Biological warfare and bioterrorism

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Since the terrorist attack on the United States in September 2001 attention has been focused on the threat of biological warfare. The disruptive effects of deliberate release of anthrax in civilian settings have been well documented, and several other pathogens could also be used as biological weapons. We have described the key features of such pathogens, how they might be used in biological warfare, and the clinical syndromes they cause. We also discuss the medical and logistic response to their possible use.

Summary points

- Appropriate dispersion of even a small volume of biological warfare agent may cause high morbidity and mortality, which may be exacerbated by public panic and social disruption
- Early symptoms of disease induced by a biological warfare agent may be non-specific or difficult to recognise
- Healthcare workers should be alert for unusual single cases or clusters of illness, especially in otherwise healthy adults
- Unusual illness should be notified immediately to public health authorities
- Strategic responses to the deliberate release of biological warfare agents must be rehearsed locally and nationally with multiple agencies
- Healthcare professionals should familiarise themselves with national and local sources of advice on deliberate release

The use of pathogens as weapons

Biological warfare agents are defined as "living organisms, whatever their nature, or infected material derived from them, which are used for hostile purposes and intended to cause disease or death in man, animals and plants, and which depend for their efforts on the ability to multiply in the person, animal or plant attacked."[1] Many such agents are zoonotic and have a considerable impact on agriculture as well as on human health. Biological warfare agents are well suited for use in bioterrorism or for attack by poorer nations against the rich (so called "asymmetric methods" of attack[2]) as they are cheap and easy to obtain and disperse, although full scale use as a weapon may be difficult.

Infectious diseases have always played a major part in limiting military campaigns, and invading armies may also be assisted by disease, deliberately or inadvertently (box 1). Western powers, including Britain,[7] the United States, and Canada,[8] and the former Soviet Union[9] had biological research programmes for both offensive and defensive purposes, and several other nations are known or thought to have such programmes. Bioterrorism, usually from within, has become reality in both the United States[10] and Japan.[11]

Essentials of delivery

The criteria for a successful biological warfare agent are listed in box 2.[1] Agents that might potentially be used as biological weapons can be classified according to their clinical characteristics and impact on public health (see table A on bmj.com).[12] Clinical effects vary from high mortality (for example, smallpox, pneumonic plague) to prolonged incapacity (for example, Venezuelan equine encephalitis). The mere threat of use in a military setting will impair the effectiveness of opposing troops—for example, the need for alliance troops to work in full protective (nuclear, biological, and chemical) suits in high temperatures during the Gulf war. In a civilian setting, logistic and economic disruption and longlasting psychological effects on the general population may greatly outweigh the direct medical effects of deliberate release,[13] as exemplified by recent anthrax releases in the United States.

In a military setting, biological warfare agents are most likely to be delivered by aerosol. The optimum particle size is 0.3-5.0μ in diameter, which is small enough to reach the alveoli when it is inhaled.[14] This can be achieved by aerosol generators mounted in fixed locations or on trucks, cars, or boats as well as from cruise missiles and planes equipped with tanks and spray nozzles. Numerous climatic factors affect the efficiency of such methods including wind velocity and direction, humidity, degree of cloud protection from direct sunlight, and rainfall. In optimum circumstances the distribution of a biological warfare agent from a cruise missile could cover a large enough area and produce casualties equivalent to that due to fallout from a nuclear device.[15] In the bioterrorist setting aerosols could be disseminated the same way, by direct delivery into ventilation or air conditioning systems or via letters or parcels. Suicide attacks would be extremely effective for disseminating diseases such as

Box 1: Role of infectious disease in warfare in history

- The inhabitants of Central and South America were decimated by smallpox and measles that accompanied the Spanish conquistadors[3]
- British forces used blankets contaminated with smallpox to infect North American Indians in the 18th century[4]
- The Tartars catapulted bodies infected with plague into Kaffa in the Crimea in 1346 at the end of a three year siege[5]
- The Japanese released fleas infected with plague in Chinese cities in the 1930s and 1940s[6]

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Two tables on categories of biological warfare agents and clinical syndromes can be found on bmj.com

Box 2: Optimum conditions for effective biological warfare[1]

The agent
- Consistently produces a given effect—death or disease
- Highly contagious and infective in low doses
- Short and predictable incubation time
- Difficult to identify in target population
- Suitable for mass production, storage, and weaponisation (that is, conversion of the biological agent into a form that can then be used as a weapon)
- Stable during dissemination
- Low persistence after delivery

The target population
- Little or no natural or acquired immunity
- Little or no access to immunisation or treatment

The aggressor
- Has means to protect or treat own forces and population against the agent

smallpox. Food and water are suitable vehicles for local delivery of pathogens. The Rajneeshee cult caused over 750 cases of salmonellosis by contamination of salads in Oregon in 1984.[10]

Effects of delivery

The effects of a deliberate release will be obvious if a large number of troops become ill with similar symptoms at the same time. It may be less clear in a civilian population unless the incubation period is short, when the outbreak will resemble a chemical attack or disaster and will be obvious to local practitioners and hospital emergency rooms. However, an unexpected covert release in an urban civilian setting could affect individuals living in widely dispersed areas, who may then present to several different healthcare providers.

