Bioterrorism:
A Small Risk with Huge Potential

Ethan Rubinstein, MD, LL.B.

Biological warfare has already been described in the Bible in the Exodus of the Hebrews from Egypt. Biological weapons (BWs) have been utilized as early as in the Tartar invasion of Europe in 1346 (Figure 1) and continuously through the Zimbabwean Independence War in the 1970s. BWs have been extensively developed in the 1950's to 1970s and as late as the early 1990s by Iraq.[1]

Biological weapons are divided into three categories (Table 1):[2]

Category A: Diseases/agents

These are high priority pathogens because they:

- can be easily disseminated or transmitted from person to person,
- result in high mortality rates and have the potential for major public health impact,
- might cause public panic and social disruption,
- require special action for public health preparedness.

Category B: Diseases/agents second

These are the highest priority agents including those that:

- are moderately easy to disseminate,
- result in moderate morbidity rates and low mortality rates,
- require specific enhancements of diagnostic capacity and enhanced disease surveillance.

Category C: Diseases/agents

These include emerging pathogens that could be engineered for mass dissemination in the future because of:

- availability,
- ease of production and dissemination,
- potential for high morbidity and mortality rates and major health impacts.

Anthrax (Figure 2) as a prime BWs have been recently used in Tokyo by the Aum Shinrikyo group in 1990's and in the US in September 2001, resulting in 18 confirmed cases (seven cutaneous and 11 inhalational cases of whom five died [mortality 45%]). Recently, an additional incidental case of the inhalational of anthrax was reported from New York, the victim acquired the infection while producing drums from imported skins. Agriculturally-acquired cases of predominantly cutaneous anthrax continue to occur in:

- Canada,
- Asian Russia,
- South America and
- Turkey.

Spores that are available in nature, are able to cause human disease of various forms. Luckily, most of these strains are pan-susceptible to conventional antibiotics. Nonetheless, penicillin resistant strains have been isolated in nature[4]. As anthrax is widespread and the spores survive in nature for decades, it is obvious that anthrax can be easily cultured in the

Table 1

Classification of biological weapons

Category A	Category B		Category C
Anthrax (*Bacillus anthracis*)	Brucellosis (*Brucella species*)	Psittacosis (*Chlamydia psittaci*)	Emerging infectious diseases such as Nipah virus and hantavirus
Botulism (*Clostridium botulinum toxin*)	Epsilon toxin of *Clostridium perfringens*	Staphylococcal *enterotoxin B*	
Smallpox (*variola major*)	Food safety threats (*e.g., Salmonella, species Shigella Escherichia coli* O157:H7)	Typhus fever (*Rickettsia prowazekii*)	
Tularemia (*Francisella tularensis*)	Q fever (*Coxiella burnetii*)	Water safety threats (*e.g., Vibrio cholerae, Cryptosporidium parvum*)	
Viral hemorrhagic fevers (filoviruses [*e.g.*, *Ebola, Marburg*] and arenaviruses [*e.g.*, *Lassa,* Machupo])	*Glanders and Melioidosis* (*Burkholderia mallei*) (*Burkholderia pseudomallei*)	Viral encephalitis (alphaviruses [*e.g.*, Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis])	

laboratory and manipulated. Pan-resistant strains can be produced without loss of their pathogenic potential. Of particular concern is the ability to develop resistance to fluoroquinolones, which are the drugs of choice in anthrax.[5] The major drawbacks of using anthrax as an efficient weapon are the absence of effective methods in the hands of non-military, non-scientific organizations to lyophilize the anthrax spores into a small-particle, non-sticky powder and to be able to disperse them effectively. Naturally, intelligence services need to be vigilant of the potential of sinister organizations to overcome such difficulties by acquiring effective technologies and instruments. Presently, great improvements in rapid diagnosis, based on novel technologies, antibodies and antidotes against anthrax toxins, newer effective vaccines, increased knowledge of the pharmacodynamics of antibiotics against *Bacillus anthracis* and increase in the capabilities of intelligence services and global cooperation have diminished the threat of this threat

Yersinia pestis (Y. pestis), the organism causing plague, has also been considered a potential BW. From 1982 to 1996, 23,904 cases of plague, with 10% mortality were reported to the World Health Organization.

