

Biological warfare: the facts

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Recent international situation has brought our attention back to the imminent threat of biological weapon. Contrary to other weapons of mass destruction, biological warfare is relatively silent and invisible. This review will examine the history and characteristic of biological warfare. Several biological agents like Anthrax, Plague, Smallpox, Tularemia and Viral Haemorrhagic Fever will be discussed in details. (*Hong Kong j. emerg.med.* 2001;8:232-240)

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Introduction

In modern day wars, people are increasingly worried about the use of biological weapon, the so-called "poor man nuclear bomb".¹ In this review, the characteristic of biological weapon will be examined. Numerous common biological agents will be discussed.

What is biological warfare?

Biological warfare (BW) is defined as "the deployment of biological agents to produce casualties in man or animals or damages to plants".² This can be dated back as early as 1346 during the conflict between Christian Genoese sailors and Muslim Tatars at the Crimean port of Caffa on the Black Seas. Rats and their fleas carried the disease "plague" attack the Tartars army.³ In 1754, the British infiltrated smallpox-infested blankets to unsuspected American Indians at the French and Indian war.⁴

More recently in 1932, the Japanese conducted a series of horrific experiments on Chinese subject at "Unit 731" outside Harbin, Manchuria of China.⁴ It was

estimated that at least 11 Chinese cities had been attacked with Anthrax, Cholera, Plague and Salmonella and at least 10,000 died as a results.⁵

Advantages of biological warfare

As mentioned before, biological warfare is sometimes called "the poor man nuclear bomb". As the name implies, it is relatively cheap and can cause a devastating effect.

From a military point of view, BW is capable of producing a large number of casualties. The WHO⁶ has estimated that if a city of 5 million population was attacked with BW like Anthrax (50 kg), at least 100,000 would died and 250,000 would be incapacitated in an projected affected downwind area of 20 km.

AGENT	Downwind reach (KM)	Dead	Incapacitated
Anthrax	>20	100,000	250,000
Tularemia	>20	30,000	125,000
Brucellosis	10	500	100,000
Q-fever	>20	150	125,000

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From a technical point of view, the making of BW is relatively easy. All the equipment needed is obtainable off the shelf for a variety of legitimate purposes.⁷ This

means that the manufacture of BW can escape international surveillance easily. The raw materials are easily obtainable from the market as well. Western universities have also produced an abundance of graduate in the field of biological science and biotechnology.

From an economy point of view, BW is affordable. The start-up cost is far less than those of nuclear weapons. It was estimated that to achieve a similar effect on civilian attack, conventional weapon would cost US\$2000 per square km, while nuclear weapon will cost US\$800. BW only cost US\$1 per square km for similar results!⁸

BW can also be used to attack animal and material. Suppose a pig rearing community is attacked by BW with "swine fever virus". The attack is silent and leaves no trace. The community will be devastated, as it is usual practice for mass slaughtering of infected animal in order to prevent the spreading of disease.⁸

Some BW are capable of degrading material like rubber or metal, others could produce clog in fuel. The result will be disastrous if such an agent is introduced into the fuel system of jet fighter aircraft or civilian airplane!

Disadvantages of biological warfare

BW agents pose hazards to the users. Most are dependent on optimal weather condition for effective dissemination. The agents are susceptible to inactivation by solar irradiation and other climatic conditions.

The effect of conventional weapons is immediate and clear. It can be used both tactically and strategically in the battlefield. The effect of BW is usually delayed and countermeasures are available. With the use of flea insecticide, immunization with plague vaccine, insect repellents and protective clothing against plague during the Vietnam War by the American, there are only 8 cases of plague in the American troops.⁹⁻¹¹ The effect of BW will be minimal if the defending nation

is well aware of the attack, as countermeasures are available.

How to recognize a biological warfare attack?

The first indicator of a BW attack would be a tremendous increase in the number of patients presenting with clinical features that is suggestive of a disseminated disease agent. A good intelligent network is needed to prevent this from occurring. Diligent epidemiological investigation is needed to track down the source. It could be difficult to diagnose and recognize the attack as most of the victims are presented with non specific symptoms. It is the pattern of disease that evolved which distinguishes a biological attack from an epidemic. The following are telltale signs of BW attack:^{2,12}

1. There will be a far greater number of patients seeking medical attention within a shorter period of time.
2. There may be a large number of rapidly fatal cases with few recognizable symptoms and signs.
3. The disease pattern will be unusual for the geographical area.
4. Patient will have disease that is atypical to its usual occurrence. A clear example is Anthrax. The common form of presentation is cutaneous. Pulmonary form is exceedingly rare. A sudden upsurge of pulmonary Anthrax should point towards BW attack as it is usually disseminated through aerosols.
5. Multiple diseases or serial epidemic of different diseases may be found in the same population simultaneously.
6. Patient may have more severe disease than is usually expected for a specific pathogen or a failure to respond to standard treatment.
7. A vector that is unusual to that area may transmit the disease.
8. We may found case of disease by an uncommon agent (smallpox!) or the age group affected is unusual for the disease.
9. There may be a higher attack rates in confined area if the agents is released indoors and vice versa.

