Advances in life sciences and bioterrorism

Risks, perspectives and responsibilities

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The First World War left millions dead on the battlefields of Europe, and the survivors returned home with the experience of the first industrial-style war fresh in their minds. It was particularly because of the horrors created by the use of chemical weapons and the mutilation that these gases caused that the main players in the war started to consider a widespread ban on such methods of attack. After several years of negotiations, on 19 June 1925, the major industrialized countries signed the protocol for the 'Prohibition of the Use of Asphyxiating, Poisonous or other Gases, and of Bacteriological Methods of Warfare' in Geneva, which is now known as the Geneva Protocol. But less than 20 years after its creation, this protocol did not prevent some contractors of the treaty from engaging in offensive biological warfare programmes. Furthermore, the development and use of biological weapons by Japan in the Second World War led to an expansion of these programmes in various Western countries and in the Soviet Union.

In the 1960s, Western countries started to critically assess their biological weapons programmes because of technical problems in the production and storage of the agents involved. In addition, it became clear that biological weapons are of limited military use because they pose a considerable risk to the attacker as well as to the attacked. The USA and the UK therefore concluded that the size of their existing conventional, chemical and nuclear weapon inventories was sufficient to retaliate against a Soviet attack and that biological weapons were no longer required. This conclusion eventually culminated on 10 April 1972 with the signing of the 'Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction' (BTWC) (www.opbw.org) that entered into force in 1975. However, rumours then started to circulate about the Soviet Union's offensive biological weapons programme, which was clearly in breach of the treaty. Since then, the number of states suspected of conducting

research into, and producing, offensive biological weapons has increased.

Why are biological agents once more considered to be valuable weapons? There are two main reasons. First, the tremendous advances that have been made in biology and all the related aspects of the life sciences, coupled with the progress in production technologies, might provide cheaper access to unconventional weapons, particularly compared with investments in nuclear and chemical techniques. Second, an increasing number of countries believe that their political and security interests could be protected or achieved only through the possession of such weapons, especially in view of the overwhelming superiority of the US armed forces in terms of conventional weapons. To be correct here, this is not an excuse for anyone to breach the BTWC; it is only the description of a reality that has to be faced.

Public discussions of risks arising from advances in science and technology are primarily connected to terrorism, particularly given how easy it is to produce microorganisms and to acquire knowledge about genetic manipulation techniques. However, without playing down the risks from lone terrorists and small terrorist groups, it has to be noted that in the past two decades only five authenticated deliberate releases of harmful biological agents occurred worldwide, with rather limited efficacy. The concerns about misuse therefore focus more on states that invest in facilities, equipment, manpower and knowledge for developing biological weapons and that have the financial resources and time to acquire such technologies. Today, many of these states are also suspected of supporting terrorists. When discussing the misuse of advanced technologies, therefore, the threats involved may differ widely between terrorists and state terrorism.

These attempts to develop offensive biological weapons are, without doubt, in breach of the BTWC. Article I defines a biological weapon as follows:

"Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict."

The charm of this definition is that it has not become outdated by any technological developments since 1972 because it does not describe what constitutes a biological weapon. The article rather defines a biological weapon by its purpose: the so-called general purpose criterion. According to the article, a weapon can be a microorganism of a type or in a quantity that has no justification for peaceful research or, for instance, it can be an aerosol generator designed for the use of such an agent. The definition leaves a lot open to legal interpretation, but it indicates the implications and risks produced by advances in science and technology that have to be discussed.

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parties to the BTWC, the World Health Organization (WHO, 1970), the North Atlantic Treaty Organisation (NATO), the European Union (2000), the Australia Group (2002a) and various nations, include 30–60 bacteria, viruses, fungi and toxins that can be used to harm people, animals and plants (see sidebar). They range from the non-contagious, such as *Bacillus anthracis* (anthrax), to highly contagious agents, such as *Variola major* (smallpox), and include the most potent natural toxin known to man, botulinum toxin. Because microorganisms and toxins cannot normally penetrate intact skin, the preferred way of using these agents as weapons is to generate aerosols of inhalable particles.

These lists, which are normally used for export controls, are more or less only a description of historical knowledge. Despite their extension to include any agent in which a gene sequence has been identified that codes for pathogenicity, virulence or listed toxins, they still lag behind current developments in science and technology. They do not include, for instance, bioregulatory substances or agents derived from biodegradation research that could lead to anti-material weapons.

