxin as a Weapon

Terrorists have tried to weaponize botulinum toxin by refining the toxin and putting it into an aerosol form. Refined or crude preparations of toxin are used to poison food or beverages, and refined toxin, with a complicated delivery system, could be used to spread the toxin by air. Botulism toxin can be disseminated via the air, water, or food. Since it is colorless,

odorless, and tasteless, botulinum toxin contamination is hard to detect. Poisoning the water supply would be difficult for terrorists, since large quantities of toxin would be needed to affect the water system. Further, chlorine in most water treatment facilities would destroy the toxin.

Symptoms

Food borne symptoms generally begin 18–36 hours after eating contaminated food but can occur as early as 6 hours or as late as 10 days after food consumption. Initial symptoms include blurred or double vision, slurred speech, drooping eyelids, difficulty swallowing, dry mouth, and muscle weakness. Botulism toxin spreads throughout the body and predominantly affects the nervous system. Within hours, a facial paralysis begins and spreads to the rest of the body. Botulism can result in respiratory failure.

Inhalational Botulism

Symptoms of inhaled botulinum toxin are similar to those of food borne botulism. Symptoms may begin several hours to several days after an air borne attack

Diagnosis

Botulism is a rare disease. A single case of illness may be difficult to diagnose, even if it is due to bioterrorism or a naturally occurring disease. The diagnosis can be made quickly if many cases appear together. In case of food borne or infant botulism, a stool sample test can be used. Traces of botulinum toxin can be detected by blood tests. For the detection of botulinum poisoning there is no single test available. Suspected foods should also be tested for presence of the botulinum toxin. Special tests (e.g., brain scan) may be needed to exclude similar conditions from botulism.

Future biological weapons

The availability of newer techniques like genetic engineering and proteomics in the last few decades help to modify living organisms and their products in precise and conventional ways. The application of these technologies to biological weapons development is obvious; indeed, it has been suspected that the Soviet biological weapon programme employed genetic engineering to generate novel agents [39]. As the innovation in genetic engineering got in progress, there are specific concerns that the new technological developments might have applications to offensive biological weapons development. The main concern was that they might allow the effortless production of aggressive large quantities of toxins (by inserting the toxin gene into a bacterium that could be easily grown in large quantities) [40]. It is almost certain, as was established in Iraq's recent offensive biological weapons program that an assailant nowadays is likely to try, at first to generate the agents which have been weaponized beforehand in major offensive programmes, or other original organisms. Thus the typical agents developed in the middle of the twentieth century by the United States, such as anthrax, botulinum toxin, tularemia, etc., would likely be the first agents of choice. Such agents, having already been confirmed to be effective, would need limited analysis by the proliferators. However, after the development of functional biological weapons these agents would be further developed through genetic engineering techniques. Further, an official American study in 1997 suggested that the following novel agents might be produced [41], a. benign microbes, genetically tainted to produce a toxin, venom or bioregulator; b. micro-organisms resistant to antibiotics, standard vaccines and medicine; c. microbes with better aerosol and environmental stability; d. micro-organisms are immunologically altered to defeat standard identification, detection and diagnostic methods; and e. combinations of the above four types with improved delivery systems.

Biotechnology is a two edged sword, while providing an increasing number of methods for the protection, it also shed light on techniques to destroy or incapacitate. Genetics and genomics figure directly and indirectly into each of these. The research could result in the manufacture of new biological weapons with numerous potential [42].

- Bacterial agents resistant to current antibiotics can be prepared. The soviet weapons program has revealed that it was possible to make agents causing plague resistant to antibiotics [43].
- Non-pathogenic organisms (such as *E. coli*) can be made pathogenic by transferring the genes liable for pathogenic character. Or such genes could be transferred to already pathogenic organisms to increase their virulence [44].
- By gene splicing the bacterium can be made stable and virulent in any conditions.
- Cells could be modified to produce larger quantities of more virulent toxin.
- Detection and treatment of diseases might become further difficult if they were modified. Russian scientists in the mid 1990s made detection tests for anthrax ineffective through genetic engineering techniques [45].

In biological warfare it is anticipated that both their production and the possibility for ultimate use will increase considerably over the next decades [46]. Specific experiments involving the exploitation of dangerous pathogens with modern technology have already been reported. Experts have made the tuberculosis bacterium more virulent [47] and are intentionally trying to alter the Asian flu virus to find out, if it can progress to spread among humans [48]. Existing anthrax vaccines has been made resistant by genetic modification [49]. Scientists have used non living commercially available chemicals to remake the polio virus and the current target of a world wide effort to eradicate the naturally occurring pathogen [50]. Similar attempt have been done with the Ebola virus.[51] The full genetic blue prints of plague, anthrax and Marburg virus, among other microbes have been determined and made openly accessible [52], and efforts to recognize and manipulate the functions of their genes are ongoing [53].

CONCLUSION

Bioterrorism may or may not build up into a severe burden in the future, but it is the most burning problems that we have on the planet today. Since the middle of the twentieth century it has been obvious that since adequate resources are available, biological weapons of mass destruction can be formed. Biological warfare can be used with liberty under the cover-up of natural outbreaks of disease to destroy human populations, livestock and crops of economic importance. To increase the possibility of a calm and logical response if an outbreak should occur, the medical community as well as the public should become familiar with the control measures. For the medical community, further education focusing on recognition of this danger is both appropriate and necessary. New threats are emerging in the production of weapons for use in terrorism and organized crime because of the accessibility of resources and technology [54]. The great proliferation of biological weapons, have implication for global and regional security and stability. In counter attack of such hazard, and in acquiring the peace, the need for formulating, protective responses has been stressed through the need for education of civilian and non-civilian persons, and their commitment in international co-operation. These responses emphasize the need for the reduction and elimination of bioterrorism threats through the constant availability and maintenance of a conventional law and order force that is knowledgeable in counter proliferation controls and vigilance protocols [55].The research community must make tough choices about what research is acceptable and must widen mechanisms for balancing national security with research performance and communication. 2010; 35: 138–141.

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