10. BW is used by terrorist against densely populated area. It will be extremely rare to find trace of BW in sparsely populated area unless the targets are plants or animals.
11. The most important clue is the intelligence information regarding the potential attack, or claims by terrorist after an outbreak.

Sophisticated detector systems have been developed. The Biological Integrated Detection system (BIDS) is a vehicle-mounted detector that detects aerosol particles and tests them against genetic and antibody-based detection system. However, it would be difficult to distinguish between background and BW agent.

The biological agent

We will discuss several biological agents that have been implicated in Biological Warfare; this includes Anthrax, Plague, Smallpox, Tularemia, and Haemorrhagic fever virus. Toxin agent like Trichothecene (T-2) mycotoxins will also be discussed.

Anthrax

Bacillus Anthracis, the causative agent of Anthrax, is a gram-positive sporulating rod. Anthrax is primarily a zoonotic disease of herbivores. The disease is endemic in western Asia and western Africa (including Afghanistan!).¹³ Human contracted the disease (cutaneous anthrax) through handling of contaminated fur, flesh and blood of infected animal. Infection is introduced through wound or abrasion in skin with formation of small papules that degenerated into painless eschar (hence the name Anthrax, from the Greek word "*Anthrakos*"=coal).¹⁴ The spores could also be ingested from infected meat, causing "gastrointestinal anthrax", though this form of transmission is exceedingly rare.

The primary concern here is intentional infection through inhalation after aerosol dissemination of the spore after a BW attack. Pulmonary Anthrax, or "wool-sorter disease" (name after the wool-sorter's infection in England) is the disease contracted through air-borne

spore. It has been estimated that the optimal size for infection is 1-5 micron. Size larger or smaller than this will not stay in the respiratory tract effectively.

The spores are capable of surviving in the lung for up to 100 days.¹⁵ The spores are resistant to heat, cold, drying and chemical disinfectant. Survival in soil for up to 200 years has been reported!¹⁶ Infected animal carcass should be burned, and not buried, as it had been shown that earthworms could carry the spores back to the surface in buried carcass.¹⁴

Clinical features

Once inhaled, the spores are picked up by the alveoli macrophage and travel through lymphatic to the mediastinum, where it causes the inevitably fatal haemorrhagic mediastinitis. This is not true pneumonia! The bacilli multiples intravascularly, releasing toxin that increase IL-1 and TNF;¹⁷ causing fatal toxæmia, haemorrhagic meningitis and septic shock. Death ensued after 24-36 hours.¹⁸

The usual incubation period last from 1-6 days, but the USSR disaster in 1979 had reported incubation period of up to 6 weeks.¹⁴ This is dependent on the dose and strain of inhaled organism. There has been **no evidence of direct person-to-person spread** of the disease from inhalation anthrax.

The onset of inhalation anthrax is gradual and nonspecific. There may be prodrome of fever, malaise, nonproductive cough and mild chest discomfort.^{13,19} The initial symptoms are followed by a short period of improvement (hours to 3 days). This is followed by an abrupt development of respiratory distress, diaphoresis, stridor and cyanosis. Patient presented at this stage is usually beyond rescue as death ensues after the onset of respiratory distress. Clinical sign is minimal but there may be widened mediastinum and/or pleural effusion on chest X-ray in up to 50% of cases.

Diagnosis

Unlike cutaneous anthrax where there is eschar formation, the diagnosis of inhalation Anthrax is difficult. *Bacillus anthracis* can be detected by Gram stain of blood and blood culture, but this is usually

too late in the course of disease. Serology is only of retrospective use for the same reason. Sputum examination is not useful, as pneumonia is not a feature of disease.

However the presence of respiratory distress with widen mediastinum AND the presence of haemorrhagic effusion or haemorrhagic meningitis should suggest the diagnosis.

