Terrorism and health 2

Confronting the threat of bioterrorism: realities, challenges, and defensive strategies

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Global terrorism is a rapidly growing threat to world security, and increases the risk of bioterrorism. In this Review, we discuss the potential threat of bioterrorism, agents that could be exploited, and recent developments in technologies and policy for detecting and controlling epidemics that have been initiated intentionally. The local and international response to infectious disease epidemics, such as the severe acute respiratory syndrome and west African Ebola virus epidemic, revealed serious shortcomings which bioterrorists might exploit when intentionally initiating an epidemic. Development of new vaccines and antimicrobial therapies remains a priority, including the need to expedite clinical trials using new methodologies. Better means to protect health-care workers operating in dangerous environments are also needed, particularly in areas with poor infrastructure. New and improved approaches should be developed for surveillance, early detection, response, effective isolation of patients, control of the movement of potentially infected people, and risk communication. Access to dangerous pathogens should be appropriately regulated, without reducing progress in the development of countermeasures. We conclude that preparedness for intentional outbreaks has the important added value of strengthening preparedness for natural epidemics, and vice versa.

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Introduction

The Biological Weapons Convention prohibits the manufacture and use of biological weapons. It came into force in 1975, and has undergone periodic reviews, the last being in 2016. To date, 180 countries are signatories to the convention. Unfortunately, terrorist groups or rogue governments are unlikely to feel bound by international agreements. The potential for bioterrorism is of particular concern, since it can cause disease, death, and panic—in great disproportion to the resources expended.[1]

There have been a few well documented cases of bioterrorism. In 1984, a religious sect in the USA deliberately contaminated restaurant salad bars with *Salmonella typhimurium*, intending to disrupt local elections.[2] The attack resulted in several hundred cases of salmonellosis and no deaths. The anthrax letters incident in 2001 in the USA resulted in 11 cases of inhalation anthrax, with five deaths, and another 11 cases of cutaneous disease.[3] Extensive circumstantial evidence strongly suggests that the perpetrator was a civilian employee of the US military. However, no evidence of a clear motive was found. Thousands of workers received prophylactic or post-exposure therapy, and affected buildings were decontaminated at huge expense.[4,5] In 1993, a cult in Japan carried out an attack using anthrax spores with no physical casualties,[6] but later, evidence of post-traumatic stress syndromes was found in victims of the attack.[7] The perpetrators were apparently planning to use other agents such as Q fever bacteria, botulinum toxin, and Ebola viruses,[8] but they were detained before they could implement further attacks.

In this Review, we discuss the threat of bioterrorism, potential perpetrators, and general preparedness principles. We examine the special characteristics of biological agents that could potentially be used for bioterrorism, advances in prevention and treatment of diseases caused by these agents, and the remaining deficiencies in the management and control of possible bioterrorist outbreaks. In all respects, the ways in which the resources developed for bioterrorism preparedness could be used for controlling naturally occurring epidemics remain a guiding principle.

Key messages

- Preparedness for intentional outbreaks will strengthen the response to naturally occurring epidemics
- High level leadership should be maintained with responsibility and authority
- Health-care providers should maintain awareness of biological agents with bioterrorism potential and consider the presence of unknown pathogens
- Emergency room and community physicians should be updated regularly about the clinical manifestations of diseases caused by potential bioterrorist agents and emerging infectious diseases.
- Personal protective equipment should be improved to become more user friendly
- Improved surge capacity (the ability to rapidly gear up the health system to cope with a sudden, large increase in patients with a serious, contagious disease) is required, particularly in peripheral areas
- The capacity of general and reference laboratories should be increased, to keep developing faster, more reliable diagnostic tests
- New and improved vaccines (pre-exposure and post-exposure) and treatment regimens should be developed
- Clinical and environmental surveillance needs to increase
- Syndromic surveillance systems can be maintained to register suspicious or confirmed cases reported by physicians, and the data can be used to improve risk communication programmes and to monitor the progress of an outbreak
- An adequate stockpile of vaccines and medications should be maintained, both nationally and internationally
- To improve preparedness for natural and bioterrorist outbreaks, international cooperation should include joint exercises involving multiple countries and constant improvement in the exchange of information on potential bioterrorism threats and management

Panel 1: **Lessons learned from the west African Ebola virus epidemic**

Poor international preparedness
- Delay before the WHO declared a public health emergency of international concern
- Delay in implementing coordinated international assistance
- Logistic challenges in delivering support to assist epidemic response
- Shortcomings in WHO's regional and country-level capacity exposed
- Lack of global plans to address an epidemic of a high-risk pathogen in the least developed urban centres
- Evaluation of promising vaccine and therapeutic interventions came too late

Poor local preparedness
- Problems in implementing border controls to regulate the entry and exit of travellers increased the risk of spread of the disease
- Quarantine measures applied inconsistently