Many biological warfare agents cause illness that could be mistaken for common diseases such as influenza. Delay in recognition will be further enhanced during natural cyclical epidemics, such as respiratory illness in winter. If the incubation period of clinical illness is long, and especially if secondary transmission to contacts occurs from index cases, huge epidemic spread may have already occurred before the release is recognised. This has recently been demonstrated by the catastrophic epidemic of foot and mouth disease in British farm animals. The same would hold true for release of smallpox into a non-immune population.

Genetic engineering of biological warfare agents can alter their pathogenicity, incubation periods, or even the clinical syndromes they cause. Resistance to antimicrobial drugs may be enhanced or added, and strains may be produced that evade the host response induced by conventional immunisation.[9]

Clinical features

Many of the major clinical syndromes produced by biological warfare agents start with a non-specific febrile illness (see table B on bmj.com). Pneumonic and gastrointestinal illness may be mistaken for naturally occurring sporadic or epidemic infections. Few clinicians will have seen illness caused by biological warfare agents, and induced syndromes may be atypical. For example, pulmonary consolidation and effusions are said to be unusual in inhalational anthrax, which was thought to have a mortality exceeding 90% if not diagnosed and treated immediately. Yet in the recent cases of inhalational anthrax in the United States six of 10 people survived.[16]

Anthrax

Anthrax is a zoonosis caused by *Bacillus anthracis*, to which man is relatively resistant (ID_{50} $8\times10^3 - 4\times10^4$ spores), but one deep breath of weaponised aerosol may contain as many as 10^5 spores.[17] Inhalational anthrax usually develops within one week of exposure, but incubation periods of up to 43 days were described after the accidental release at Sverdlovsk in 1979.[18] Septicaemia and rapid progression to shock and respiratory failure are common, and mortality is substantial even with access to full intensive care facilities, which would not be sustainable in a large scale attack.[16 19] There are many differential diagnoses, and the supposedly pathognomonic *x* ray feature of hilar lymphadenopathy may be absent or overlooked.[16] Unlike in pulmonary plague, person to person spread of inhalational anthrax does not occur and protection to prevent secondary cases is not necessary. However, spillage of blood and contaminated body fluids from severely ill patients or corpses could pose some risk as organisms will sporulate in contaminated areas and may cause an infection hazard by secondary aerosol.

AHN YOUNG-JOON/AP PHOTO

Simulated chemical warfare attack in North Korea in 1999; similar methods could be used for release of biological agents

Cutaneous anthrax, caused by local inoculation of spores through damaged skin, is much less likely to produce septicaemia and death and has a wide differential diagnosis (see table B on bmj.com). Natural cutaneous infection is common in many parts of the tropics and responds to penicillin. However, the Iowa strain of *B anthracis* used in the recent releases in the United States produces an inducible β lactamase and a cephalosporinase.[20] This is one reason why drugs other than penicillin, such as ciprofloxacin or doxycycline, are preferable for prophylaxis after exposure, especially after a high inoculum exposure, although there were no significant differences between these drugs in prophylaxis in non-human primates.[21 22] Use of penicillin is inappropriate after exposure to an unknown powder or aerosol because it would not cover plague or tularaemia. β Lactamase production by *B anthracis* means that treatment for systemic disease should include either a fluoroquinolone or a tetracycline. Recent cases were treated with a combination of antimicrobial drugs.[16] Empirical treatment for undiagnosed pulmonary syndromes induced by biological warfare should include aminoglycosides, tetracyclines, or fluoroquinolones to cover plague[23] and tularaemia.[24] UK and US vaccines are known to provide protection against anthrax when they are given before exposure, but their recent use by the military has given rise in some quarters to concerns over possible side effects.[25]

