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Biological warfare, bioterrorism, and biocrime

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Abstract

Biological weapons achieve their intended target effects through the infectivity of disease-causing infectious agents. The ability to use biological agents in warfare is prohibited by the Biological and Toxin Weapon Convention. Bioterrorism is defined as the deliberate release of viruses, bacteria or other agents used to cause illness or death in people, but also in animals or plants. It is aimed at creating casualties, terror, societal disruption, or economic loss, inspired by ideological, religious or political beliefs. The success of bioterroristic attempts is defined by the measure of societal disruption and panic, and not necessarily by the sheer number of casualties. Thus, making only a few individuals ill by the use of crude methods may be sufficient, as long as it creates the impact that is aimed for. The assessment of bioterrorism threats and motives have been described before. Biocrime implies the use of a biological agent to kill or make ill a single individual or small group of individuals, motivated by revenge or the desire for monetary gain by extortion, rather than by political, ideological, religious or other beliefs. The likelihood of a successful bioterrorist attack is not very large, given the technical difficulties and constraints. However, even if the number of casualties is likely to be limited, the impact of a bioterrorist attack can still be high. Measures aimed at enhancing diagnostic and therapeutic capabilities and capacities alongside training and education will improve the ability of society to combat 'regular' infectious diseases outbreaks, as well as mitigating the effects of bioterrorist attacks.

Keywords: Biocrime, biological agents, biological warfare, bioterror, bioterrorism, bioweapons
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Introduction

Outbreaks of infectious diseases pose a constant threat to global health. Much attention is given to the emergence of relatively new or unknown pathogens, e.g. Middle East respiratory syndrome coronavirus and Zaire ebolavirus. More often, well-known pathogens such as poliovirus may lead to epidemics. Most epidemics emerge because of external, often climatological or geographical, factors. Sometimes, however, human interference with nature influences the spread of disease. Some zoonoses jump to a human host because the rainforest habitat of former animal hosts is reduced. Deforestation of mountainous areas may also lead to flooding of populated areas, indirectly leading to outbreaks of cholera and other infectious diseases.

A very special category of human-made outbreaks of disease is the manipulation and distribution of pathogens with the intention of disrupting societies. This may be part of government policy in biological warfare (BW), but is also a means used by terrorist groups or criminals. Although sporadic, the deliberate use of biological agents can lead to general anxiety. We aim to provide a very brief historical overview of the use of biological agents in warfare and terrorist or criminal activity, in the perspective of international regulations, early detection strategies, and coordinated preventive activities. Subsequently, the requirements for deliberate use of a potential biological agent are described, followed

by a summary of lessons learnt from bio-agents used as such in the past. We conclude with trends in, predominantly, bioterrorism, and propose a future approach to deal with an unpredictable, but potentially highly disruptive, threat.

Biological Weapons and BW

The Geneva protocol, ratified as early as 1925 and currently signed by 65 of 121 states, prohibits the development, production and use in war of biological and chemical weapons [1]. The WHO identified the threat of biological and chemical warfare officially in the midst of the Vietnam War and Cold War, after UN resolution 2162B (XXI) was adopted in 1967, condemning all actions contrary to the Geneva protocol. This resulted in the 1970 WHO report 'Health aspects of chemical and biological weapons', updated in 2004 [2] into WHO guidance 'Public health response to biological and chemical weapons'. This WHO document focuses on detecting and responding to unusual disease outbreaks. Important recommendations are standardized surveillance and the provision of adequate healthcare in cases of such emergencies. In the WHO definition, biological weapons achieve their intended target effects through the infectivity of disease-causing microorganisms and other such entities, including viruses, infectious nucleic acids, and prions. The 2004 WHO guidance is mainly concerned with the effects of such pathogens on human beings.

BW is carried out by nation states that seek to undermine the will and abilities of an opponent to fight back. Thus, they may seek to kill or make ill large numbers of the opponent's armed forces, population, crops and livestock by the release of biological agents.