Shortcomings of the national medical infrastructure
- Scarcity of specialised equipment and highly trained individuals for diagnostic tests
- Early cases confused with other endemic diseases resulted in delay in recognition of Ebola as cause of epidemic
- Delays in confirming Ebola diagnosis placed others in quarantine at increased risk
- Scarcity of hospital beds and medical staff equipped to manage large numbers of high-risk patients
- Inadequate training, resources, and skills for treatment of patients at home with caregiver kits increased the risk of continued transmission
- Reduced access to appropriate training in use of personal protective equipment
- Personal protective equipment extremely uncomfortable in hot environments
- Deficiencies in medical research infrastructure delayed evaluation of potential clinical interventions

Shortcomings in the preparation for local customs and traditions
- Traditional burial customs enhanced risk of transmission
- Transport of patients and bodies increased risk of spread of disease
- Logistical challenges in ensuring safe burial for large number of dead
- Resistance to interventions among local populations at risk sometimes resulted in security risk for responders

Inadequate understanding of Ebola virus disease
- Latent virus transmitted sexually by survivors after several months
- Post-Ebola syndrome seen among survivors

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The threat of bioterrorism and the most likely perpetrators

Following the breakup of the former Soviet Union, there was concern that loss of control of their biological weapons programme could allow terrorist groups to gain access to both the weapons and scientific expertise. Additionally, in the past few years, developments in the field of microbial genetics have heightened concern about the possible abuse of new technologies. Since there are so many unknowns, it is extremely difficult to assess the risks and threats of bioterrorism.[9,10] The most likely perpetrators could be disgruntled individuals, terrorist organisations, or rogue countries that are believed to support international terrorism. Whereas individual attackers are unlikely to cause mass casualties, terrorist organisations could pose a substantial threat if they gain access to sophisticated biological weapons, materials, or scientific expertise. Although regulations and safeguards for securing dangerous pathogens in research laboratories now exist in most countries, the scope of these regulations and the extent of the safeguards vary.[11] Rogue countries have the necessary capabilities for a bioterrorist attack but might be restrained by the threat of the response of a unified global community.

Knowledge gained from legitimate research that could also be applied to bioterrorism[12] is considered dual-use. As a result, the regulation of legitimate research on infectious diseases has increased. There will always be a risk of the "insider threat",[12,13] which typically involves a single individual, so it is important to assure that new regulations truly increase security and have minimal negative effect on legitimate research. The cost of regulations applied to research on infectious diseases, in terms of missed opportunities for international collaboration, exchange of pathogens, and sharing of novel agents, is often intangible and overlooked. It is essential to promote healthy organisational cultures to enhance both safety and security in laboratories.[14]

General preparedness for bioterrorism

Since a bioterrorist attack is a low-risk, high-impact event, effective and sustained preparedness is an essential component in both the deterrence and management of an attack. A bioterrorist attack has a lot in common with naturally occurring public health emergencies resulting from infectious diseases. However, there are some important differences. Since it is a deliberate act to cause harm, there are the obvious security considerations. The resulting outbreak differs in some important ways from naturally occurring epidemics—for instance, it is more likely to be a point source outbreak initiated by simultaneous exposure to many people. The infectious agent used is likely to be uncommon and possibly not endemic to the region, might have been modified genetically to make it resistant to current medications and vaccines, and produced in a way that enhances its transmission or virulence. Therefore, early clinical symptoms and signs after infection with a bioterrorist agent might be unusual, complicating both recognition and management of the disease. These factors could create greater public panic.

Despite the many similarities with naturally occurring outbreaks of infectious disease, preparedness for bioterrorist attacks is more complex. In many aspects, a bioterrorist attack has the characteristics of a mass casualty event, and thus preparedness involves strengthening of the specialised infrastructure that is required for treatment of seriously ill patients over a very short period of time. New prophylactic and treatment regimens for unusual diseases are required, to ensure their accessibility when needed, along with clear standards for the handling and study of dangerous pathogens. When the proportion of available resources

that should be devoted to bioterrorism is decided, the potential effect on funding for other important health and security threats must be considered. Preparedness for bioterrorism will inevitably improve the ability to detect and control other infectious diseases, in particular emerging and re-emerging infectious diseases. Thus, resources diverted to preparedness for potential bioterrorism have a dual purpose. For instance, funding for new vaccine technologies for potential bioterrorist agents are very likely to lead to advances in the development and improvement of vaccines for common, important infectious agents, such as Zika virus, dengue virus, or the Middle East respiratory syndrome (MERS) coronavirus.

Despite the considerable amount of resources that have been used to meet the challenges of a bioterrorist attack, important gaps have been revealed in the preparedness for epidemics caused by highly pathogenic organisms such as the severe acute respiratory syndrome (SARS) coronavirus,[15] 2009 H1N1 influenza virus,[16] and Ebola virus.[17] The local and international responses to the 2014 west African Ebola virus epidemic revealed shortcomings that could allow highly contagious epidemics of infectious disease to spread widely before they are terminated (panel 1).[17]

Biological agents with potential for bioterrorism

During the cold war, agents that could potentially be used as biological weapons were identified on the basis of the following characteristics: pathogenicity for humans, animals, or plants; ability to cause disability or death; stability and infectivity as small particle aerosols; and capability of being readily and rapidly produced and weaponised in munitions or delivery systems. More characteristics have been added, to include other features of biological agents such as the relative ease of medical prevention or treatment and the likelihood of harm to the perpetrator.

