

René Gottschalk · Wolfgang Preiser

## Bioterrorism: is it a real threat?

Received: 25 May 2004 / Published online: 2 September 2004  
© Springer-Verlag 2004

**Abstract** The Geneva Protocol of 1925 commits the signatory nations to refraining from the use of biological weapons. However, the terrorist assaults of September 2001 and, subsequently, the anthrax-containing letters are cause for great concerns: new threats to the security of nations are expected, as terrorist organizations seem to increasingly explore novel ways of spreading terror. In this context, naturally emerging diseases such as SARS, monkeypox or West Nile fever assume new importance because it is difficult to distinguish between natural epidemics and possible bioweapon assaults. Great efforts on the part of governments and public health authorities are necessary to counteract these threats.

**Keywords** Bioterrorism · Smallpox · Anthrax · West Nile virus · Severe acute respiratory syndrome (SARS)

---

### The Geneva Protocol

The Geneva Protocol of 1925 relating to the protection of civilian persons in time of war and additional protocols commit the signatory nations to refraining from the use of biological weapons since these not only have

disastrous effects on the armed opponents involved in the conflict but also on the civilian population [26]. Nevertheless, efforts to develop such weapons continued throughout the Cold War and even after its end; not least because compared to nuclear weapons, biological ones are relatively cheap to develop and produce, earning them the attribute “a poor man’s atomic bomb”. However, it is the developments over the past years that are causing the greatest concern: new threats to the security of nations are emerging in the form of terrorist organizations that seem to increasingly explore novel ways of spreading terror [1].

---

### The smallpox and anthrax stories

Smallpox was declared eradicated in 1980, following a global eradication campaign led by the World Health Organization (WHO). The only officially remaining smallpox virus stocks are maintained at the Centers for Disease Control and Prevention (CDC) in Atlanta and at Vector, the Russian viral research institute at Koltsovo in Siberia.

These stocks were supposed to be destroyed in 1999, making the smallpox virus officially extinct. But the US President at the time, Bill Clinton, persuaded WHO members to postpone destroying them until 2002, so more research could be done on new vaccines and drugs and on smallpox genetics. The reason for the delay was a growing fear of smallpox as a bioweapon in a world no longer vaccinated against the disease, for routine smallpox vaccinations had been stopped after eradication had been achieved. Therefore, WHO members agreed to a smallpox research plan [35].

On October 4, 2001, CDC and state and local public health authorities reported a case of inhalational anthrax in Florida. Additional cases of anthrax were subsequently reported from Florida and New York City [5, 8]. This was the first known “successful” attack after the ineffective aerosolization of a *Bacillus anthracis* suspension in July 1993 by the Aum Shinrikyo sect in

---

R. Gottschalk  
Center of Competence for Highly Infectious Diseases,  
Hesse, Germany

W. Preiser  
Institute for Medical Virology,  
Johann Wolfgang Goethe University Hospital,  
Frankfurt am Main, Germany

R. Gottschalk (✉)  
Department of Infectious Disease Control,  
Public Health Office (Gesundheitsamt),  
Braubachstr. 18–22, 60311  
Frankfurt am Main, Germany  
E-mail: rene.gottschalk@stadt-frankfurt.de  
Tel.: +49-69-21236252  
Fax: +49-69-21231498

Tokyo (also responsible for the sarin nerve gas attack on the Tokyo subway system in 1995) [32]. Epidemiological findings indicated that these cases of inhalational anthrax most likely occurred through aerosols generated when opening or processing letters containing *B. anthracis* powder. There is some evidence that these attacks may have been carried out by a US scientist, although their exact background and circumstances remain officially unresolved until now. They resulted in 22 people developing anthrax, 11 of whom suffered the pulmonary form and of whom 5 died [17].

Following the anthrax attacks in the US, the US Department of Defense decided that smallpox stocks should not be destroyed before two anti-smallpox drugs and a new, safer vaccine were licensed, along with new diagnostic methods. Not surprisingly, Russia consequently also refused to destroy its stocks.

Following this, the government of the Federal Republic of Germany—like those of several other states—decided to acquire and to stockpile sufficient smallpox vaccine for an emergency vaccination program for the whole population of Germany (around 82 million people) in case of a smallpox attack [4]. Preparations were made for such a program, such as training of medical staff to conduct the vaccinations, etc. Compared to other vaccines currently in routine use, smallpox vaccination using vaccinia virus entails a considerable rate of side effects. Based on previous experiences, 1 in 1,000 vaccinees will develop a serious illness requiring symptomatic medical treatment, and there will be about 30 cases of permanent damage and 1–2 deaths per million vaccinees [10, 15]. In addition, it is likely that during a mass vaccination program, some individuals, who have unrecognized contraindications, will receive the vaccination, increasing the rate of complications further. Transmission of the vaccinia virus to contacts with or without contraindications is another risk.