Historically, until World War II, the number of soldiers dying from disease far outweighed the number killed in combat [3,4]. Although the numbers of soldiers dying from both combat and disease have been much reduced by advances in military healthcare and casualty extraction, morbidity in relatively modern wars (95% of US hospital admissions in World War II and 82% of those in the Korean war) has been related to soldiers being incapacitated because of disease and non-battle injuries rather than because of combat actions [3]. For example, malaria alone contributed to 56–75% of all hospital admissions of US Forces in the Vietnam War [5]. It is therefore not surprising that the impact of disease on the ability of an opponent to fight was recognized by the Romans and probably before that, and BW has been carried out in the past by trying to foster an outbreak. Some examples are the catapulting of manure, bodies of dead plague victims or cattle into besieged cities in medieval times, the distribution of blankets from smallpox victims to the native American Indian population in the eighteenth century, the use of shigella and cholera organisms to poison wells, and the distribution of plague-contaminated fleas by Japanese troops in Manchuria and China during World War II [6–8]. It is probable that examples of retreating troops using dead animals or manure to poison water sources can be found in any war. The discovery of the pathogenic abilities of microorganisms in the 19th century by Pasteur, Koch and others gave insights into the manner of transmission of diseases. It led to the development of industrial-scale microbiology and great advances in ways to prevent and treat infectious diseases, with tremendous benefits for humankind. However, ironically, it also provided insights into ways to misuse this knowledge.

Nowadays, being much less hampered by technical considerations and only inhibited by international opinion or fear of retaliation, nations have a wide number of options to carry out an offensive biological weapons programme. From 1928, a number of nations had offensive biological warfare programmes, and most likely some still do [9]. The USA (until 1972) and, most notably, the former Soviet Union (until 1992) had large and highly developed biological warfare programmes. Both nations developed ten or more agents, including toxins, weaponized to kill or incapacitate humans and to destroy crops and livestock [8,10,11]. The ability to use biological agents in warfare is prohibited by the Biological and Toxin Weapon Convention (BTWC). Since 1972, nations have not been allowed to carry out research to develop biological weapons, or to produce and stockpile them. The BTWC has been signed and ratified by 170 nations. Having said that, the BTWC has no inspection mechanisms, and a biological weapons research and production programme is relatively easy to hide within a nation's biotechnological infrastructure. Furthermore, the Biological Weapons Convention requires, in Article I, of nations who have signed not 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'. As such, the convention does not specifically define which agents or toxins are prohibited, and what quantities would go beyond the justification. Regardless of whether or not nations have ratified the BTWC, it is fairly certain that a number of rogue nations or those willing to risk international outrage are secretly carrying out BW research.

Bioterrorism and Biocrime

According to the CDC, bioterrorism is defined as the deliberate release of viruses, bacteria or other agents used

to cause illness or death in people, and also in animals or plants [12]. Bioterrorism aims to create casualties, terror, societal disruption, or economic loss, inspired by ideological, religious or political beliefs. It is carried out by terrorists, also called non-state actors. Usually, terrorists seek to achieve their goal through terror, caused by violence. Bioterrorism may also cause this terror. The 2001 series of anthrax letters contaminated hundreds if not thousands of people, but caused only a few casualties. However, the impact of this attack is still felt today, through the number of powder letters and suspicious packages regularly sent to public offices. Also, there are apocalyptic groups such as Aum Shinrikyo that actually seek to cause mass casualties to further their own goals. Terrorists operate within the borders of a nation that may seek to destroy them. The need to operate below the law enforcement detection threshold and with relatively limited means severely hampers their ability to develop, construct and deliver a successful biological attack on a large scale. On the other hand, success for most of them will most likely be defined by the amount of societal disruption and panic, and not necessarily by the sheer number of casualties. Thus, making even only a few individuals ill by using crude methods may be sufficient, as long as it creates the impact that is aimed for. The assessment of bioterrorism threats and motives has been described before [13–15].