The US Centers for Disease Control and Prevention (CDC) identified bacteria, viruses, and toxins that could potentially be weaponised (panel 2). In 2002, they categorised them into three groups—A, B, and C—depending on ease of dissemination, severity of illness caused, and ability to cause death.[18] Biological agents can be infectious and contagious, infectious but not usually contagious, or toxins if they are neither. Category A agents were considered the greatest risk to public and national security. The more recent classification of Tier 1 select agents and toxins is similar to the category A classification (table 1).

Other agents, such as naturally occurring pathogens, produce diseases that are considered of intermediate risk to the public (eg, brucellosis, glanders, Q fever). They are moderately easy to disseminate, and include emerging and re-emerging infectious diseases. However, genetic modifications could make them more virulent, produce uncharacteristic clinical signs, increase their resistance to treatment and vaccines, and even change their transmissibility or host range. Genetic modifications could be made using the tools of synthetic biology; such activities might be an example of dual-use research.[19,20] For instance, in 2005, the 1918 Spanish influenza pandemic virus was reconstructed,[21] and the poliovirus was synthesised nearly 20 years ago.[22] The addition of an immuno-modulatory gene to the mousepox virus genome in 2001,[23] rendered a mousepox vaccine ineffective, and this technology could potentially be applied to the smallpox virus.[24] The recent synthesis of the extinct horsepox virus[24] has been a reminder that the smallpox virus could be reconstructed, and that the regulations that have been put in place to prevent the misuse of powerful, cheap, and globally available tools must be reconsidered.[25] This possibility has also raised the issue of whether research results should sometimes be censored, or even refused publication, if the potential to cause harm is too high.[19]

Panel 2: **US Centers for Disease Control and Prevention potential bioterrorist agents and the conditions they are associated with**

Bacteria

- *Bacillus anthracis* (anthrax)
- *Clostridium botulinum* (botulism)
- *Brucella* species (brucellosis)
- *Burkholderia mallei* (glanders)
- *Burkholderia pseudomallei* (melioidosis)
- *Coxiella burnetii* (Q fever)
- *Escherichia coli* O157:H7 (haemolytic uraemic syndrome)
- *Francisella tularensis* (tularaemia)
- *Salmonella* species (salmonellosis)
- *Salmonella typhi* (typhoid fever)
- *Shigella* species (shigellosis)
- *Vibrio cholerae* (cholera)
- *Yersinia pestis* (plague)

Viruses

- Arenaviruses (Junin and Lassa fever)
- Ebola virus (Ebola virus haemorrhagic fever)
- Lassa virus (Lassa fever)
- Marburg virus (Marburg virus haemorrhagic fever)
- Variola major (Smallpox)

Toxins

- Botulinum toxin (botulism)
- Ricin toxin from *Ricinus communis*

Dissemination of bioterrorist agents

Although bioterrorist agents could be disseminated through multiple routes, the aerosol route would likely maximise exposure. Contagious agents could produce a large number of second and later generation cases, depending on the number of people initially exposed, the

For more on **Tier 1 classsification** see https://www.selectagents.gov/faq-general.html

	Characteristics	Associated condition	Likelihood of transmission
Bacteria			
Bacillus anthracis	Gram-positive, spore-forming, rod-shaped bacillus	Anthrax	None
Francisella tularensis	Gram-negative, spore-forming, aerobic coccobacillus	Tularaemia	Moderate
Burkholderia mallei and *Burkholderia pseudomallei*	Gram-negative, rod-shaped, aerobic bacteria	Meliodosis	Moderate
Viruses			
Ebola virus	Family Filoviridae, negative-sense RNA virus	Ebola virus haemorrhagic fever	High
Marburg virus	Family Filoviridae, negative-sense RNA virus	Marburg virus haemorrhagic fever	High
Variola major and Variola minor	Family Poxviridae, DNA virus	Smallpox	Very high
Foot and mouth disease virus	Family Picornaviridae, positive-sense RNA virus	Foot and mouth disease	High
Rinderpest virus	Family Paramyxoviridae, negative-sense RNA virus	Rinderpest	High
Toxins			
Botulinum toxin	Neurotoxin	Botulism	None

Table 1: **Characteristics of Tier 1 agents**

Panel 3: Aspects of food and water security to consider when assessing a potential bioterrorist threat

Safety and security of food[29–31] and water supplies [32] are important components of primary prevention:

