Containing and combatting bioterrorism

At 09.28 Eastern Standard Time on September 11 2001, President George W Bush stated that the US had succumbed to a serious asymmetric threat and vowed to hunt down the perpetrators. American Airlines flight 11 hit the north tower of New York's World Trade Center at 08.48 Eastern Standard Time, followed by United flight 175 at 09.18 hitting the south tower. The south tower collapsed, followed by the north tower at 10.28. In 100 minutes the world had changed forever. Simultaneously American Airlines flight 77 hit the west wing of the Pentagon in Washington DC, and at 09.43 80 miles south of Pittsburgh United Airlines flight 93 crashed.

In times past military leaders fought battles in terms of symmetric warfare: the enemy was known and could be identified; goals were clearly stated; weaponry understood and rules of engagement agreed. Asymmetric warfare is exactly the reverse: unknown, invisible, with indefinable aims, attacks on mainly civilian targets with a complete disregard for collateral damage, including their own lives. There is no pattern, balance, consistency or coherence with this type of warfare. The response will not just be military but also political, diplomatic, psychological and financial. Progress will be slower.

ANTHRAX

On September 11, enhanced surveillance for any possible bioterrorist event was commenced with active surveillance at 15 sentinel emergency departments. This was accompanied by frequent broadcast alerts to prompt reporting of unusual clusters of disease manifestation. On October 4 the USA began active surveillance for inhalation anthrax after Robert Stephens, a 53-year-old photo editor for a Florida newspaper, was diagnosed with the disease. He died on 5 October, the first case of inhalation anthrax in the USA for over 25 years.

There were 21 further cases of confirmed or suspected anthrax. Eleven people developed inhalation anthrax, of whom 4 died, and there were 11 cases of cutaneous anthrax with no deaths. Eleven of the 22 were postal workers. It is probable that no more than five or six letters were sent in two batches, which resulted in gross contamination of mail. A letter sent to Senator Leahy was intercepted and found to contain 0.871 g of anthrax powder (spore count about 1 trillion spores per gram). The anthrax powder appeared to be more refined in the second postings. The Senator Leahy letter when examined at the US Army Medical Research Institute of Infectious Diseases confirmed the dangerous implications of a highly sophisticated preparation of anthrax spores.

All cases of inhalation anthrax occurred in persons over the age of 43 years (median 56 years, range 43–94 years). Evidence from these US cases and those following the Sverdlovsk outbreak in 1979 suggests that older people have an increased risk of contracting inhalation anthrax following environmental exposure. In response to the outbreak, public health authorities recommended some groups of individuals to receive a 60-day regimen of antibiotic prophylaxis such as ciprofloxacin or doxycycline. As of January 2002 about 32 000 persons in the USA had been prescribed such prophylaxis. To date it is gratifying to note that there have been no further cases of inhalation or cutaneous anthrax occurring in these individuals. However, there has been a laboratory-acquired cutaneous anthrax infection in a technician working with environmental samples who disobeyed certain containment rules.

Most of the current US cases have been traced to letters heavily contaminated with anthrax spores and sent through the US mail system. All of the strains recovered from mail, office environments such as the computer keyboards in the office of the first case and clinical specimens from the subsequent patients have the same molecular fingerprint, indicating dissemination from a single source. These mail-related cases have occurred among postal workers (n=11), or among the intended recipient of the letter or others in the surrounding work environment (n=7).

There were four other cases, two inhalation (both elderly women, both fatal) and two cutaneous, in whom there appears no relationship to intended recipients or the US postal system. However, a mathematical model has been developed (Webb and Blaser, 2002) which proposes these 'unrelated' cases were caused by receipt of cross-contaminated mail. This model has been developed to analyse the transmission of inhalation anthrax through the postal system by cross contamination of mail. The model consists of vectors describing the numbers of cross-contaminated letters generated, numbers of anthrax spores in these letters, the number of expected infections in recipients and matrices of transition probabilities acting on these vectors. The model simulates the USA outbreak and provides a framework for investigating the potential impact of possible future outbreaks.

BIOLOGICAL WARFARE

So what is terrorism and what is a biological warfare agent? Definitions of terrorism have changed with time and the political environment at that time. The word terrorism originated in revolutionary France at the end of the 18th century. The first definition in the Oxford English Dictionary states 'government by intimidation as carried out by the party in France during the Revolution of 1789–1797'. Today a workable definition may be that used by the US State Department: 'premeditated, politically motivated violence perpetrated against civilian targets by sub-national or clandestine operatives, usually intended to influence a target audience'.