Treatment

Unfortunately, almost all inhalation anthrax cases in which treatment was begun after patients were significantly symptomatic have been fatal, regardless of treatment! Penicillin has been regarded as the treatment of choice, with 2 million units given intravenously every 2 hours. Tetracyclines and erythromycin have been recommended in penicillin allergic patients.¹⁸

The American army recommends ciprofloxacin (400 mg IV q 12 hours) or doxycycline (200 mg IV load, followed by 100 mg IV q 12 hours) as initial therapy, with penicillin (4 million U IV q 4 hours) as an alternative once sensitivity data is available. JAMA recommends ciprofloxacin as initial therapy. Recommended treatment duration is 60 days.

What should we do in known or imminent exposure? (Post exposure prophylaxis, PEP)

Ciprofloxacin (500 mg po b.d.) recently became the first medication approved by the FDA for prophylaxis after exposure to a biological weapon (anthrax). Should an attack be confirmed as anthrax, antibiotics should be continued for at least 4 weeks in all those exposed, and until all those exposed have received three doses of the vaccine. Those who have already received three doses within 6 months of exposure should continue with their routine vaccine schedule. In the absence of vaccine, chemoprophylaxis should continue for at least 60 days.

Anthrax vaccine is derived from sterile culture fluid supernatant taken from an attenuated strain. Therefore, the vaccine does not contain live or dead organisms. The vaccination series consists of six

0.5 ml doses SC at 0, 2, and 4 weeks, then 6, 12 and 18 months, followed by yearly boosters. Studies in rhesus monkeys indicate that good protection can be afforded after only two doses (15 days apart) for up to 2 years. Hypochlorite is used in disinfecting medical equipment.

Plague

Plague has cost 200 million lives throughout the history of mankind.²⁰ Plague is a zoonotic infection that passes from flea to human through skin inoculation. The organism responsible is *Yersinia pestis*, a gram-negative bacillus; that is carried in the guts of flea. Up to 30 types of flea and over 200 species of mammals in 73 genera are implicated in the spreading of disease.²¹

Clinical features

After a flea injects a blood meal into the victim, the bacilli are engulfed by monocytes and neutrophils. The bacilli then multiply in the monocytes. It then travels to lymph nodes and blood throughout the body, especially to the spleen, liver, lungs and meninges.²⁰ The naturally occurring disease is characterized by the abrupt onset of fever, painful lymphadenopathy (bubonic plague, Greek "*boubon*"= groin) that drains to the exposure site and septicaemia. Blood-borne spread to the lung results in secondary pneumonic plague, which is rapidly fatal and transmissible.

In the setting of BW attack, the bacilli can be spread through aerosol, causing primary pneumonic plague. This carries a mortality of 80-100%. Person-to-person spread through cough or sneezing is possible. Respiratory droplets can be inhaled within 5 feet. The median infective inhaled dose is 100-500 bacilli. The victim presented with flu-like illness 2-3 days after inhalation. The clinical downturn is rapid with overwhelming pneumonia, haemoptysis, bleeding diathesis and cardiovascular collapse. If treatment is not started within 24 hours of symptoms, nearly all patients will die.¹²

Diagnosis

In the setting of naturally occurring plague, the

presence of painful bubo should raise the alarm. The *Y. pestis* capsular antigen can be identified through "direct fluorescent antibody" staining of lymph node aspirate. The organism can also be identified by Gram stain and culture of blood and sputum.

Treatment

Treatment within 24 hours of symptom is needed to save life in pneumonic plague. Streptomycin 30 mg/kg/day i.m. in twice daily dose is used. Intravenous Doxycycline 100 mg twice daily is an alternative. Treatment should be continued for a minimum of 10 days or 3-4 days after clinical recovery. Intravenous Chloramphenicol 50 mg/kg/day should be added in those that are haemodynamically unstable or with suspected meningitis. Patients should be isolated for at least 48 hours until the sputum cultures are negative.

PEP includes oral Ciprofloxacin for 7 days. Pregnant women and children should receive Septrin. Plague vaccine, with killed whole cell, is available for pre-exposure prophylaxis against bubonic plague, but not pneumonic plague. The U.S. military currently requires vaccination for troops deployed to high-risk areas.²² The organism is susceptible to heat, disinfectant and sunlight. Soap and water is effective for decontamination.