The use of resistance to antibiotics as a marker is a standard method in biological research, and it is a matter of concern that this could be abused to make bioweapons even more deadly. However, to generate stable clones of an infectious microorganism that are resistant to all known antibiotics is a difficult task. And is there any need to do so? The ability to detect an infectious agent in the early stages of dissemination is still very limited. Because of the lag between release and the onset of symptoms, which can vary from days to weeks, the outbreak of a disease will normally not be recognized until an unusual number of casualties appears. Symptoms caused by massive inhalation can also differ from those of the usual onset of disease, and can for some time camouflage the underlying cause. In addition, for pathogens with toxic mechanisms, such as *B. anthracis*, treatment or prophylaxis with antibiotics would probably start too late anyway.

Vaccination is the usual method of protecting people and animals against infectious diseases, but this is not applicable for most bioweapons. For some agents, vaccines do not exist at all, or they are not licensed for public use, or political decisions prevent their use because of their side effects (for example smallpox) or for economic reasons (such as foot-and-mouth disease). It is not only the wide spectrum of bacteria, viruses and toxins that makes it difficult to vaccinate populations against all possible agents; we are also lacking information about whether vaccines really protect against the very high infectious doses generated by aerosol attacks. In addition, existing vaccines can be rendered useless by genetic modification of the infectious agent. This was shown, for example, for the anthrax vaccine by the insertion of genes from *Bacillus cereus* into *B. anthracis* (Pomerontsev *et al.*, 1997). The possibility of circumventing immune mechanisms was also demonstrated by an Australian attempt (Jackson *et al.*, 2001) to develop a vaccine that provokes the rejection of oocytes in mice, to control mouse populations. The insertion of a gene expressing interleukin-4 into the virus that was used severely affected the immune system and led to increased lethality, even in animals that were genetically resistant to the virus.

Recently, scientists also showed that it is no longer necessary to start with a living organism to create a disease-causing agent. The synthesis of poliovirus (Cello *et al.*, 2002) solely from published gene sequences opens new avenues of concern. And the oligonucleotides necessary to begin DNA synthesis are commercially available from companies that sell made-to-order genetic materials. It might be much more difficult to repeat the experiment with more complex viruses, but the door to abuse is open. Which agent might be created next is already being debated, and scientists themselves will probably try to do similar experiments with more complex systems.

The synthesis of poliovirus will not influence the present WHO programme to eradicate polio, but the WHO has already stopped vaccinations against smallpox now that the disease has been eradicated. From the present point of view of biodefence, this might turn out to be a rash decision. It is true that the old vaccine has many side

AGENTS AND TOXINS THAT CAN BE USED TO PRODUCE BIOLOGICAL WEAPONS

The export of these items is restricted by national export controls (www.opbw.org).

Human and zoonotic pathogens

Viruses

1. Crimean–Congo haemorrhagic fever virus
2. Eastern equine encephalitis virus
3. Ebola virus
4. Sin Nombre virus
5. Junin virus
6. Lassa fever virus
7. Machupo virus
8. Marburg virus
9. Rift Valley fever virus
10. Tick-borne encephalitis virus
11. Variola major virus (smallpox virus)
12. Venezuelan equine encephalitis virus
13. Western equine encephalitis virus
14. Yellow fever virus
15. Monkeypox virus

Bacteria

1. *Bacillus anthracis*
2. *Brucella melitensis*
3. *Brucella suis*
4. *Burkholderia mallei*
5. *Burkholderia pseudomallei*
6. *Francisella tularensis*
7. *Yersinia pestis*
8. *Coxiella burnetii*
9. *Rickettsia prowazekii*
10. *Rickettsia rickettsii*

Protozoa

1. *Naegleria fowleri*

Animal pathogens

1. African swine fever virus
2. African horse sickness virus
3. Bluetongue virus
4. Foot-and-mouth disease virus
5. Newcastle disease virus
6. Rinderpest virus

Plant pathogens

1. *Colletotrichum coffeanum* var. *virulans*
2. *Dothistroma pini* (*Scirrhia pini*)
3. *Erwinia amylovora*
4. *Peronospora hyoscyami* de Bary f.sp. *tabacina* (Adam) skalicky
5. *Ralstonia solanacearum*
6. Sugar cane Fiji disease virus
7. *Tilletia indica*
8. *Xanthomonas albilineans*