Dr. Ethan Rubinstein is a Sellers Professor of Infectious Diseases and Section Head of Infectious Diseases, University of Manitoba, Winnipeg, Canada. He was previously Head of the Infectious Diseases Unit, Sheba Medical Center, Tel Hashomer, Tel Aviv Univesity, School of Medicine, Israel. Main intersts: Gram-positive Infections, endocarditis and new antibacterials.

Table 2

Characteristics of common stockpiled and weaponized biological weapons[3]

Disease Agent	Anthrax: *Bacillus anthracis*
Signs and Symptoms	Malaise, Fatigue, myalgia, fever, non-productive cough (early); followed by severe respiratory distress, bhest pain, sweating, swelling, shock.
Theoretical Toxicity	One gram of spores could kill the entire Canadian population. 50% exposed will develop meningitis. Has a mortality rate of 50% (despite appropriate treatment)
Time to onset	1 day to 6 days (inhaled)
Disease Agent	Botulism: Botulinum Toxin,Type-A; *Clostridium botulinum*
Signs and Symptoms	Blurred vision, lid droop, difficulty swallowing, difficulty speaking, muscle weakness, respiratory distress, death
Theoretical Toxicity	Few tenths of a microgram is lethal. 8oz could kill every living creature
Time to onset	2 days to 4 days
Disease Agent	Brucellosis: *Brucella suis, melitensis, abortus, canis* (human pathogenic types)
Signs and Symptoms	Localized inflammatory process, acute febrile illness or chronic infection.Depression, headache, irritability
Theoretical Toxicity	Relatively large amounts.
Time to onset	3 days to several weeks
Disease Agent	Plague: *Yersinia pestis*
Signs and Symptoms	Fever, headache, vomiting, chills plus: pneumonia with blood-tinged sputum (pneumonic); painful large skin blisters, altered mentation, abdominal pain (bubonic) or purpura, disseminated intravascular coagulation cyanosis, necrosis of fingers and toes (septicemic).
Theoretical Toxicity	Disease caused by 1organism to 10 organisms through the skin, or 100 organisms to 20,000 organisms inhaled. Up to 12% of those infected die from disease
Time to onset	24 hours (inhaled); 1 to 8 days (skin); 2 to 6 days septicemic).
Disease Agent	Q-Fever *(Coxiella burnetii)*
Signs and Symptoms:	No common pattern
Theoretical Toxicity	1 organism
Time to onset	10 days to 40 days
Disease Agent	Smallpox: *Orthopoxviridae varioloa*
Signs and Symptoms	Malaise, Fever, rigors, vomiting, headache, backache, typical skin erruption
Theoretical Toxicity	-
Time to onset	12 days (average).
Disease Agent	Tularemia: *Francisella tularensis*
Signs and Symptoms	Fever, chills, headache, cough, myalgias, pneumonia. This includes single ulcer and lymphadenopathy (ulceroglandular), or systemic symptoms, more common and severe pneumonia, without local skin lesion or marked lymphadenopathy (typhoidal).
Theoretical Toxicity	10 to 50 inhaled organisms cause disease. Without treatment, has a mortality rate of 4% (ulceroglandular) to 35% (typhoidal).
Time to onset	Three days to six days
Disease Agent	Typhoid: *Salmonella typhosa*
Signs and Symptoms:	Chills, fever, cough, nosebleed, weakness, abdominal pain, delirium, rash
Theoretical Toxicity	1 lb of culture in drinking water is as toxic as 11 lbs. of *botulinum toxin* or 10 tons of potassium cyanide
Time to onset	-

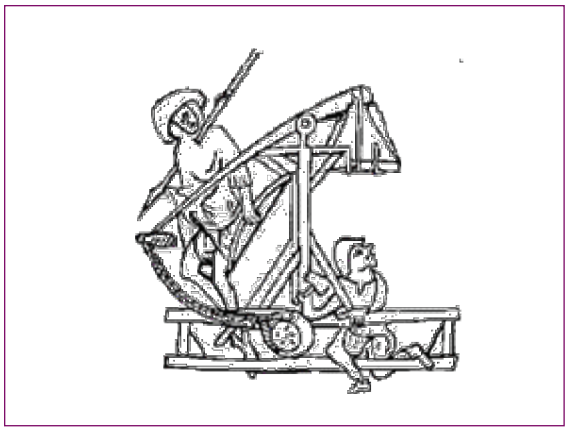

Figure 1. Catapult used by the Tartars to throw bodies of soldiers and animals who died of infectious diseases above the walls in the Siege of Kaffa 1346.