Smallpox

Smallpox is caused by Poxvirus, a DNA virus that is relatively resistant to drying and many disinfectants.²³ Smallpox was endemic in 31 countries affecting 15 million people each year (2 million died). Fortunately, this was the story 30 years ago. WHO has declared a smallpox free world in 1977 after a 10-year eradication program.^{5,24} However, smallpox is still stocked in CDC of USA and Russian State Research Centre for Virology and Biotechnology in Koltsovo of Russia.

The termination of vaccination program, high mortality and high rate of person-to-person aerosol transmission make smallpox a perfect BW agent. It would be a matter of *International Emergency* if there is an outbreak of smallpox.²⁵

Clinical features

Transmission is through aerosol,²⁶ where the Variola travels from the respiratory tract to regional lymph nodes. It then replicates and causes viraemia. Patient is most infective 4-6 days after the illness started and continues until scabs separate. Around 30% of susceptible contact will be infected.²⁴ Infectivity is higher in patient who cough. The incubation period ranges from 7-17 days with a prodrome of fever, headache or backpain. About 10% of light-skinned patient will develop an erythematous rash during the prodrome.²⁷ Usually after 2 days of prodrome, an exanthem appears on the buccal and pharyngeal mucosa. A centrifugal rash spread from face to upper limb, later to lower limb and trunk within a week. The rash changes from macules to pustules, which later turns into scab and heals with hypopigmented scar. All the lesions are in the same stage of eruption, which distinguishes it from chickenpox.

Mortality is 3% in the vaccinated and 30% in unvaccinated patients. Secondary bacterial pneumonia carries 50% mortality.

Diagnosis

Diagnosis is usually a clinical one. The diagnosis can be confirmed with polymerase chain reaction or electron microscope. Virus could be cultured from the lesion.

Treatment

Treatment is mainly supportive. All exposed person should be quarantined strictly with respiratory isolation for 17 days. Any fever above 38°C during the quarantine period is suggestive of smallpox infection. They should also be vaccinated and vaccinia-immune globulin should be given. Medical personnel should have a history of vaccination and should undergo immediate revaccination to ensure immunity.

Tularemia

Tularemia is a zoonosis, caused by *Francisella tularensis*, a gram-negative coccobacillus. The disease is extremely infective but not highly fatal. Six forms of Tularemia have been described. Untreated tularemia

carries a 8% mortality for all types, 4% for ulceroglandular and 35% for typhoidal type.²⁸ The Ulceroglandular tularemia is transmitted through exposure to diseased animal fluids and blood-sucking by ticks, deerflies or mosquitoes. Typhoidal and pulmonary tularemia can occur after inhalation of the bacilli in the setting of BW attack. It has been weaponized by the United States in 1950s.¹²

Clinical features

All forms of Tularemia start with sudden onset of fevers, chills, headache and myalgia after an incubation period of 3-6 days.²⁸ The fever is often accompanied by a pulse-temperature disassociation i.e. the pulse increases less than 10 beats per minutes per 1°F increase in temperature. Ulceroglandular is the most common form of tularemia. A punch-out ulcer is seen at the bite site. The bacilli then spreads to local lymph nodes and cause bacteremia. Pneumonia occur secondary to bacteremia.

Inhalation of the bacilli through BW attack causes typhoidal tularemia. Patient will present with fever, headache, malaise, substernal discomfort, prostration, weight loss and non-productive cough. Around 80% of patient will develop pneumonia, as compared to 30% in ulceroglandular type. Chest X-ray may show patch infiltrates and hilar adenopathy, but not large area of consolidation.²⁹

Diagnosis

The diagnosis is usually a clinical one. The organism is difficult to culture. The diagnosis can be confirmed with serology and ELISA test. Antibodies level rise significant only after 2 weeks.

Treatment

Intramuscular Streptomycin is the drug of choice. The dose is 1 gram every 12 hours for 14 days. Gentamicin has been used as an alternative.

PEP includes 2 weeks course of oral tetracycline or doxycycline. A live, attenuated vaccine is available as an investigational new drug for pre-exposure prophylaxis. There has been *no known case of person-*

to-person transmission. No isolation or quarantine is required. The organism can be rendered harmless by mild heat (55°C for 10 minutes) and standard disinfectants.