Finally, there is biocrime. This implies the use of a biological agent to kill or make ill a single individual or a small group of individuals, motivated by revenge or monetary gain through extortion, rather by than political, ideological, religious or other beliefs. Examples are the use of, for example, ricin to get rid of a partner, or the use in 1996 of *Shigella dysenteriae* by a disgruntled hospital laboratory employee in making pastries as a gift for her colleagues [16]. The murder of the Hungarian dissident Georgi Markov in London in 1978 with a ricin-containing pellet injected with an umbrella could be considered an act of biocrime. However, as the murder was undoubtedly meant to convey a message on behalf of the KGB to other dissidents, one might equally argue that this is an example of state-driven BW.

Countering bioterrorism, from a responsive and policy-making point of view, usually focuses on measures to mitigate human casualties. Without doubt, this part is essential, and a simulation conducted by the Center for Nonproliferation Studies demonstrated that preparedness and being able to respond efficiently may reduce the ultimate casualty figure by 75% [14]. However, bioterrorism might also be used to cause significant economic losses by infecting livestock or crops, or contaminating buildings. Outbreaks of diseases such as foot and mouth disease, rinderpest and Newcastle disease lead to loss of the nation's disease-free status and subsequent bans on the export of animals, meat, and derived products, causing significant economic losses [17]. Although not an attack, the foot and mouth disease outbreak in the UK in 2001 directly affected the private and public sectors, with an estimated loss of £8 billion [18]. The 2003 avian influenza outbreak in the Netherlands resulted in a loss of nearly €800 million in direct costs and loss of trade for the Dutch government and industry [19]. The clean-up of various buildings involved after the 2001 anthrax letters costed the US government $320 million [20]. Although this kind of agroterrorism has not yet occurred, the threat should be taken seriously, given the impact that it may have.

Requirements for Potential Agents for Use in Bioterrorism

The requirements for a biological attack are obtaining a pathogenic organism or toxin, multiplying it in such a way that the agent retains its viability and pathogenic attributes, and developing a method whereby the agent can actually reach and enter a human being in sufficient quantities to cause disease. Regarding the last of these, this means that the agents need to be inhaled or swallowed by the target population, which requires either aerosolization or covert distribution in food or water. Thus, a vial containing an organism, even if it is pathogenic, does not constitute a biological weapon. The Aum Shinrikyo attack shows that, unless the technological hurdles are successfully overcome, the outcome will be 'a dud'. Probably, the uncertainty in the outcome will act as a deterrent for terrorists, and be a reason for them to use more conventional weapons.

Those contemplating the commission of an act of bioterrorism can think of an array of organisms, which may be more or less suited for this purpose. The traditional BW agents of both the US and former Soviet biological weapon programmes were chosen for this task after a long and careful selection process that narrowed the long list of potentials down to a few. The agents selected were considered to be suited for causing mass casualties because they were found to share a number of characteristics, namely:

1. High morbidity, and potentially highly lethal
2. Highly infectious or high toxicity (low ID50 or ICt50)
3. Suited for mass production and storage until delivery without loss of pathogenic potential
4. Suited for methods aimed at wide-area delivery, and hardy enough to withstand the delivery process
5. Relatively stable in the environment after dissemination for a period long enough to infect humans

6. Suitable for having the potential as a BW agent improved by genetic engineering and weaponization processes.

Terrorists, however, may not need the requirements for, for example, long-term storage or mass delivery. This means that they have a wider array of opportunities. However, first of all, agents must be available to them. Ricin, in particular, seems to enjoy great popularity as an agent of choice, as suggested by a long list of incidents or attempts [21], most likely because of its toxicity and accessibility.

The US Department of Health and Human Services and the US Department of Agriculture have declared three categories of biological agents that have 'the potential to pose a severe threat to health and safety'. These agents are called Biological Select Agents or Toxins, and are divided into three categories: (i) those that affect only humans; (ii) those that affect only animals or crops; and (iii) and those that overlap and affect both (http://www.selectagents.gov/).

