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CONTRIBUTED REVIEW

Bioterrorism: menace of microbiological science

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In this paper, Bruce Short reviews the development of biological warfare technologies and the international safeguards and monitoring systems enacted since World War I. He describes some recent agents that have been weaponised by genetic engineering; outlines the Soviet experience with inhalational anthrax disease; discusses who the presumed terrorists of today are; and overviews recently developed global public health surveillance systems which may provide early warning of bioterrorism. As the threat posed by the possible existence and use of biological warfare agents is a substantial weapon in its own right, the spectre of bioterrorism is likely to continue unremitting.

Biological warfare is not a new threat. Perhaps one of the earliest documented instances involved Hannibal the Great. Having fled to the court of King Prusias I of Bythynia, he was given command of the Bythynian naval forces. In 184 BCE[2], King Eumenes II of Pergamum fought a small naval engagement with Prusias. Hannibal achieved a victory by allegedly throwing poisonous snakes onto the decks of the enemy ships. Snake venom toxin is regarded as a biological agent (Cary and Scullard 1984, 165; Hammond and Carter 2002, 5). Numerous other examples of the use of biological warfare have been recorded during the subsequent centuries.

The terminology used in relation to biological warfare can be confusing. Biological warfare, or germ warfare, is the deliberate use of microbial agents – which include bacteria, parasites of the genus *Rickettsia*, viruses and, to a lesser extent, fungi – as well as toxins, to produce death or short-term and long-term morbidity to humans, animals and plants, with a view to causing maximum public health chaos and economic disruption. The media have added to the opacity of the meaning with other terminologies: 'Bioarmageddon', 'Bioterror' and 'germ weapons' (Robertson 2000).

Biological Weaponry, or bioweapons, refers to munitions, equipment and other delivery systems including aerosols, aircraft, artillery and explosives, intended to disseminate biological agents.

The word, terrorism, was coined in 1793 as a reign of terror was perpetrated on the citizens of France by the Jacobins, led by Maximilian Francois Robespierre (Davies 1999, 698). It is now commonly used to describe attacks on the community launched by extremist groups to achieve political and social change and first appeared in this context in American newspapers in 1997 (Zubay *et al*. 2005, 327).

Biosecurity describes the efforts required by states to protect against attacks from forces using germ warfare, with a particular emphasis on securing a nation against bioterrorism. It not only incorporates security threats from biological warfare but also from naturally occurring infectious diseases (Fidler 2006, 197). Within the United States, biosecurity forms part of the larger strategy of strengthening homeland security in the prevention of attacks, the protection of citizenry and the national response to terrorist attack (Fidler 2006, 197).

Modern International Biological Warfare Programmes

The sociologist, Jeanne Guillemin, groups modern international biological warfare programmes into three periods (Guillemin 2005, 75-91). Commencing in the 1920s, the initial offensive period was characterised by an international environment that permitted both development and production of biological agents and weaponry, whilst at the same time trumpeting condemnation. The French were the first to investigate the technologies of disease dissemination with new air power capabilities. Britain followed in 1940 with the establishment of Biology Department Porton at Porton Down, Wiltshire.

In 1942, George W. Merck, a chemist and president of Merck & Co., headed the new and innocuously named United States War Research Service, where early work centred on anthrax and botulism. The War Research Service later built many research facilities, the most notable at Camp Detrick, Maryland, where Theodore Rosebury, a microbiologist, became the director. By 1944, the United States had prepared only a few anthrax bombs for testing. Agents against plants were also analysed and ammonium thiocyanate was recommended for the decimation of Japan's rice crop. The United States Air Force commander later rejected the use of this crop defoliant on tactical grounds. In the end, American beliefs about the morality of biological warfare during World War II were never put to the test – instead senior advisers later sanctioned the atomic bomb. Meanwhile, and for reasons

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[2]Before the Christian era

that remain unknown, Hitler had banned all research on offensive German biological warfare (Bernstein 1987).

The Japanese also commenced biological experimentation during the 1920s. In 1936, secret establishments were located south of Harbin in Manchuria[3]. These infamous facilities, benignly titled, Unit 731, Unit 100 and Ei unit 1644, involved offensive biological warfare production with associated human experimentation, and defensive vaccine manufacture, principally a typhus vaccine. Chinese allegations that the Japanese attacked civilians with plague-infected fleas during the Sino-Japanese War (1937-45), however, were not investigated after World War II.