Viral Haemorrhagic fever

Haemorrhagic fever is a clinical syndrome featuring fever, myalgia, haemorrhage and cardiovascular collapse. It is highly infectious through aerosol route and carries high mortality and morbidity. Person-to-person spread can occur through direct contact of blood and body fluid.³⁰ They are RNA virus. Four viral haemorrhagic fevers have the highest risk of nosocomial spread and are quarantinable conditions. These include Ebola and Marburg (filovirus); Lassa fever (Arenavirus) and Congo-Crimean haemorrhagic fever (Bunyavirus)[CCHF].³¹

Filovirus could be used as BW agents as they are highly infectious, lethal and can be stabilized for aerosol dissemination. However, they are also considered too dangerous to be used, as there is no protective vaccines to protect the users. CCHF has been tried in the past but it's susceptibility to heat, drying and ultraviolet makes them poor candidates for BW agents.³² Hantavirus replicates poorly in cell culture and are not considered to be a good BW agent. Dengue is not infectious by aerosol and is not a candidate for BW agent.

Clinical features

All viral haemorrhagic fever is characterized by acute febrile illness and increase vascular permeability as the endothelial cell is primarily affected.¹² Flushing, periorbital oedema, conjunctival injection, petechiae are commonly seen. Tourniquet test is positive. Differentiation from other endemic febrile illness is difficult early in the course of illness. The disease progresses with generalized mucosal haemorrhage and cardiovascular collapse. Pulmonary, haematopoietic and neurological involvement is not uncommon.¹² Exanthem is common in filovirus, uncommon in Lassa fever and absent in CCHF.

However, the most severe haemorrhage is seen in CCHF. Filovirus exhibit significant Disseminated Intravascular Coagulation (DIC) as well. Neurological involvement and haemorrhagic is less common in Lassa fever.³³

Diagnosis

This is done by ELISA, PCR and electron microscopy under strict containment.

Treatment

Treatment is supportive with special attention paid to fluid and electrolyte balance. Intensive care is frequently needed. The role of heparin for DIC is controversial and should be reserved for patient with significant haemorrhage and laboratory evidence of DIC. Aspirin and intramuscular injection are contraindicated. Intravenous ribavirin has been used in Lassa fever, Hantaan virus and CCHF.³⁴ But safety in child has not been established and it is tetratogenic in animal study. Immunotherapy with convalescent plasma has been used in Argentine and Bolivian haemorrhagic fever.

The only licensed Viral Haemorrhagic fever vaccine is Yellow fever vaccine.

In suspected Lassa fever, CCHF or Filovirus, contact isolation with surgical mask and eye protection for those that come within three feet of the patient is indicated. Hypochlorite or phenolic disinfectants is used in decontamination.³⁵

Trichothecene (T-2) Mycotoxin

It is also called the "Yellow Rain". The mycotoxin had been used in Laos and the attacks was described as sticky yellow liquid that fell and sounded like rain. The T-2 mycotoxins are extremely stable compound produced by 5 fungal genera: *Fusarium*, *Aspergillus*, *Alternaria*, *Claviceps* and *Penicillium*.³⁶ The mycotoxins can be entered the body through skin, mucous membrane, inhaled or ingested. It has been used in Southeast Asia between 1974 and 1981 as a BW agent.³⁷

Clinical features

At low dose, mycotoxins can cause skin irritation with erythema, necrosis and sloughing of the epidermis. It can also cause eye irritation and corneal damage. It is estimated that mycotoxin is 400 times more potent than Mustards in producing skin injury.³⁸ Cough, wheezing, emesis and diarrhoea occurred at higher dose. Since the mycotoxins can be absorbed through skin, a high dose exposure can cause bone marrow suppression though inhibition of protein and RNA synthesis. Inhaled mycotoxins can cause death in minutes to hours by destroying the alveoli.

Diagnosis

Blood and environmental sample can be tested with gas chromatography-mass spectroscopy. T-2 mycotoxins attack is suspected when "yellow rain" occurs with resulting cutaneous effect.

Treatment

There is no antidote. Treatment remains supportive. Soap and water washing within 1 hour may prevent toxicity. Activated charcoal can be used in ingested case. All outer clothing should be removed and decontaminated with soap and water. Eye exposure should be irrigated with copious amount of saline. Contact with contaminated skin is known to cause secondary dermal exposure. Secondary aerosol is not hazardous. 1% sodium hypochlorite and 0.1M NaOH is used for environmental decontamination.

Conclusion

We have examined various aspect of biological warfare. Several BW agents have been discussed. BW has been the weapon for developed and developing countries. The low cost, "silent" nature and ability to inflict large number of casualties make it the choice of offence from terrorist. Hong Kong is politically stable and terrorist attack is unheard of. We should, nevertheless, be prepared to deal with such situation, as BW attack is not a remote possibility. Prompt recognition and awareness of the frontline staff is of great importance. We should be familiar with the contingency plan and the HAZMAT procedure.

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