Toxins

Bacteriotoxins

1. Botulinum toxins
2. *Clostridium perfringens* toxins
3. Staphylococcal enterotoxins
4. Shigatoxins

Phycotoxins

1. Anatoxins
2. Ciguatoxins
3. Saxitoxins

Mycotoxins

1. Trichothecene toxins

Phytotoxins

1. Abrins
2. Ricins

Zootoxins

1. Bungarotoxins

effects; however, the development of new ones has stopped, and today we still have only the 30-year old vaccine at hand. It is legitimate to ask whether other countries really have variola viruses beyond the controlled stocks at the Centers of Disease Control and Prevention in Atlanta, GA, USA, and Vector in Koltsovo, Russia, and therefore whether smallpox is only a theoretical risk or a real threat. Even so, a lot is known about the genetic similarities between the orthopox viruses, and the first experiment to introduce synthetic sequences on the basis of published variola genome data into another orthopox virus has already been done (Rosengard *et al.*, 2002). This alone might be reason enough to develop a better vaccine against smallpox that also protects against other members of the orthopox family.

Every cell of an organism has the same set of genes, but not all genes in a cell are active at a given time. Gene expression studies that started at the level of individual genes have now shifted to whole genomes and should lead to a better understanding of the interaction between the proteome and the genome of an organism. In addition, gene microarrays and protein chips now bring genome expression analysis much closer to the level of function. This makes it possible to understand medicine from the perspective of genes and proteins and to move medicinal treatments beyond symptomatic cures. It also creates new concerns. One of the risks is the possibility of integrating an infectious viral genome into the genome of possible victims and activating it at a later date. Such controlled molecular switches have already been tested experimentally. Another area of risk is the increasing access to highly specific bioregulators that are designed on the basis of an understanding of molecular interactions. The main areas of concern are substances that affect the nervous system or control the blood pressure and components of the endocrine and immune systems. This might sound like science fiction, but it has already been shown with substance P, a tachykinin that induces fluid loss from the small intestine (Koch *et al.*, 1999).

The marked increase in knowledge in the life sciences would not have been possible without the development in parallel of information technology. The storage, comparison, processing and integration of biological data have a central role in the biosciences. Data collection, data mining and mathematical approaches to detecting data patterns have been commercialized. Not only is this being done at the molecular and cellular levels, but information technologies are also being used to collect and compare the genetic information of whole populations and in health insurance systems to collect data on diseases. This information can be combined with that on sex, age, race and, for example, the individual behaviour of patients. Such data are already commercially available to drug developers. Their fusion with our increasing understanding of the genetic and molecular mechanisms behind normal bodily functions might in the future lead to the identification of vulnerabilities in selected populations, thus taking the theory of ethnic weapons one step closer to reality.

In parallel to this increase in knowledge are major improvements in production capabilities. Modern fermentation techniques enable higher cell densities; continuous production processes permit higher throughputs; and improved tissue- and cell-growth techniques allow the large-scale production of viruses. The stabilization of biological agents by freeze-drying, microencapsulation and other methods, and antistatic additives for the stabilization of particle sizes in aerosols, have all been established through former programmes in offensive weapons. These technologies have since been used in a wide variety of industrial processes and for the development of consumer-friendly applications of pharmaceuticals, vaccines and other products. In addition, there are efforts to allow larger molecules to be absorbed through the skin to improve the consumer compliance of pharmaceuticals.

Unimpeded access to knowledge and technology is a problem that becomes even more complex if we leave the purely academic discussion of possible misuses of science and technology and advance to the level of intelligence information, political intentions and national security. Then, risks turn rapidly into threats. And whereas risks can be controlled with mid-term and long-term strategies, threats demand immediate action. Even if there are slight differences between governments, the politically dominant perception today is that biological weapons are an increasing threat. Many countries have already started to invest in research and development in biodefence, to improve their biodefence measures, and to tighten national legislation.