- Intentional contamination of food should be considered, particularly during a large foodborne epidemic with a common source
- *Salmonella* and *Shigella* species, enterohaemorrhagic *Escherichia coli* (all serotypes), *Vibrio cholerae*, *Cryptosporidium parvum,* and noroviruses are all potential candidates for intentional contamination of food
- Contamination of water with biological agents should still be considered, even though it is unlikely to be the major target of bioterrorism, due to chlorination, dilution, and the need for large quantities of the agent to cause a substantial outbreak
- *C parvum* and noroviruses are more resistant to chlorination than other agents, so can be a threat to the water supply
- Food-borne or water-borne dissemination of these biological agents might lead to higher rates of morbidity and case fatality than previously observed, if the population has been exposed to substantially higher infectious doses
- Algorithms could be developed to measure the likelihood that outbreaks of disease were a consequence of intentional contamination of food or water, using descriptive, analytical, and molecular epidemiologic tools (none are known to be available so far)

average number of people who acquire the disease from one infected individual (R_0), and the disease generation time in humans. For instance, the R_0 of pneumonic plague has been estimated to be around 1·3,[26] whereas the R_0 for smallpox is likely to be around 5.[27] For diseases that are not contagious, such as inhalational anthrax, the number of cases of disease will depend almost entirely on the size of the population exposed and the timing of post-exposure antibiotic prophylaxis.[28] Aerosolised agents remain the threat of most concern, but safety and security of food[29–31] and water supplies[32] are also important components of primary prevention (panel 3). New methods to detect toxins in food, such as antibody based assays, are being developed.[33]

Diagnosis of disease caused by bioterrorist agents

Rapid diagnostics take on additional urgency in a bioterrorist event, because of both health and security concerns.[34] Since the 2001 anthrax letters, there have been major advances in diagnostic capabilities. Some of the greatest advances in the past decade have been in the speed and reduced cost of sequencing capabilities.[35,36] Highly sensitive and specific PCR-based systems, coupled with modern sample preparation technologies, have enabled sequencing technologies to become less costly, more portable, and multiplexed. With fieldable patient-side diagnostics and sequencing outputs directly connected via cloud-based networks,[37] health-care providers globally can make decisions more rapidly and respond more quickly for individual care or outbreak detection. A rapid, cartridge-based assay for *Francisella tularensis* has been developed for use at point of care.[38] A system that uses a sensitive microsphere technology to detect both antibodies and antigens is now available to diagnose infections with Ebola virus and Lassa virus.[39]

Although diagnostic ELISA tests are available for anthrax antibodies,[40,41] a compact system (GeneXpert) that includes both sample processing and PCR amplification can produce a result in about 90 minutes.[42] A rapid and sensitive method to detect smallpox virus has been developed for use at point of care, based on antibody immuno column for analytical processes (ABICAP) immunofiltration, that produces results in about 45 minutes.[43] However, diagnostic electron microscopy is also still considered a fast and efficient method[44] to identify smallpox and other viral agents. Ebola virus was rapidly sequenced during the outbreak in Sierra Leone to link sporadic cases with the transmission chains.[35] Advanced proteomics are also being developed as reference assays[45] and a new method for simultaneous immunodetection of anthrax, plague, and tularaemia from blood cultures has recently been reported,[46] using multiplexed suspension arrays. Next generation

Panel 4: **Precautions and treatment regimens for patients affected by selected agents**

Smallpox
Standard contact and airborne precautions should be taken.[65] Supportive therapy and antibiotics can be provided for secondary infections. There is some evidence of the potential efficacy of thiosemicarbazones. Cidofovir has shown in vitro efficacy against variola, and has shown efficacy against other diseases caused by human orthopoxviruses, notably diseases caused by vaccinia viruses. It has also shown efficacy in animal models of orthopoxvirus infections. Since 2012, the US Food and Drug Administration (FDA) has approved drugs and biologic agents developed under the Animal Rule. This rule allows for approval of a drug that cannot be tested for efficacy in humans, but is effective in animals and safe in humans. The first drug approved under this rule was the monoclonal antibody raxibacumab for treatment of inhalation anthrax. Tecovirimat is a drug that inhibits all orthopoxviruses tested in vitro. It was found to be highly effective in treating monkeypox and rabbitpox in animals and is considered safe in humans.[66] Tecovirimat is being considered by the FDA for approval for use in humans to treat smallpox under the Animal Rule.

Pneumonic plague
Standard and droplet precautions should be taken.[65] Ciprofloxacin, levofloxacin, and doxycycline have been approved for the treatment of pneumonic plague. Streptomycin and gentamicin have been found to be effective in treatment, although there is some evidence of the development of multiple resistance.[67,68]

Tularaemia
Isolation of the patients is not necessary and standard precautions should be taken. Ciprofloxacin, levofloxacin, and doxycycline are all approved for the treatment of tularaemia. Streptomycin and gentamicin have been found to be effective.[68,69]

Haemorrhagic fevers
Standard contact and airborne precautions should be taken until diagnosis is confirmed. Subsequently, droplet precautions can be considered. Supportive care and treatment of secondary infections can be provided. Ribavirin is now approved for treatment of Lassa fever and it also appears to be effective against new world arenaviruses and Crimean-Congo haemorrhagic fever.

Inhalation anthrax
Protective N95 respirators and clothing should be provided to health-care personnel. Clothing of patients should undergo decontamination and thorough handwashing. Supportive therapy is available, with antibiotics such as ciprofloxacin, doxycycline and ampicillin. If the bacteria are resistant to some of the antibiotics, the treatment regimen will depend on sensitivity testing.