Additional educational resources

- Bioterrorism Watch in Harrison's online textbook (www.harrisonsonline.com/amed/public/amed_news/news_article/281.html)
  Chapters from the book, specific links to *New England Journal of Medicine* and extensive links to other primary sources and major websites
- Zajtchuk R, Bellamy RF, eds. *Medical aspects of chemical and biological warfare. Textbook of military medicine.* Office of the Surgeon General, Department of the Army, USA, 1997 (www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html)
  Detailed chapters including potential biological agents. Information complements that in other major infectious disease textbooks.
- Centers for Disease Control (www.bt.cdc.gov)
  The bioterrorism section of the main CDC website. Best information is gained by going to "Biological" in the "Agents and Threats" index. Includes extensive links, patient information sheets, downloadable presentations, and indexed press releases/advisory notes, etc. Separate index listing *MMWR* reports on anthrax and other bioterrorism agents at www.cdc.gov/mmwr/indexbt.html
- Public Health Laboratory Service (www.phls.co.uk/facts/deliberate_releases.htm)
  Expanding site with full British protocols for several biological and chemical agents, general advice, and patient information leaflets. Teaching slide sets still on secure website only at time of going to press
- World Health Organization (www.who.int/emc/deliberate_epi.html)
  Information for general public, online publications including 2002 second edition of *Health aspects of biological and chemical weapons* and downloadable photographs and presentations
- American Society for Microbiology (www.asmusa.org/pcsrc/bioprep.htm)
  Collected links with emphasis on microbiological aspects
- Infectious Diseases Society of America (www.idsociety.org)
  Several good articles and many links available from home page. Also has a number of slide presentations available for download
- Center for Civilian Biodefense Strategies, Johns Hopkins University (www.hopkins-biodefense.org)
  Combination of policy, politics, debate, and outputs of exercises and think tanks, together with both medical and political links
- Center for the Study of Bioterrorism and Emerging Infections, Saint Louis University School of Public Health (www.bioterrorism.slu.edu)
  Another site providing collated links to primary sources, and downloadable presentations
- United States Army Medical Research Institute of Infectious Diseases (USAMRIID) (www.usamriid.army.mil/links/bdr.htm)
  Large collection of military and political links as well as US military medical manuals online
- Australia Group (www.australiagroup.net/)
  Informal consultative gathering of over 30 nations committed to ridding the world of chemical and biological weapons. Policy statements, press releases, external links to websites concerned with export controls of many countries
- Department of Peace Studies, University of Bradford (www.brad.ac.uk/acad/sbtwc/)
  Debate, videos to download, and reports on effects of suspension of Fifth Review Conference of the Biological and Toxin Weapons Convention

Smallpox

Smallpox has proved potential as a biological warfare agent even before any possible genetic enhancement in weapons programmes.[26] Although it was declared to have been defeated in 1980, virus stocks are believed to exist in laboratories other than the two designated for this purpose in the United States and in Russia. The usual incubation period is about 12 days (range 7-17), but strains produced by the Russian biological warfare programme had much shorter incubation periods in non-human primates.[9] Abrupt onset of fever and headache may initially be mistaken for influenza. Two to three days later, however, a non-specific erythematous rash develops (see table B on bmj.com). In non-immune populations this may be the only skin manifestation as the illness rapidly progresses to multisystem failure and death. In most patients, flat skin lesions evolve into pocks in crops that all appear at the same time and in the same form and are concentrated more on the face and peripheral limbs than on the trunk; the eyes and pharynx may also be affected. There is no practical antiviral treatment and over 30% of patients die, depending on the population and the infecting strain. Vaccination before exposure is effective, but the vaccine has measurable side effects and immunity fades after 10-20 years or earlier in some people. Vaccination after exposure is moderately effective if it is given within four days. The infection is highly contagious. Modelling has confirmed the potentially disastrous effects on the general population if smallpox were to be released.[27 28] International stocks of vaccine are acknowledged to be inadequate, and the WHO has urged countries to consider means of increasing these stocks.

Response and preparedness

Over the past decade the possibility of biological warfare and especially bioterrorism attacks has been taken increasingly seriously by Western governments. Theoretical models of deliberate aerosol release of agents such as smallpox or anthrax in urban settings have shown that regional infrastructures would rapidly be overwhelmed.[29 30] Recent experience on both sides of the Atlantic with genuine release episodes, and with many more hoaxes and false alarms, has revealed logistic weaknesses and false assumptions in treatment and prevention strategies. Planning needs to improve horizontal and vertical liaison between medical

providers, public health, and veterinary agencies. Interagency, intersectoral, and international cooperation are also essential. Vaccines and antimicrobials may need to be stockpiled so that they can be mobilised rapidly and distributed to large numbers of people. Protocols to deal with expected scenarios have to be prepared and tested in exercises. The major challenges are to conduct and learn from these exercises and to provide adequate education, especially at grass roots level, about the resources available and their uses.

Recognition of covert release of biological warfare agents requires a continued state of awareness of the possibility of abnormal disease patterns in humans, animals, and plants. Clinicians, microbiologists, and public health doctors should be vigilant for unusual pathogens in sterile sites or for unusual patterns of febrile illness, with or without features of septicaemia or respiratory, gastrointestinal, or dermatological manifestations. Awareness should be high if previously healthy young adults are affected, especially if mortality is high or there is clustering of cases. Immediate notification of suspect cases or outbreaks should prompt rapid epidemiological investigation with a level of laboratory investigation and empirical prevention measures appropriate to the determined risk.[31] Early prevention measures have to take into account the risk:benefit ratio of off-licence use of antimicrobial drugs and vaccines, and include education of the public about such risks. Such guidelines are increasingly available in the public domain in the United Kingdom as well as in the United States.

Meanwhile, current international agreements designed to limit the use of biological warfare agents need strengthening. In particular, methods of verification need to be agreed, analogous to those used for verifying compliance with chemical weapon treaties.[14]

AXEL SEIDEMANN/AP PHOTO

Rescue worker in biohazard suit in Frankfurt, Germany, carries letter thought to contain anthrax

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