In Geneva in June 1925, an agreement between participating states prohibited the use of asphyxiating poisonous or other gases and of bacteriological methods of warfare in the military conduct of future wars. The *Geneva Protocol*, however, did not prohibit the development of biological warfare agents nor did it ban the use of such weapons against countries not party to the protocol. Although the United States signed the 1925 *Geneva Protocol*, it did not ratify the treaty until 1975 (Bernstein 1987).

Following World War II, the United Nations established, as its first agency in 1948, the World Health Organisation (WHO). The basic principle of the WHO was: 'The health of all peoples is fundamental to the attainment of peace and security and is dependent upon the fullest cooperation of individuals and States'[4]. Despite the WHO's governing charter supporting the notion of international security by promoting health, the WHO is not the international forum to either monitor or enforce bans on the use of biological warfare agents.

According to Guillemin (2005, 75-91), the second period in the modern history of biological warfare began in 1969 when President Richard Nixon renounced biological weapons and ended the United States offensive programme. This decision was followed in 1972 by the Biological Weapons Convention, which brought a new emphasis on international norms and laws. The *Biological Weapons Convention Treaty*, which came into force in March 1975, bans the development, production or stockpiling of any biological agent and toxic weapon which may be used other than for peaceful purposes. It also mandated the destruction of existing stocks of biological warfare agents. It thus became the main instrument of international law banning biological warfare. However, it contains no verification provisions to ensure compliance, nor procedures on inspection and data-reporting. It lacks modern enforcement or sanction mechanisms. After complex negotiations during the 1990s to review the treaty, the Bush administration, in November 2001, declared its irretrievable opposition to the draft amendment, because it failed to provide adequate inspection apparatus to detect violations and the inspection intrusions it did allow would be unacceptably expensive for industry (Koplow 2004, 99-100).

Following the demise of the Cold War, the third defensive period evolved during which time the United States became increasingly concerned with the threats from asymmetric warfare and bioterrorism.

Who are the Presumed Terrorists Today?

According to Jerrold Post (2004), terrorism is not a homogenous phenomenon and there is a spectrum of terrorist groups and organisations, each with a different motivation and hierarchy. Some terrorist sources include social revolutionaries, otherwise known as terrorism from the left, which seek the overthrow of the capitalist economic and social order. These are exemplified by the Red Army Faction in Germany and the Red Brigades in Italy during the 1970-80s. Nationalist-separatist terrorism, also called ethno-nationalist terrorism, is the fight for a new political order or state based on ethnic dominance or homogeneity – examples include the Irish Republican Army, the Liberation Tigers of Tamil Eelam (LTTE) of Sri Lanka, and Basque Fatherland and Liberty (ETA) in Spain. Religious extremists have always bedevilled autonomous states. In the 1970-80s, religious fundamentalist terrorism represented the majority of the acts of terrorism and religious terrorists would regularly claim responsibility for their acts. Other groups consist of: non-traditional religious extremist groups representing 'new religions', such as Aum Shinrikyo in Japan; right-wing extremist groups; and right-winged communities of belief consisting often of individuals not attached to a formal group, such as Larry Wayne Harris, a United States anti-government activist, arrested for possessing 'military grade' anthrax (Post 2004).

In February 1998, a meeting took place in Afghanistan between Osama bin Laden, Ayman Zawahri of the Egyptian Al Jihad, Rahman Khalil of the Pakistani Ansars, Abdul Salem Muhammad from Bangladesh, and Abu Yassir Ahmed Taha representing the Maghreb of north-western Africa. They agreed to coordinate their efforts through an Islamic Struggle Front. Later, in June, Osama declared war on America through an interview with John Miller of ABC News (Akbar 2002, 212). The United States was attacked on 11 September 2001 and, on 7 October 2001, the United States declared war on the Taliban, the Osama bin Laden-led Al-Qaeda, and 'terrorism' (Akbar 2002, 213). The global Muslim community, the *ummah*, had again rallied in a jihad, with terrorism by Islamic Fundamentalists to be inflicted anywhere in the world.

In the past decade, however, no responsibility has been claimed for upwards of 40 per cent of terrorist acts. This may be as a consequence of radical Islamic terrorists trying to expel the secular modernizing West without trying to influence the West. They are 'killing in the name of God' and do not need official notice – after all, God knows.