Botulism
No isolation is needed and standard precautions should be maintained. Patients require supportive care and passive immunisation with equine antitoxin. The licensed antitoxin (Emergent BioSolutions, Winnipeg MB, Canada) neutralises botulinum toxin serotypes A, B, and C. A licensed heptavalent (A, B, C, D, E, F, G) equine antitoxin produced by Cangene (Emergent BioSolutions, Winnipeg MB, Canada) is available from the CDC.

sequencing and new informatics tools have identified viruses in samples also containing human or other nucleic acids.[47] Increased networking and collaboration of laboratories will also improve the response to intentional outbreaks.

Infectious disease surveillance and early detection

Effective global surveillance of infectious diseases is essential to control both intentional and naturally occurring epidemics.[48] Surveillance data can be used to monitor the progress of an outbreak, and for risk communication. To obtain information rapidly, the ongoing collection of health-related data (termed syndromic surveillance) has been introduced, to monitor patterns of symptoms and signs that are suggestive of an outbreak.[49–52] Although it was hoped that syndromic surveillance would be a more sensitive method for early detection of an epidemic, frequent reports of unusual increases in incidence of non-specific illnesses can desensitise and paralyse the system.[53] In fact, early detection will depend largely on alert, prepared clinicians. For example, when the 2001 anthrax attacks occurred, an astute clinician identified the index case.[34] Emergency room and community physicians should be updated regularly on the clinical signs and symptoms associated with the most common bioterrorist agents.[54] The syndromic surveillance system would be more useful after suspicious or confirmed cases have been reported by physicians. A focused analysis of the surveillance data against non-specific, background disease rates could detect changes and provide information about the dynamics of the disease. Special legislation might then be necessary, to gain access to medical records.[55]

The internet facilitates other potential forms of surveillance and communication about infectious diseases.[56,57] One such system is ProMed, which was established by the user community and has proven effective in connecting clinicians and scientists around the world; it has already served as an early warning system[58] for unusual outbreaks of undiagnosed and diagnosed diseases—SARS and MERS are recent examples. Social media has also been examined as a possible means of monitoring an epidemic. During the

For more on **ProMed** see https://www.promedmail.org/

2010 cholera epidemic in Haiti, social and news media enabled the estimation of epidemiological patterns.[59]

WHO introduced the International Health Regulations in 1969, and the updated version in 2005 takes into account the threat of bioterrorism.[60] The regulations require immediate reporting of serious health risks by all member countries. Additionally, WHO has established the Global Outbreak Alert and Response Network, and the European Union has a programme called BICHAT to improve cooperation between member states in preparedness and response to biological and chemical attacks. They operate the Early Warning and Response System for outbreaks of communicable diseases. The World Organisation for Animal Health has developed plans to identify and deal with a bioterrorism attack on populations of food-producing animals. Canada has established the Global Public Health Intelligence Network for worldwide monitoring of threats to public health.[61]

A major benefit of a less formal global collaboration is the development of networks of trust among knowledgeable scientists and clinicians, who are considered early warning posts for both natural and intentional outbreaks.[62] The One Health initiative encourages collaboration between health professionals and is as important for bioterrorism preparedness as it is for management of emerging infectious disease and the global spread of antimicrobial resistance.[63]

For more on **One Health** see http://www.onehealthinitiative.com/

Treatment of patients

The management of patients that have been infected during incidents of bioterrorism can be challenging.[64] Precautions and treatment regimens for several bioterrorist agents are summarised in panel 4. Although supportive care serves as the basis of management for all agents, treatments for some of the relevant diseases have substantially progressed. The management of inhalation anthrax has advanced since the 2001 attack,[64,70,71] with improvements in critical care, and in treatment of acute lung injury and acute respiratory distress syndrome, severe sepsis, and septic shock. Pleural effusions are routinely drained and there are more options for antimicrobial therapy. Antibiotics are still recommended for 60 days after exposure or diagnosis, together with the anthrax vaccine. If the vaccine is given concurrently with antibiotic treatment, the period of treatment could be shortened. Antibiotics for treatment of other bacterial infection are usually given for shorter periods, since the causative agents do not sequester spores. Tularaemia is treated with ciprofloxacin or doxycycline.[72] For smallpox, antivirals such as cidofovir or a related acyclic nucleoside phosphonate analogue appear to be more effective than post-exposure vaccines in preventing mortality, according to experiments in non-human primates infected with monkeypox virus.[73] This suggests that antivirals might play an important role when preparing for a smallpox outbreak. For viral haemorrhagic fevers, ribavirin might have some efficacy in post-exposure prophylaxis. A small-molecule antiviral drug, GS-5734, has been developed that appears to be effective in treating Ebola virus infection.[74]

For more on the **National Ebola Virus Training and Education Center** see https://netec.org/

Isolation of patients and quarantine of contacts

For intentional and other sudden outbreaks of contagious disease, isolation of patients and controlling risks to health-care workers remains extremely challenging, as was noted in the MERS coronavirus, SARS, Ebola virus disease, and avian influenza epidemics.[75] Hospital units adequately equipped for isolation are needed, similar to those equipped to care for filovirus-infected patients, with negative pressure air filtration.[76] If facilities are too small for the number of patients, a lower level of isolation with strict barrier nursing should be implemented, and in the event of a very large outbreak, there might be a need to set up isolation facilities in public buildings. In regions with poor infrastructure, it might be necessary to consider treating patients in their homes. People who have died should be regarded as infectious and handled with the same precautions used for patients. Burial procedures might have to be modified, but every effort should be made to respect religious practices and traditions of the local culture.