The US CDC recognizes three categories of bioterrorism agent [12]. Category A includes the highest-priority agents, which pose a risk to national security because of the following features:

1. They can be easily disseminated or transmitted person-to-person, causing secondary and tertiary cases.
2. They cause high mortality with the potential to have a major public health impact, including the impact on healthcare facilities.
3. They may cause public panic and social disruption.
4. They require special action for public health preparedness.

A number of organisms and toxins are presented in Table 1, e.g. anthrax, plague, smallpox, botulinum toxin, and ricin. The properties, pathogenic mechanisms and medical countermeasures against them have been well described in the past [2,22–42]. The agents in Table 1 are selected because they have either been weaponized for warfare purposes or have been actually used in bioterrorism. These agents are likely to cause the most significant impact, and could be considered to be the most suited. However, this is not to say that agents that are not on the list are entirely harmless, only that they are less suitable. Listing agents as in Table 1 is useful to create an overview for, for example, focusing research priorities or other aims; it should not lead to too many agent-specific measures and a false sense of security if countermeasures were to be developed solely against a specific set. Generic measures strengthening public health, bio-preparedness and biosecurity, with agent-specific measures filling in the gaps, would probably be most cost-effective. Many pathogens may be used for bioterrorism in one way or another, and the popularity of ricin suggests that terrorists tend to use something that is, first of all, accessible.

Examples of Bioterrorism

The study of the National Consortium for the Study of Terrorism and Responses to Terrorism lists 74 separate incidents involving biological agents during 1990–2011 [43]. Carus [13] reports 153 incidents in the period 1990–1999 alone (Table 2), and the trends depicted there seem to have continued well throughout the first decade of the new millennium. However, many of these are biocrime-related, and are not taken into account by the National Consortium for the Study of Terrorism and Responses to Terrorism report. What is clear is that bioterrorism is hardly a new phenomenon, and that the numbers of attempts and attacks have increased significantly since 1989. Fortunately, most of these attacks failed, and caused neither deaths nor casualties.

In 1984, 751 people fell ill in The Dalles, Oregon, USA, in two successive waves after eating at salad bars. None of the casualties died. Proper outbreak investigation quickly determined the disease to be salmonellosis caused by *Salmonella typhimurium*, and identified four salad bars in the first wave and ten restaurants in the second wave as the origins of infection. What was not established by the health authorities at the time, and was only revealed by accident much later in 1986, was how the salad bars became contaminated in the first place. It turned out that the Bhagwan Shree Rajneesh cult had purposefully contaminated the assorted salad bars with *Salmonella* cultures in order to influence local elections, in a bid for power [44,45]. This demonstrates the difficulties in detecting a biological attack if agents and methods are used that mimic the accidental food-poisoning outbreaks that happen regularly, and if other indicators that raise awareness and suspicion are absent or not taken into account.

In 1995, the Aum Shinrikyo sect disseminated sarin in a coordinated attack on five trains of the Tokyo metro system, in an effort to ultimately start an apocalyptic war, from which the sect was meant to emerge as rulers of Japan and possibly even the world [46]. The attack resulted in 12 deaths and at least 1400 people being injured. An earlier attack in 1994, using sarin in Matsumoto, central Japan, resulted in seven deaths and 200 people being injured. At the time, the cult had several thousand members and assets worth millions of dollars, including a sheep farm in Australia for field testing. Its chemists were able to synthesize sarin and VX nerve agent gases, among other agents, by themselves. Only in 1998 did the authorities