The spectrum of terrorist acts is also important. These extend from sham chemical and biological warfare attacks with potential devastating psychological fall-out; to use of conventional weapons to produce low level (<20) or large-scale (20-100s) casualties; to catastrophic or super-terrorism in which thousands of casualties may result, as exemplified by the two explosive impactions of hijacked

[3] Later renamed Manchukuo, a puppet state of the Japanese Empire.
[4] Constitution of the World Health Organisation, 22 July 1946, p. 1.

aircraft on the World Trade Centre and one on the Pentagon on 11 September 2001 (Post 2004, 74).

What Biological Agents are Available?

The question as to what agents may be used either as part of an operational combat attack or to clandestinely deliver biological poisons, is as difficult to address as the one asking what is the scope of agents available. In spite of the high annual global mortality figures, HIV, tuberculosis and malaria are not considered agents of bioterrorism, since their action takes from weeks to even years to be felt. Time to impact and infect is a fundamentally important component of bioterrorism (Zubay 2005, 2-3).

The Centres for Disease Control and Prevention, Atlanta, Georgia, functioning as the epidemiological eye of the American Public Health system, has ranked biological agents based on the dangers they pose. Class A agents are those which are easily disseminated and/or highly infectious and are characterised by high mortality rates. They have a high speed of action; many are untreatable or difficult to treat; and they are able to produce very high levels of public alarm and panic. In 2005, the following diseases were classified as Class A agents: anthrax, smallpox, Ebola virus, *Francisella tularensis, Yersinia pestis and Clostridium botulinum*.

Class B agents are associated with lower mortality rates and ease of treatment: examples include *Vibrio cholerae*, salmonella, and viral encephalitis. The fact that simple oral re-hydration solutions lower the lethality of cholera from 50 per cent to 1 per cent is the reason for its downgrading to Class B.

Class C represents emerging agents with potential for weaponisation due to their potentially high morbidity and mortality and their availability: examples include the Severe Acute Respiratory Syndrome (SARS) coronavirus, influenza virus, hantavirus, *etc*. (Zubay 2005, 3).

Commencing in November 2002, SARS coronavirus was responsible for the first pandemic of the 21st century. Within six months, it had spread via air travel from its source in southern China to at least three continents, with case reports received from 30 countries (Short 2004). SARS coronavirus also met the definition of the ideal biological agent, *i.e.* a pathogen that is easily transmitted and not easily detected, causes severe injury, affects the public psychologically and drains national resources during the response (Wong and Chan 2004).

Currently the United States is preoccupied with the threat of bioterrorism from very diverse sources. From the poisoning of the milk supply with botulinum toxin to the hypothetical dissemination of smallpox by self-infected terrorists, the possibility of a massive release of aerosolised anthrax spores in the subway and even the newly-raised spectre of the misuse of a reconstructed 1918 influenza virus. The evoked concerns impact on the biomedical research agenda, funding priorities and the regulatory environment (Relman 2006).

In 1942, a United States team led by Rosebury and Kabat prepared a secret report listing 33 candidate pathogens for analysis as effective biological warfare agents. They classified efficient biological agents as those with high airborne infectivity, such as anthrax, smallpox, brucellosis and tularaemia, as well as those delivered by insect vectors, such as yellow fever and dengue carried by mosquitoes. Their report also described biological agents responsible for animal diseases (glanders, anthrax, Rift Valley fever virus) and crop failures (microbials and insects such as boll weevil and corn borer). Their report ranked *Bacillus anthracis* in its dormant spore as overall the most important agent (Guillemin 2005,34-6).

A Rosebury and Kabat-type list offers only some information of past events. The release of anthrax spores through mail articles in the United States postal service in 2001 is clearly not an example of an effective use of anthrax as a weapon of indiscriminate mass destruction. Likely agents to be used by terrorists would be bacteria rather than Rickettsias or viruses, due to cultivation and production problems. Toxins are more stable, easy to manufacture and often more toxic than biological agents. The modes of dissemination may be problematic for attacks on large populations, such as military targets, since humidity, sunlight, smog, temperature and winds all impact on the final dose of the agent received. Simple aerosols are the preferred method of delivery in small community or group bioterrorist attacks. In Australia, the microorganism, *Burkholdera pseudomallei*, responsible for melioidosis, which is highly endemic during the wet season in the Top End region, would be an easily accessible source of an effective agent for bioterrorism (Short 2002).