Quarantining of people who might have been exposed to the infectious agent can be problematic,[77] as was the case in the SARS and west African Ebola virus epidemics.[78] Since the quarantined population includes both people who were exposed and people who were not, the risk of disease transmission is higher. During the Ebola virus outbreak in west Africa, suspect cases were held until they could be cleared as negative, which took about 3 days pending the PCR results. On a national level, reducing the movement of populations is a sensitive issue, potentially interfering with commerce.[79] Closure of schools is an important means of achieving social distancing to reduce spread. Whether the public should use masks during an outbreak of a contagious disease is less clear,[80] and the efficacy of the masks is extremely variable. The most important reasons for variable efficacy are differences in facial shape, incorrect application, and duration of use.

Protection of health-care workers during infectious disease outbreaks

A substantial proportion of the cases and fatalities in the SARS and Ebola virus epidemics were among health-care workers. Clear guidelines specific to each agent are available to health-care personnel, public health workers, and emergency workers for the use of masks and personal protective equipment. The National Ebola Virus Training and Education Center has been established in the USA to train health-care workers and assist hospitals in preparing for patients infected with high hazard virus in the USA and other countries. Laboratory workers must be trained to work with dangerous pathogens and wear protective gear. Designated threat pathogens must be stored, handled, and transported under a different set

of regulations than common public health pathogens identified routinely in clinical laboratories.[11]

The role of vaccines in pre-exposure and post-exposure prophylaxis

Measures should be in place to protect the population from biological agents likely to be used in an attack before an incident occurs. However, since a bioterrorist incident is likely to be caused by biological agents not covered by routine immunisation, pre-exposure prophylaxis is generally confined to vaccines for military forces, health-care workers, and emergency response personnel. To the majority of the population, only post-exposure prophylaxis is relevant. Post-exposure prophylaxis for an intentional outbreak would include both those people known to be exposed during the incident and those people who were infected by others. The prophylaxis itself might consist of both vaccines and antimicrobials. When using live, attenuated vaccines, the relatively large proportion of the population who has some form of immunodeficiency has to be taken into account.[81,82] Monoclonal antibody preparations are now being considered for prophylaxis in select, high risk groups.[83] Table 2 summarises pharmacological prophylaxis for Tier 1 pathogens.

Currently, the vaccines that would most likely be used for pre-exposure or post-exposure prophylaxis are the smallpox and anthrax vaccines. Since routine vaccination against smallpox was stopped in the 1980s, less than 50% of the world's population has been vaccinated, and antibody titres usually decline markedly after 5 to 10 years.[84] Residual cell-based immunity can persist for many years.[85,86] Post-exposure prophylaxis involves ring vaccination, which requires intensive tracing and vaccination of primary contacts, followed by vaccination of secondary contacts,[86] and finally, vaccination of all people in a defined affected region. For post-exposure prophylaxis of those directly exposed during the incident, vaccination can be effective if given within 3 to 4 days of exposure.[87] Since it might take that amount of time to detect the first cases after exposure, the vaccine will generally only be effective for secondary and subsequent contacts. Immune-boosting adjuvants[88] and toll-like receptor agonists have the potential to improve the immune response to post-exposure vaccination.[89] Serious side-effects are relatively rare[90,91] but can affect compliance.[92] In those cases, lower doses of vaccine might be administered, to provide adequate protection with fewer side-effects.[93] Newer smallpox vaccines are in development,[94] including those that could immunise people who have atopic dermatitis.[95] Because it is produced in small quantities by collecting antiserum from immunised humans, there might be a shortage of vaccinia immune globulin, used to treat people who would have serious side-effects with the vaccine. One possible solution to this shortage would be to use antibodies against other poxviruses, such as cowpox and monkeypox,[96] because of their cross-protective properties.