TABLE I. Selected biological agents potentially involved in bioterrorism

Disease	Agent	Organism persistence	Infective dose	Human-to-human transmission	Infectivity	Incubation period	Symptoms	Mortality	Treatment
Anthrax	Spores of Bacillus anthracis	Very stable, spores may be viable for >40 years in soil	8000–50 000 spores	No	–	1–6 days	Fatigue, fever, malaise, cough, mild chest discomfort, respiratory distress, shock	High	Ciprofloxacin or doxycycline
Brucellosis	Genus Brucella (B. melitensis, B. suis, B. abortus, B. canis)	6 weeks. In dust to 10 weeks. In soil or water	10–100 organisms	No	–	5–60 days	Fever, headache, malaise, chills, sweating, myalgia, arthralgia, depression	5% if untreated	Doxycycline + rifampicin
Glanders	Burkholderia mallei	Very stable	Unknown	Rare but possible	–	10–14 days	Pulmonary form: cough, chest pain,	Very high if untreated	Ceftazidime, imipenem, or meropenem. Post-exposure prophylaxis with co-trimoxazole
Melioidosis	Burkholderia pseudomallei	Very stable	Unknown	Rare but possible	–	10–14 days	fever, rigors, sweating, pleuritis	Very high if untreated	
Plague	Yersinia pestis	Up to 1 year in soil, but viable only for 1 h after aerosol release	100–20 000 organisms	High	Patients contagious for up to 3 days after starting treatment	1–6 days	High fever, headache, malaise, chest pain, cough, haemoptysis, dyspnoea, stridor, cyanosis	Very high if untreated, <10% with antibiotics	Streptomycin or gentamicin with ciprofloxacin or doxycycline
Q-fever	Coxiella burnetii	Resistant to heat and drying, persists for weeks to months	1–10 organisms	Rare but possible	–	7–41 days	Fever, chills, headache, malaise, fatigue, anorexia, weight loss, endocarditis (as presenting symptom of chronic disease)	1% untreated, chronic form 30–60%	Tetracycline or doxycycline
Salmonellosis	Genus Salmonella (S. typhi, S. paratyphi)	Resistant to heat up to 57–60°C	Unknown	Faecal–oral transmission	Up to 4–5 weeks in faeces	6–48 h	Nausea, vomiting, mucopurulent or bloody diarrhoea, abdominal cramps, headache, maculopapular exanthema	<1%	Supportive care to prevent dehydration. In severe infections fluoroquinolones or third-generation cephalosporins
Shigellosis	Genus Shigella (S. dysenteriae, S. flexneri, S. sonnei and S. boydii)	Mean survival of 2–3 days, up to 17 days in favourable circumstances, several hours on infected hands	10–100 organisms	Faecal–oral transmission	In acute phase, high excretion in faeces; without antibiotic treatment, up to 4 weeks	1–7 days	Fever, abdominal cramps, diarrhoea, haemorrhagic colitis	<1%	Usually self-limiting. In severe infections, trimethoprim–sulphamethoxazole and ciprofloxacin shorten duration of symptoms and excretion in faeces
Tularaemia (rabbit fever)	Francisella tularensis ssp. tularensis	Weeks in water, soil, or carcasses, and years in frozen meat	10–50 organisms	No	–	1–25 days (mean 3–5 days)	Fever, chills, myalgia, arthralgia, headache, nausea, vomiting, diarrhoea, sore throat	4–50% mortality without treatment. With treatment, 1%	Streptomycin or gentamicin
Smallpox	Variola virus: Variola major	Highly stable for up to 1 year in dust and cloth	10–100 organisms	Yes, transmission requires close contact	Mostly contagious during first week of rash	4–19 days (mean 10–12 days)	Severe headache, high fever, extreme prostration, backache, chest and join pains, anxiety, exanthema, maculopapular rash that becomes vesicular	Ordinary-type smallpox: 30% if unvaccinated; 3% if vaccinated	No antiviral treatment, vaccination immediately or up to 4 days after exposure can reduce mortality
Venezuelan equine encephalitis	Alphavirus, (Venezuelan equine	Unstable in environment	10–100 organisms	No	–	2–6 days	Malaise, spiking fevers, rigors, headache, myalgia, nausea,	<1%	Supportive treatment

Table 1 (*Continued*)