The notion that only a small number of agents pose a plausible threat is largely an artefact of weapon programmes that predated our current knowledge of molecular biology. A litany of specific agents can also inhibit creative thinking since an updated robust biodefence plan must be flexible and respond rapidly.

The need for a flexible biodefence plan is best exemplified by the increasing use of genetic engineering to devise very new ultra-virulent biological warfare agents. Genetic manipulation of known pathogenic microorganisms for malevolent purposes is now an entirely practical development. The ability to genetically examine and manipulate nearly any microorganism to upscale virulence and accelerate transmission times for use as a biological warfare agent forms a new paradigm for constructing an efficient biodefence strategy. A worrying example of weaponising a genetically-manipulated agent is the splicing of an Ebola virus glycoprotein, a Biosafety Level 4 pathogen, into a smallpox virus, which then expresses it. The Ebola virus, the cause of Ebola haemorrhagic fever (EHF), was first documented in the Ebola River region in northern Zaire and, like other filoviruses, has no known natural hosts. It targets circulating monocytes and macrophages, including tissue macrophages, and infected circulating phagocytes disseminate the virus. The virus is spread by aerosolisation, has very high transmissibility and is associated with very high mortality (Zubay *et al.* 2005, 59-68)[5].

[5]The centre portion of the Ebola virus glycoprotein (GP2), comprising 26 residues in the C-terminal third of the protein, functions as an immunosuppressive domain. GP2, in particular, causes suppression of cytotoxic T-lymphocyte responses, monocyte chemoprophylaxis and cytokine gene expression (Zubay *et al*. 2005, 66-7).

The Soviet defector-scientist, Colonel Kanatjan Alibekov, known as Ken Alibek, attests that Soviet scientists have developed a recombinant chimera of the Ebola and smallpox genomes. The ebolapox hybrid would cause pruritic smallpox, or 'blackpox', due to severe haemorrhagic pustulation of the skin lesions. Ebolapox would thus combine the violent haemorrhaging and high fatality rate characteristic of the Ebola virus and the contagiousness of the smallpox virus with resultant near-100 per cent fatality rates (Zubay *et al.* 2005, 73-6)[6].

Rosebury and Kabat reported in 1942 that *Bacillus anthracis* in its dormant spore to be the most important biological warfare agent. Inhalational anthrax leads to a fatal massive and painfully compressive enlargement of the mediastinal glands together with circulatory microorganism dissemination. An outbreak of anthrax occurred in the large Siberian city of Sverdlovsk during 1979. This was initially reported by the Soviets as linked to the consumption of contaminated meat causing cutaneous and intestinal anthrax. It was later confirmed in 1992 from the defector-scientist, Ken Alibek, to have resulted from an accidental release of anthrax spores through an unfiltered vent from a close-by military installation, 'Compound 19'. The consequent outbreak of inhalational anthrax was attended by a high death toll (Abilek 2000, 73-5). Military grade anthrax and other microorganism-spores are robust and easily cultured on a large scale. Spore transportation and dissemination offers no major problems to effect. There is, however, no historic evidence of the use of anthrax by any state or state-sponsored agency as a weapon of biological warfare.

In 1992, the newly-elected Russian President, Boris Yeltsin, who had been the Communist Party chairman for Sverdlovsk at the time of the accidental anthrax emission, publicly announced that the Soviet Union had retained an illegal offensive bioweapon programme. He subsequently signed a decree banning offensive biological warfare research (Koplow 2004, 80). A significant consequence of this ban was the possibility of the now unemployed Russian scientists seeking employment in other countries including 'rogue states'.

United States Central Intelligence Agency reports in 2001 deemed at least ten countries to possess their own secret, illegal caches of biological warfare agents, to be pursuing forbidden offensive biological military investigations, or to be progressing rapidly in those directions. In 2001, the United States publicly accused five states, North Korea, Iraq, Iran, Syria and Libya of violating the biological weapons convention and to be in the 'variola race' (Koplow 2004, 85). Following the 11 September 2001 terrorist attacks, the Bush administration sought US$500 million in emergency funds to procure 300 million doses of smallpox vaccine, enough to treat everyone in America, by the end of 2002. This proposal by Bush provoked vigorous public debate as to the inherent wisdom of the programme and centred on the risks and disadvantages of mass smallpox vaccination. Although there is a real possibility that smallpox will be used by bioterrorists, the degree of risk is most likely small (Fauci 2002).