	Vaccines		Medications	
	Pre-exposure	Post-exposure	Pre-exposure	Post-exposure
Smallpox	Yes	Yes	No	..
Pneumonic plague	In development	No	No	Yes
Tularaemia	No	Yes	No	Yes
Haemorrhagic fevers	A vaccine for yellow fever has been licensed in the USA and a vaccine for Junin virus has been licensed in Argentina	No	No	No
Inhalation anthrax	Yes	Yes	No	Yes
Botulism	In development	..	No	Yes

Table 2: **Pharmacological prophylaxis for Tier 1 agents**

Since naturally occurring inhalation anthrax is extremely rare, there have been safety and immunogenicity profiles of the anthrax vaccine in humans,[97] but the efficacy has only been tested in animal models, and not in clinical trials.[98–100] The current anthrax vaccine is made from culture filtrates of a toxigenic, avirulent, non-encapsulated mutant of the *Bacillus anthracis* Vollum strain, and is administered in five intramuscular doses, followed by annual boosters. The protective, antigen specific memory B cells persist for many years after vaccination and are associated with humoral immunity.[99] Serum IgG response to the vaccine has been 100% after the fourth dose.[101] For post-exposure prophylaxis in unvaccinated people, the vaccine should be administered as a three-dose subcutaneous series (at 0, 2, and 4 weeks), in conjunction with a 60-day course of appropriate antimicrobial drugs. It has been given to thousands of US military personnel, and notable adverse events have been rare.[102] The anthrax vaccine is not recommended for pregnant women, although one study[103] with women in the US military, inadvertently vaccinated during pregnancy, did not show evidence of an increase in birth defects. In this study, 4418 women received the vaccine in the first trimester and 423 in the second and third trimeseter. More effective anthrax vaccines that require fewer doses are constantly being tested,[104,105] such as the NEAT protein anthrax vaccine,[106] a dual purpose influenza vaccine that protects against anthrax,[107] and a combined anthrax-plague vaccine.[108]

Apart from the 17D yellow fever live attenuated vaccine and the Junin virus vaccine, no vaccines for haemorrhagic fevers have been licensed. Since the west African Ebola virus epidemic, new Ebola virus vaccines that have been long under development are being used successfully in the 2018 epidemic in the Democratic Republic of the Congo.[109] Essentially no other licensed vaccines are available for other Tier 1 select agents. The previously licensed, formalin-inactivated, whole-bacilli plague vaccine has not proven effective against primary pneumonic plague in non-human primate models,[110] but new plague vaccines are under development.[111,112] A live attenuated vaccine against tularaemia for high risk personnel is held as an investigational new drug by the

US military. The vaccine has not been used widely for pre-exposure prophylaxis and has no place in post-exposure prophylaxis. New vaccines against tularaemia are under development[113,114] including one that might provide cross-protection between plague and tularaemia.[115]

The investigational pentavalent (ABCDE) botulinum toxoid vaccine was provided by the CDC for laboratory workers at high risk of exposure to botulinum toxin and it has also been given to military members that are at risk. The botulinum toxoid vaccine produces effective immunity after several months and has no value for post-exposure prophylaxis because of the short latent period of the toxins. This vaccine was discontinued in 2012,[116] because of declines in immunogenicity and adverse events. New recombinant botulism vaccines are being developed, in addition to vaccines against glanders and Rift Valley fever.[117–119]

Efforts are ongoing to greatly shorten the time required to develop and produce new vaccines and other immune approaches. Improved technologies are important for rapid scale-up and production of new treatment regimens, particularly following an attack with a contagious agent.

For more on the **Strategic National Stockpile** see https://www.cdc.gov/phpr/stockpile/index.htm

Risk communication

The largely unpredictable nature of an epidemic initiated intentionally is likely to increase uncertainty and reduce public trust in the authorities. Public education and effective risk communication are essential to increase public confidence and improve cooperation and compliance with recommended medical counter-measures.[120] The anthrax vaccine in military populations has caused considerable scepticism regarding the need for, safety, and efficacy of the vaccine.[121–123] Clinicians and public health personnel should have access to up-to-date information, and the general public should be provided with non-technical information and simple instructions on how to act during an emergency. Sandman[120] has proposed that "one should not over-reassure, acknowledge uncertainty, and share dilemmas". This behaviour would only cause overreaction or panic when new information about the risk is made public.

Risk communication will be necessary at all stages: before a bioterrorist incident occurs, when an incident is suspected, when it is confirmed, while it is taking place, and in the aftermath. Credible and trusted spokespersons, including respected clinicians, scientists, and public servants for a country, should be adequately informed before an incident. During an outbreak, there could be unexpected events, such as atypical presentation of cases, varying responses to treatment (including unusual side-effects), and false positive and false negative diagnoses. The public might lose trust in the authorities if apparently unexposed people become ill. The advent and global distribution of social networking increases the risk of the dissemination of false or misleading information. Lastly, a major infectious disease incident will also require flexibility and possible changes of established government policy.

Environmental aspects

Environmental detection of biological agents is another area of research that should be developed. To date, most systems of environmental detection have focused on anthrax, as a result of the anthrax attacks.[124,125] However, a sensitive and specific set of recombinase polymerase amplification assays for fast screening, detection, and identification of *B anthracis* in a field setting has recently been developed.[126] The rare occurrence and likely small effect of an aerosol bioterrorist attack limits the practical use of environmental detection to special event venues, public transportation systems, and possibly some government buildings thought to be likely targets.