Research and development in biodefence has closely followed general advances in the life sciences and focuses on two main areas: the development of vaccines, and rapid detection systems. But we do not yet have fully satisfactory solutions in either area. Detection systems designed on the basis of antibodies or DNA probes have achieved impressive time reductions for specific agents, but these systems provide detection that is still far from real-time. And they can easily be countered by the genetic manipulation of disease agents. The development of vaccines against specific agents might not solve the problem of genetically manipulated agents either—even multivalent vaccines might only cover specific sections of the whole spectrum of threats and leave many loopholes. The question is whether investments into research on non-specific immune responses can provide better solutions in the future. In general, it is questionable as to whether improvements in biodefence will convince those states that are developing biological weapons to refrain from these activities.

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All biodefence essentially deals with damage control at the operational level. As we do not have real-time detection or a full spectrum of effective medicines to protect against or provide treatment for all agents of concern, societies must increase their preparedness for a potential attack. One way of reducing threats is by controlling access to technology and knowledge. This is not an unusual step—even before the genetic revolution, many countries restricted the handling of human, animal and plant pathogens to persons with appropriate expertise. As technologies for manipulating organisms genetically became more accessible, the existing mechanisms of self-regulation and control were rapidly converted into laws and regulations to ensure biosafety and biosecurity in most developed countries. In addition, the biotechnology industry further limited access to new developments to protect proprietary information. Although these limitations help to minimize domestic risks, governments now use export

controls to prevent the spread of potentially harmful technology. Export controls are not a new tool for threat prevention; they have existed for decades, and they are not restricted to biological material but include other sensitive areas, such as nuclear, chemical or missile technology. Being nationally executed, export controls work only on the basis of a mutual understanding between like-minded states that share the same concerns. In the field of the life sciences, export controls mean restricted access to certain agents, production equipment and technologies for countries that are thought not to be in full compliance with Article I of the BTWC.

After the terrorist attacks of 11 September 2001, many countries started to revise their national legislation and further restricted access to biological materials and technologies. France (French Government, 2001), the USA (US Government, 2001, 2002) and the UK (UK Government, 2001) rapidly issued new laws to regulate specifically biological issues. Most of the European Union (EU) countries followed an EU proposal to review existing laws and regulations relating to biological agents and human, animal and plant diseases. Germany, for instance, identified more than 20 laws and regulations (German Government, 2002) that govern these areas, which are all enforced by penal legislation. Some of them are also applicable to activities against national law committed by German nationals outside national territory.

In mid-2002, the industrialized countries also discussed strengthening export controls, proposing the inclusion of the intangible transfer of information and knowledge (Australia Group, 2002b) that could be used to develop biological weapons. In this context, the question is how to define boundaries for 'constrained knowledge', by which access to certain research data would be limited. This can mean merely restricting access to certain areas for students from countries of concern, but it can also mean that some as yet unidentified national authority decides who will get access to certain research data. The latter requires that such an institution should be the exclusive provider of restricted knowledge and that it should make decisions about what research data need to be restricted. Several issues need to be addressed: who should decide on the disclosure of knowledge about new scientific and technological knowledge, who should maintain the repository of such knowledge, who should make decisions about what knowledge is released to whom, and who should decide who will be permitted to use new knowledge in research and development.

It is clear that scientists should engage actively in these discussions if, in the future, they do not want to have to apply to a government agency to obtain research data from their colleagues. The US Government has already issued stricter regulations for accessing material and agents that could be abused to make biological weapons, which is causing concerns about the restriction of free speech in the scientific community. An unpublished European study among representatives from academia and industry about possible restrictions on the freedom of the biosciences shows that most academic scientists disagree with requirements for additional restrictions, and believe that the existing ones already result in too many limitations. Industry representatives see fewer problems with additional restrictions, possibly because they are already accustomed to internal restrictions to protect proprietary information. Most participants in the survey are convinced that regulating access to information will have a negative effect on science and technology, and think that this will be serious or even very serious. In addition, most believe that restrictions will not reduce the risk of misuse; instead the loss of transparency in science might create more uncertainties and risks than would unimpeded publication. Nevertheless, there are questions that each scientist should ask himself or herself: should I publish or not publish? Does publishing a particular finding add to the progress of mankind or will it increase the risk of misuse? The discussion has already started vehemently in the USA and it is only a matter of time before it reaches Europe. The academic community in Europe should find convincing arguments to support their position of freedom of reseach; otherwise, governments might see a need to fill voids. And it is rather doubtful that politicians can offer better solutions to this problem than self-regulatory mechanisms in the academic community.

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