Biological weaponry has never been at the forefront of any army's arsenal. As the terrorist killings today in Iraq and Afghanistan attest, conventional explosives (particularly the widely-used improvised explosive devices), small arms and rocket-propelled grenades are still the preferred weaponry. However, the danger of a lone sociopath dabbling with biological agents as an offensive weapon is clearly evident in the case of the United States microbiologist, Larry Harris from Ohio, who was arrested once for freeze-drying samples of *Yersinia pestis* and later for the cultivation of 'military-grade' anthrax (Robertson 2000).

Global Public Health Surveillance Systems

Although the threat of bioterrorism in Australia has been assessed as low, the threat of bioterrorism is increasing in Australia like other countries around the world (Robertson 2000). Australia has not been totally immune to terrorism[7]. Small scale attacks included the Sydney Hilton bombing in 1978, the assassination of the Turkish Consul-General by the Justice Commandos of the Armenian Genocide in December 1980, and the bomb attack on the offices of the Israeli Consulate-General by the 15 May Organisation in December 1982 (Cronin 1986). In May 2002, the chief medical officer, Dr Richard Smallwood, stated that although the risk of bioterrorism to Australia is regarded as low, no public health or security system can guarantee complete safety from bioterrorism attack, but Australia's public health expertise will ensure that harm to the community is minimised (Smallwood *et al.* 2002).

The Sydney Olympic Games preceded the meticulously planned and delivered attacks on the World Trade Centre and Pentagon by 12 months and, fortunately, the Games were free of biological and chemical attacks. In 1997, Australia had adopted a surveillance process, the 'Global Outbreak Alert and Response Network' (GOARN), formally launched in 2000 by the WHO. GOARN involves formal and informal sources of health information, including 191 WHO member countries, collaborating laboratories, non-government organisations and others. During the Sydney Games, disease surveillance involved a daily reporting of notifiable diseases, emergency department presentations and other ambulance, health and security reporting from the Olympic sites (Raphael and Harris 2004).

Canadian public health workers also developed a version of global public health surveillance, with input from the WHO, known as the Global Public Health Intelligence Network (GPHIN). Its first test of effectiveness became evident during the SARS outbreak in Toronto in 2003.

[6]For a scenario of how this might be developed and employed by terrorists, see Adrian d'Hagé (2007), The Beijing Conspiracy (Penguin Australia: Camberwell), which was reviewed in *United Service* **59** (2), 35 (June 2008).

[7]For a summary of medical emergency lessons learnt from these and terrorist attacks in foreign cities, see Graham (2007).

A similar system of health intelligence monitoring was developed in the United States after 11 September 2001, when US$918 million was allocated to the Centres for Disease Control. Among the newly-developed techniques was the 'syndromic surveillance' programme. Like the GPHIN, syndromic surveillance is an online early warning outbreak detection technique and has great potential as a provider of early warnings of bioterrorism. All techniques are driven by the pressure of 'timeliness', i.e. the earliest possible outbreak alert. The syndromic system attempts to recognize outbreaks by identifying unanticipated clusters of data.

Necessarily, effective health intelligence systems can only exist under conditions where electronic data are widely available, thereby excluding large parts of Africa, Asia and South America (Weir and Mykhalovskiy 2006). Global public health surveillance aims to protect the global population, rather than national or provincial ones.

Conclusion

It is less than 150 years since the science of microbiology was founded, yet the present capabilities of the discipline, in the hands of malevolent forces, may threaten the very existence of modern man. Nevertheless, the litany of bombings in recent times in areas as diverse as Afghanistan, Bali, Jakarta, Dar es Salaam, London, Madrid, Nairobi, Pakistan, Kashmir, New York, Washington, and throughout the entire Middle East, supports the contention that there is a current unexplained reluctance or aversion by rogue-state sponsored terrorists to employ unconventional weaponry theatre-wide. Despite the existing world tensions, it seems that the mere threat posed by the possible existence and use of biologico-chemical ordinances, for the terrorist is a substantial weapon in its own right. Notwithstanding that the most important present worldwide security threat remains global warming, the spectre of bioterrorism will continue unremitting.

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