International preparedness

Many countries have national stockpiles of drugs and vaccines, for use in the event of a biological or chemical attack, or for serious outbreaks that might achieve epidemic proportions. The USA, for instance, maintains a Strategic National Stockpile of vaccines and other medical countermeasures. Global stores of smallpox vaccines are held by WHO, in addition to stores held by individual countries. Some countries have undertaken active vaccination programmes against smallpox and anthrax in the military and first responder populations. Preparedness for bioterrorist incidents requires constant re-evaluation of policies.[127] Although there is no evidence that the 2009 H1N1 influenza pandemic or the 2014–16 Ebola virus epidemic in west Africa were initiated intentionally, the local and international responses revealed strengths and weaknesses in the current state of preparedness for bioterrorist incidents.[128] The Ebola virus epidemic spread to a number of countries, with more than 20 000 cases reported worldwide and a case fatality rate of more than 60%. Imported cases of Ebola virus disease were identified in the USA and Spain. Locally, in the affected countries in west Africa, 10% of the people who died because of Ebola virus disease were health-care workers. Various shortcomings in the response to the epidemic have been identified since (panel 1).

Preparing for future threats

Accurately predicting the intentional misuse of a biological agent to cause harm is difficult without intelligence data, but several attempts have been made to rationally predict the categories of risk: man-made, natural, accidental, contagious, and non-contagious.[129,130] In 2016, the United States President's Council of Advisors on Science and Technology proposed likely infectious disease risks, dominated by naturally emerging diseases, new powerful technologies to manipulate microbial agents, and human misjudgment or error.[131] Bioterrorism threats must be considered rationally and integrated into preparedness plans along with other infectious disease

risks.[132] The risk of bioterrorism has called into question some of the dogmas related to eradication of diseases such as poliomyelitis and measles.[133] For example, if polio is successfully eradicated, universal vaccination might have to continue because of the risk of poliovirus being used as a bioterrorist agent.[134–136] Emerging and re-emerging infectious diseases will continue to be a threat,[137] but preparedness for bioterrorism is, in many ways, similar to preparedness for naturally emerging disease.

Conclusions

All countries should collaborate to address the root causes of terrorism, and develop appropriate preventive strategies. Effective preparedness is, in itself, a deterrent to bioterrorism, since it reduces the incentive to use biological weapons by making a country or region a hard target. It is also the cornerstone of consistent and effective responses to naturally occurring epidemics. The abuse of biological agents can be further reduced or discouraged with reliable intelligence and an effective response if it does occur. National and regional resources and capabilities will vary, but all will require infrastructures that are capable of recognising and dealing with a variety of biological agents.[138] The needs of specific populations, such as the paediatric population, pregnant women,[139] elderly people, and people with immunological disorders, must also be addressed.[140] Funding for biodefence is crucial to adequate preparation and response to bioterrorist threats.[141]

International preparedness for bioterrorism has the dual benefit of strengthening the infrastructure for responding to naturally occurring epidemics of highly pathogenic organisms. Lessons from the 2014 west African Ebola virus epidemic show that health-care providers must always be watchful for unusual presentations of disease, and new and improved approaches must be developed for early detection and response. Health-care providers need more effective means of isolating infected patients, and better methods to control the movement of potentially infected people outside of the affected areas. Personal protective equipment should be inexpensive and effective, and available to use with minimal training and under harsh environments. Protection of health-care workers against infection remains particularly problematic, and should be a focus of research and development. The Ebola virus epidemic has highlighted the importance of improving the logistics of moving human and material resources in areas with relatively poor infrastructure. Risk communication and public education before and during an outbreak need to be improved. More clinical trials should be fast-tracked during development of new vaccines and antiviral drugs. Preparedness for a low-risk, high-impact event that is bioterrorism should be monitored constantly, tested in tabletop exercises,[142,143] and integrated into the routine functioning of the health system. Here it would serve the dual purpose of ensuring that countries are prepared to meet the challenges of controlling epidemics of emerging and re-emerging infectious diseases.

Search strategy and selection criteria

We searched PubMed and Google Scholar using the terms "bioterrorism", "sustainable bioterrorism preparedness", "all-hazards Infectious disease preparedness", "biological threat agents", "bioterrorism preparedness", "emerging infectious diseases", "smallpox", "anthrax", "plague", "tularemia", "botulism", "hemorrhagic fevers", and "risk communication". We searched national and international reports from the WHO and US Centers for Disease Control using the terms "bioterrorism", "bioterrorism preparedness", and "emerging infectious diseases". We also completed web searches for "disease surveillance", "infectious disease diagnostics", "medical countermeasures", "emergency healthcare delivery", and "risk management". We focused on academic literature in English and restricted most of our searches to documents published since 1990, with an emphasis on those published after 2001, and included mainly those published since 2008.

Contributors

MSG designed the Review, did the literature search and was responsible for writing the manuscript. JLD assisted in the literature search, revised the manuscript, and supplied technical expertise. DC assisted in the literature search and revised the manuscript. DRF helped design the Review, contributed source material, did the literature search, and helped write and revise the manuscript.

Declaration of interests

We declare no competing interests.

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