Disease	Agent	Organism persistence	Infective dose	Human-to-human transmission	Infectivity	Incubation period	Symptoms	Mortality	Treatment
	encephalitis virus complex)						photophobia, vomiting, cough, encephalitis (4% children, <1% adults), diarrhoea, sore throat		
Botulism	Botulinum toxin produced by Clostridium botulinum	Weeks in non-moving food or water	LD50 is 0.001 μg/kg for type A (parenteral), 0.003 μg/kg (aerosol)	No	–	2 h to 10 days (mean 12–72 h)	Acute afebrile, symmetric paralysis descending from the head	Without supportive treatment: high mortality resulting from to respiratory failure	Supportive treatment, trivalent or heptavalent antitoxins
Ricin	Derived from beans of castor plant Ricinus communis	Stable until heated above 80°C	LD50 1 mg	No	–	Inhalation 4–8 h (mild symptoms), 18–24 h (severe symptoms)	Inhalation: fever, respiratory distress, cough. Ingestion: gastrointestinal haemorrhage. Both: multiorgan failure	High	Supportive treatment
Staphylococcal enterotoxin B	Produced by Staphylococcus aureus	Resistant to freezing, inactivated at 100°C	0.03 μg/person	No	–	Inhalation 3–12 h, ingestion 4–10 h	Fever, chills, dyspnoea, non-productive cough, headache, myalgia, retrosternal chest pain	<1%	Supportive treatment

TABLE 2. Trends in bio-agent cases 1900–1999 (modified from Carus [13])

Decade	Bioterrorist	Biocriminal	Other/uncertain	Total
1990–1999	19	40	94	153
1980–1989	3	6	0	9
1970–1979	3	2	3	8
1960–1969	0	1	0	1
1950–1959	1	0	0	1
1940–1949	1	0	0	1
1930–1939	0	3	0	3
1920–1929	0	0	0	0
1910–1919	0	3	0	3
1900–1909	0	1	0	1
Totals	7	56	97	180

learn that the cult had previously tried to attack metropolitan Tokyo with anthrax spores or botulinum toxin on at least eight different occasions in the period 1990–1995. All of these attempts failed, owing to the use of non-pathogenic preparations and technical difficulties in creating an aerosol [8,47]. Apparently, even if considerable financial, structural and logistical resources are available, successfully delivering a large-scale biological attack is harder than it may seem to be.

In the autumn of 2001, a series of letters containing anthrax spores were sent by mail to US senators, journalists, and media buildings. In the process, 22 people were seriously injured, five of whom died, and probably thousands were contaminated and advised to use antibiotics for an extended period of time. Forensic research ultimately implicated a former US research scientist, but his suicide prevented a satisfactory end to the investigation [48,49]. It must be noted that, although the number of clinical cases may have been small as compared with other diseases of public health concern, the impact on society was nevertheless very significant. At the time, there was much anxiety and stress [50], and the direct and indirect costs related to the investigation, clean-up and installation of detection equipment, scanning mail and other measures to prevent further attacks were high. Furthermore, the quality of life of those involved at the time has been badly affected [51]. To this day, powder letters are a regular phenomenon worldwide, usually containing hoax materials, but occasionally containing other toxic materials such as ricin [21,43]. The risk perception of events that are out of the ordinary usually results in an impact that goes beyond the mere number of casualties. In addition, communities and individuals involved in biological and chemical events may suffer from psychological effects, some of which are acute, and some of which are delayed in onset [52]. Bioterrorism falls in this category of events, and (bio)terrorism preparedness measures should take this into account.

Roxas-Duncan and Smith [21] described >20 bioterrorist attempts and attacks involving the use of ricin in the period 1990–2011. Ricin can be obtained from castor plant beans

(*Ricinus communis*), and these can be easily and legally purchased. Ricin is a highly toxic compound, and there is no effective antidote. Attempts involving ricin usually generate a high media profile. These reasons might be sufficient to explain the seeming popularity of ricin. In addition, the use of ricin may be an indication that the tightening of regulations on agents of concern and increases in other biosecurity measures have made it much more difficult for many individuals to obtain these materials.