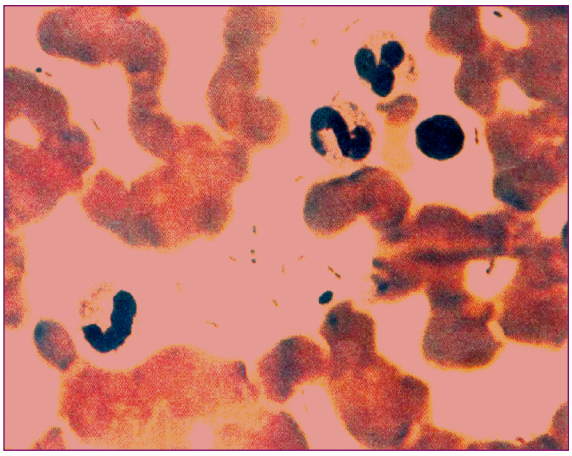

Figure 2. *Bacillus anthracis* as visualized in blood from a septicemic patient.

Outbreaks of plague were reported from:

- Madagascar,
- Peru and
- India (the last causing global alarm).

While most strains are pan-susceptible to antibiotics, some in nature occurring strains are:

- aminoglycosides,
- beta-lactams,
- chloramphenicol and
- rifampin-resistant.

Pan-resistant *Y. pestis*, secondary to a common plasmid present in enterobacteriaceae have also been described. Trans-conjugation occurs in the flea gut, the vector for transfer of *Y. pestis*. Thus such resistant strains could be produced by treating fleas with antibiotics and allowing them to feed on *Y. pestis* containing sources. As *Y. pestis* is occurring in remote countries and is infective to the person who deals with this organism, the chances of the use of this agent as a BW is slim.[6]

In summary, bioterrorism is posing a limited but an important threat. While in nature most BWs are antibiotic-susceptible and pathogenic to man and animal, there are a number of exceptions. It is relatively simple to produce (select) antibiotic resistant *Bacillus anthracis* mutants. Whether resistant mutants possess the same pathogenic potential as non-resistant mutants is a question that can be only answered indirectly. Fluoroquinolone resistant *Streptococcus pneumonaie* and gram-negative *bacilli*, which possess the same underlying resistant mechanisms (efflux pumps, *gyras* and topoisomerase mutations) are producing disease in man and animal. It is logical to speculate that the same will occur in *bacillus anthracis*.

Thus, the risk for bioterrorism attack while slim, is nevertheless existent. The major obstacle is not laboratory-based, but rather the lack of means of effective packaging and dispersion.

cme

References

1. Rotz LD, Khan AS, Lillibridge SR, et al: Public health assessment of potential biological terrorism agents. Emerg Infect Dis. 2002; 8(2):225-30.
2. Dudley JP, Woodford MH: Bioweapons, bioterrorism and biodiversity: Potential impacts of biological weapons attacks on agricultural and biological diversity. Rev Sci Tech, 2002; 21(1):125-37.
3. Karwa M, Currie B, Kvetan V. Bioterrorism: Preparing for the impossible or the improbable. Crit Care Med, 2005; 33(1):S75-95.
4. Inglesby TV, Henderson DA, Bartlett JG, et al: Anthrax as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense, JAMA, 1999;281(18):1735-45
5. Athamna A, Athamna M, Abu-Rashed N, et al: Selection of bacillus anthracis isolates resistant to antibiotics. J Antimicrob Chemother. 2004;54(2):424-8.
6. Inglesby TV, Dennis DT, Henderson DA, et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA. 2000; 283(13):2281-90.