Any useful definition must encompass domestic and international groups and include all possible motivation, including quasi-religious ones. A biological warfare agent can be defined as 'living organisms or infected material and toxins derived from them, which are intended to cause disease or death in man, animals or plants'. Bioterrorism is a combination of the two: 'an act or threat of the use of biological warfare agents against non-combatants with the object of intimidation or otherwise influencing an (audience(s)'. The outcome of their use, in terms of fatalities, cannot be predicted with certainty, but what can be predicted is a scale of psychological damage to the public which would far exceed that of disease or death.

WHY BIOTERRORISM, WHY NOW?

Previously the aim of traditional terror groups was to obtain a seat at the conference table and establish the legitimacy of their cause via 'few deaths, but lots of people watching'. Today fundamentalist terror groups are much less interested in legitimacy and their motto has become 'lots of people dead, lots of people watching'. As these potential adversaries know they are unable to win a conventional challenge to the US or North Atlantic Treaty Organization forces, they will increasingly revert to 'asymmetric threats', be it an aeroplane, radio-nuclear bomb or a biological agent.

The potential for future scenarios can be considered in three groups:

1. Deliberate release of a 'weaponised' form of a biological agent, e.g. *Bacillus anthracis*
2. Use of a 'naturally' occurring pathogen, e.g. *Salmonella* or *Shigella*
3. Hoaxes.

TABLE 1.
Characteristics of bioterrorist events

Increased frequency of cases
Rare or non-endemic 'out of town' diseases
Cases may be limited to certain postal areas of town or city
Trouble identifying cause of symptoms

The use of other agents in several forms and the characteristics which may alert us to the possibility of a bioterrorist attack are shown in *Table 1*.

Release could occur covertly (no warning), overtly (with a warning) or on the discovery of a suspect device or package (*Table 2*). Before October 2001 experience of such incidences was limited. In 1984, 751 people became ill following deliberate contamination by the Rajneeshee sect of salad bars in ten restaurants in Oregon with *Salmonella typhimurium*. Following the use of sarin by the Aum Shinrikyo sect on the Tokyo underground in 1995 subsequent investigations revealed they had already experimented with the use of *Bacillus anthracis* (albeit the avirulent Sterne vaccine strain) and *Clostridium botulinum* toxin.

Following covert release the first indication of an incident will be the presentation of cases of unusual illness to the front line of a health-care system. The symptoms of these first cases of unusual illness will often be indistinguishable from naturally occurring common diseases – a 'flu-like illness'. Alert physicians may recognize an unexpected pattern of presentation. It is essential that the laboratories supporting the front-line health-care responders have the potential to recognize the bioterrorism agents, provide initial identification and initiate without delay the backup public health and reference laboratory capabilities. Following a deliberate release there is a small window of opportunity in which correct and early decisions will reduce the impact on the population.

The threat agents to be considered in such a planning process are those on the Centers for Disease Control list A (available on their website):

- *Bacillus anthracis* (anthrax)
- *Yersinia pestis* (plague)
- *Francisella tularensis* (tularaemia)
- Variola virus (smallpox)
- *Clostridium botulinum* toxin (botulism).

LABORATORY REQUIREMENTS

It is necessary to have levels of laboratory capabilities in each country and the final structures will depend on the normal health infrastructure, population and geography. Three suggested levels are:

1. Local laboratories where patients will first present
2. Regional laboratories to support a cluster of local laboratories
3. National reference laboratories – providing definitive and comprehensive capability.

The local laboratories, of which there are about 300 in England and Wales, are based in hospitals and they need to:

- Be aware of the threat
- Be suspicious of odd clinical presentations, e.g. unexpected numbers of patients presenting with 'pneumonia'
- Be able to recognize unexpected bioterrorist agents in clinical samples
- Be able to carry out first-line tests as described in the standard operating procedures and immediately alert the regional and reference laboratories
- Alert the local public health systems
- Be able to access web-based information systems.

The regional laboratories must support the local laboratories in the classical laboratory diagnosis of the bacterial agents. Molecular tests using the polymerase chain reaction (PCR) for the detection of specific DNA sequences will be extremely helpful, providing rapid (<1 hour) and specific diagnosis. There is now a need to develop these rapid tests. In the past orthopox viruses were

TABLE 2.
Types of bioterrorist events

	Announced* (overt)	Unannounced (covert)
Recognition	Early	Delayed
Responses	Early	Delayed
Treatment	Early	Delayed
Responders†	Traditional first responders (fire, ambulance, police)	Health-care workers (GPs, staff of accident and emergency or intensive care units)

*Assume hoaxes to be real; †If agent active against animals, vets may be among first responders

detected using electron microscopy. Molecular PCR tests need to be available for detection of pox viruses, herpes viruses and varicella zoster virus at the regional laboratory level to improve the diagnostic capability of vesicular rashes. At the regional level there also is a need to look for gastrointestinal pathogens in food and water samples.