Trends in Bioterrorism

So far, bioterrorism has claimed few lives as compared with the more traditional forms of terrorism using guns and explosives. The risk that use of the infectious agents as selected in Table 1 will result in casualties is real, but also should not be overestimated. For example, natural variations in incubation period, as can be seen from Table 1, will usually allow for diagnosis before the peak of symptomatic cases for most of the agents (and the longer the incubation period, the more this is so). Then, unless a multiresistant but highly aggressive 'superbug' is envisaged, effective antibiotics are available for the majority of bacterial agents at least. Nevertheless, there is some reason for concern that future bioterrorism attacks may be more effective than incidents in the past. Terrorists will usually use readily available weapons, but some also will keep trying to adopt tactics to inflict mass casualties to achieve ideological, revenge or religious goals. Sects such as Aum Shinrikyo have tried to master the method of aerosol dissemination of biological agents. Al-Qaida sought to acquire biological weapons [53]. Many of its assets in Afghanistan may have been destroyed in the past decade, but its aims and motivation have probably not changed. Also, because of increasing technological innovation and sophistication of equipment, and the proliferation of knowledge through the Internet across the world, equipment has become cheaper, smaller, and easier to operate, and methods have become easier to execute. What once required an expensive laboratory may now be done by a skilled individual in a garage, and will be difficult to prevent or detect. Laboratories have oversight mechanisms, colleagues peering in, and preventive measures in place to protect workers and the environment against inadvertent releases, but this is not the case in the do-it-yourself (DIY)-type garage box biology. Beyond doubt, in almost all cases the ingenuity and creativity displayed by these researchers and engineers is fully transparent within the community, and will be applied for beneficial purposes. Ultimately, it may result in biofuel-producing bacteria, lighting from luminescent microorganisms, or even biological computers [54]. The dual-use nature of life sciences technology and the diffusion of advanced technological capabilities could facilitate the development of a biological weapon, including mechanisms for effective dissemination. However, it must also be noted that, although equipment and techniques have become more readily available, considerable skills and expertise are still required to carry out this kind of DIY research [55]. The likelihood of rogue individuals carrying out DIY biology is real, but small. Self-regulation and transparency of DIY biology research should be encouraged. Possibly more disturbing for the future, some terrorists might gain access to the expertise and or agents generated by a state-directed BW programme. Civil war, revolt and lawlessness in countries possessing such a BW programme would cause a significant proliferation risk.

On the bright side, the technological innovations and rapid advances in life sciences have greatly increased our understanding of the ways in which pathogens interact with the host, and have stimulated the development of medical countermeasures. It must be stated that the benefits for society provided by these advances far outweigh the potential adverse effects. Also, they have greatly increased our abilities to detect and identify pathogens in a timely manner. At the same time, technological advances such as networked video cameras and software designed to identify important intelligence information have become powerful tools for counterterrorism operations, and have increased the effectiveness of antiterrorism countermeasures in order to prevent attacks. In the USA, the majority of bioterrorism attempts [21,43] were foiled in the early stages, indicating the success of the surveillance and counterterrorism activities. Technological advances have resulted in an increase in our forensic ability to investigate an incident and track down the origins.

Conclusions

Bioterrorism or BW is neither something new, nor something that is likely to go away. The likelihood of a successful bioterrorist attack is not very large, given the technical difficulties and constraints resulting from the need to work in secret, and more probably at the low-technology end of the spectrum than the high-technology end. However, even if the number of casualties is likely to be limited, the impact of a bioterrorist attack can still be high, will affect many lives, and is certainly to be costly in direct and indirect ways. Thus, it is best to be prepared to deal with the consequences. Measures aimed at enhancing public health in, among other areas, diagnostics, including microbial identification and typing, surveillance, generic antimicrobial therapeutics and therapeutics to over-

come drug resistance, training and education will both enhance the ability of society to combat 'regular' infectious disease outbreaks and mitigate the effects of bioterrorist attacks. Such an approach is likely to be the most cost-effective.

Authorship and Contributions

M. P. Grobusch conceived the paper. H. J. Jansen, F. J. Breeveld and C. Stijnis wrote the first draft of the paper. All authors contributed to structuring the paper, and to the final version of the paper.

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Transparency Declaration

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