The regional laboratory should work closely with local laboratories and the specific reference laboratories who will provide the definitive capability for agent confirmation and importantly strain characterization and fingerprinting. The reference laboratories will be instrumental in the development of PCRs for use in regional laboratories. These diagnostic tests must be harmonized, standardized and validated through international collaboration.

It is tempting to believe that, as there have been no new anthrax cases, resulting from deliberate release, that the scenario is now at an end. This would be foolish – at the time of writing the perpetrator(s) of the bioterrorist attacks have not been apprehended. All countries still remain at risk from subsequent attack with *Bacillus anthracis* and other microbial agents or toxins.

ISSUES FOR HEALTH-CARE PROFESSIONALS

The lessons learned during this last year should have motivated everyone in the provision of health care, whether planners, managers, nurses, technicians or doctors, to become involved in interactive programmes. This will improve communication, local and national preparedness and response capabilities.

Informed doctors, working in an integrated NHS, which is prepared and ready to support the necessary diagnostic and treatment facilities for the effective management of infected patients, in cooperation with public health, will in the future provide the firm foundation for detecting and treating these bioterrorist threats to the health of the public.

While the threat from biological weapons is currently 'low' (as judged by intelligence sources), the consequences of such an attack will, as we know from the US experience, be enormous. Predicting when and how attacks, overt or covert, might occur will be extremely difficult. There is a need not to over-exaggerate the threat and thereby cause undue public alarm. Coordinated national and international contingency plans must be made for dealing with a possible attack. The national response, although a formidable challenge, must be available and such preparedness needs to be identified as a key priority by the Departments of Health in each country.

On September 24 2001 Dr Gro Harlem Brundtland, Director General of the World Health Organization, stated:

'Countries need to strengthen their capacity to respond to the consequences of the use of biological or chemical agents as weapons'.

Health ministers from around the world met on 14 March 2002 to progress the coordinated international initiative to better prepare for, and respond to, acts of chemical, biological and radionuclear terrorism. The European Union, Germany, France, UK, Italy, USA, Canada, Japan and Mexico were represented. Their discussions followed meetings in November and December 2001, when an urgent need for more cooperation and communication between countries on matters of health security was recognized. Within Europe the need for more collaboration between countries on the detection, containment and mitigation of biological and chemical incidence has also been recognized. A European programme on preparedness and response to biological and chemical agent attacks, drawn up by the European Commission and member states, was also announced in November 2001.

With current levels of global transport, an outbreak of smallpox in one area of one country will soon become a concern not only for the whole of that country, but also a concern worldwide, requiring an international response. At the same time every effort must be made to ensure a successful conclusion to the negotiations over the protocol to strengthen the verification of the Biological Weapons Convention, despite withdrawal of US participation in July 2001. The authors believe that these coordinated actions offer the best route to contain and combat future bioterrorist events. We must be able to give better advice than that given to survivors of the Tokyo subway sarin attack – 'flee in the direction of the fewest bodies'. HM

KEY POINTS

- Western democracies are susceptible to asymmetric threats.
- Deliberate release of *Bacillus anthracis* spores via the US Postal Service resulted in five deaths and mass panic in the civilian population, with repercussions worldwide.
- Planning processes must accommodate the types and characteristics of bioterrorist events.
- Laboratories need to be integrated into a national response network.
- An urgent need exists for the improvement in education of health-care workers and first responders, local and national preparedness, response capabilities and communication.

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Further reading and information

General
Beeching NJ, Dance DAB, Miller ARO, Spencer RC (2002) Biological warfare and bioterrorism. *Br Med J* **324:** 336–9
Eurosurveillance (2001) Special Issue on Bioterrorism **6:** 157–78
Spencer RC, Lightfoot NF (2001) Preparedness and response to bioterrorism. *J Infect* **43:** 104–10

Anthrax
Inglesby TV, O'Toole T, Henderson DA et al (2002) Anthrax as a biological weapon, updated recommendations for management. *JAMA* **287:** 2236–52

Modelling
Webb GF, Blaser MJ (2002) Mailbourne transmission of anthrax: modelling and implications. *Proc Nat Acad Sci* **99:** 7027–32

Psychological impact
Wessely S, Hyams KC, Bartholomew R (2001) Psychological implications of chemical and biological weapons. *Br Med J* **323:** 878–9

Websites
Center for Civilian Biodefense Strategies, John Hopkins University (www.hopkins-biodefense.org)
Centers for Disease Control (www.bt.cdc.gov)
Public Health Laboratory Service (www.phls.co.uk)

HEALTH SERVICES IN THE DETECTION OF AND DEFENCE AGAINST BIOTERRORISM

The events of September 11 2001 changed the United States' view of terrorism. Equally the covert deliberate release of anthrax in that country, and the chaos arising from thousands of 'white powder' releases worldwide, has changed the view of the defence services and governments of the role of health services against bioterrorism.

The contribution of health services is not just in dealing with casualties (Lightfoot et al, 2001). As Spencer and Lightfoot describe, the American anthrax 'terrorism' was detected through clinicians promptly diagnosing unexplained anthrax, and appreciating its significance. They did so because within hours of September 11 many had been alerted to look out for key diagnoses by the Centers for Disease Control and Prevention's Health Alert Network (http://www.phppo.cdc.gov/han/). Clinical services and microbiology can provide the earliest detection of covert releases of biological or clinical agents while public health services will contribute to preparation, risk assessment and primary and secondary responses (Lightfoot et al, 2001; Gerberding et al, 2002).

The USA Center for Disease Control redirected over 2000 staff, including trainees from the Epidemiological Intelligence Service and its most experienced public health and microbiology personnel. They were deployed centrally, in Center for Disease Control's laboratories and incident and coordination room, and where anthrax had been released, to support overstretched public health services. Even so, and with only two salvoes of letters and five deaths, public health and microbiology services were nearly overwhelmed.

Anthrax is only one of many diverse chemical, biological, radiological and nuclear (CBRN) threats. Others such as smallpox, if it exists in a releasable form, and mixtures of agents pose more difficult problems. Deliberate release of CBRN agents is a permanent fixture on the heath service agenda and a good start has been made preparing for it in the UK (House of Commons Defence Select Committee, 2002). However, a considerable further programme of preparation is now needed. This will only be successful if it is undertaken by clinicians, microbiologists, toxicologists and public health specialists working together, with the security services and local and national government (House of Commons Defence Select Committee, 2002; Lightfoot et al, 2002).

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Gerberding JL, Hughes JM, Koplan JP (2002) Bioterrorism preparedness and response: clinicians and public health agencies as essential partners. *JAMA* **287**(7): 898–900

House of Commons Defence Select Committee (2002) Defence and Security in the UK. House of Commons Defence Select Committee, London (http://www.parliament.the-stationery-office.co.uk/pa/cm200102/cmselect/cmdfence/518/518.pdf)

Lightfoot N, Nicoll A, Wale M, Spencer M (2001) Appropriate responses to bioterrorist threats. *Br Med J* **323:** 877–8

BETTER SYSTEMS ARE STILL NEEDED

Spencer and Lightfoot discuss issues arising since September 11 last year, and the subsequent anthrax attacks via the US postal system. The likelihood of further attacks of this nature must only have increased, as the publicity and panic engendered by this relatively small-scale release cannot have failed to have encouraged potential perpetrators. Furthermore, anthrax does not spread from person to person, and the strain used remained susceptible to antibiotics so that the majority of cases survived. The spectre of a larger scale release, or one using a transmissible or genetically modified agent, remains a chilling possibility.

Even when an event could have disastrous consequences, it is difficult to divert scarce resources to preparation when the probability of it occurring is considered to be low. So how have we fared in the 12 months since the earth-shattering events of last year? Can we depend on the 'integrated NHS' referred to by Spencer and Lightfoot to protect the population from these threats?

Although a great deal of excellent work was done, and continues to be done, by many dedicated individuals since last autumn, I would agree with the speaker at a recent meeting on bioterrorism who said 'No country is prepared in any meaningful way'. The American experience demonstrated the wide range of health-care professionals who might be the first to encounter those infected by a covert release, and yet few have so far received training in what to expect and how to respond.

Specialist infectious disease units and physicians are distributed unevenly and illogically, across England at least, although medical microbiologists do their best to fill the gaps. Consultants in communicable disease control are experiencing sequential changes in employers and the dispersal of their colleagues to primary care. The ability of diagnostic laboratories to detect the majority of potential bioterrorist agents has never been tested and, even more worryingly, the very network (of Public Health Laboratory Service 'Group' laboratories) that was initially set up to provide protection against biological attack during World War II, looks like being disbanded.

The Health Protection Agency, that will subsume the Public Health Laboratory Service and the centres in communicable disease control, will at least bring together many of the various experts who would deal with biological, chemical and nuclear threats. However, these are dangerous times to be dismantling established networks, and we must hope that the benefits of the existing arrangements will survive the flurry of reorganizations that currently characterize public health in the UK.

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