---

### The likelihood of bioweapon attacks

In the case of biological warfare, the aim of which would be to kill or to incapacitate the largest possible number of enemy soldiers, the aggressor will consider measures to protect his own army and civilian population. In contrast, the aim of bioterrorism is to cause maximum disruption and to seed terror. This may be achieved by actual acts or by simply causing panic. While this does not necessarily imply actually harming more than a few people, many modern terrorist groups on the other hand do not seem to pay much attention to the safety, well being or even survival of their own followers. Terrorists will know that using highly infectious agents such as the smallpox virus for biological attacks might well mean their spread also to their own followers because they do not have smallpox vaccine or other preventative measures available.

How likely is a bioweapon attack and, more tightly focused, how real is the chance of such an attack by a

terrorist group? It has to be taken into account that sophisticated microbiological and biochemical techniques are required to cultivate highly pathogenic biological agents and to make them suitable for use as bioweapons. Due to the high infectiousness of many potential bioweapon agents, all handling and manipulation would have to be done under Biosafety Level 3 (BSL 3) or BSL 4 conditions to protect the handlers [36].

The CDC have developed a classification system for potential biological agents [9, 29]; Table 1 lists their definitions and gives some prominent examples for each of the three categories. Particularly categories B and C may be of interest to bioterrorists, due to the fact that some of these agents are not as infectious as those in category A and that dealing with them is, therefore, much easier. For example, multidrug-resistant *Mycobacterium tuberculosis* is relatively easy to cultivate at a relatively low biohazard level, and with its incubation period between weeks and years it would be very difficult for public health systems to realize that a large number of patients were the result of a bioweapon attack. However, the insidious course might compromise its terrorising effect. On the other hand, Marburg or Ebola viruses are, despite their fearsome reputation, rather unsuitable, not only because those involved in their propagation are likely to succumb to them before achieving their goals, but also because of their low ability to survive outside the human body. Efforts are underway to develop refined methods for assessing the suitability of biological agents as bioweapons [6].

However, even such “impractical” agents might still be utilized, for it might be much more efficient to paralyze public health organs and healthcare systems through threats and alarms rather than doing much direct damage. Hoaxes were common in many countries

---

**Table 1** Classification system for potential biological agents [9]

Category A diseases/agents (e.g., Variola virus, <i>Bacillus anthracis</i> )
High-priority agents include organisms that pose a risk to national security because they:
- can be easily disseminated or transmitted from person to person
- result in high mortality rates and have the potential for major public health impact
- might cause public panic and social disruption
- require special action for public health preparedness
Category B diseases/agents (e.g., <i>Brucella</i> species, ricin toxin)
Second highest priority agents include those that:
- are moderately easy to disseminate
- result in moderate morbidity rates and low mortality rates
- require specific enhancements of diagnostic capacity and enhanced disease surveillance
Category C diseases/agents (e.g. drug resistant <i>M. tuberculosis</i> , Nipah virus)
Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of:
- availability
- ease of production and dissemination
- potential for high morbidity and mortality rates and major health impact

---

in the aftermath of the 2001 anthrax attacks, with numerous letters allegedly containing *B. anthracis* spores causing considerable disruption and costs. Cleverly planned arrangements pretending biological attacks can indeed wreak havoc and can cause great expense, particularly because of a lack of systems for the rapid and accurate detection of real bioterrorism incidents and their reliable distinction from hoaxes [3].

---

### Natural threats: lessons to be learned

#### West Nile virus

West Nile virus (WNV) emerged in the New World for the first time in late summer 1999 when an outbreak of human encephalitis occurred in New York, concurrent with extensive mortality in free-living crows as well as deaths of several exotic birds at a zoological park in the same area [7, 24].

The strain of WNV found in New York in 1999 was indistinguishable from one isolated 1 year earlier in Israel. How this virus covered such a vast distance is unknown; possibilities include importation of infected birds, infected mosquitoes, or viremic human beings [18, 20]. Although there is no evidence that the virus was introduced deliberately, it nonetheless would represent an extremely effective biological weapon. Despite intensive control efforts, WNV has now firmly established itself in the Americas, spreading across the continent and reaching the West coast, and so far has caused almost ten thousand of cases of clinical illness and hundreds of deaths in humans in the United States alone [11]. In addition, surveillance and control measures such as the implementation of blood-donor testing for WNV by polymerase chain reaction have caused enormous expenditure.

#### Severe acute respiratory syndrome

It can be difficult to distinguish between natural epidemics and possible bioweapon assaults. In the first half year of 2003, a novel infectious disease termed severe acute respiratory syndrome (SARS) impacted significantly on the medical and scientific world. With approximately 800 deaths in total, the SARS outbreak did not reach the number of annual influenza victims by far, but it nevertheless became the nightmare of public health systems all over the world.

In addition, SARS had grave social and economic consequences for several countries in East and Southeast Asia as well as in the Western world. In China, unemployment especially among the migrant workforce nearly doubled to over eight million; air traffic to Hong Kong fell by 80% in May 2003; tourism to Southeast Asia virtually came to a standstill; and in Canada, the loss of tourism and airport revenues amounted to \$950 million, \$570 million in Toronto alone [22].

Through an unprecedented level of international cooperation led by WHO, the agent responsible for this first epidemic of the new century was soon identified as a previously unknown coronavirus and the outbreak was brought under control within a few months [2]. Although the source of the new virus is still not known for sure, it is likely to be linked to the so-called “wet markets” of Southern China and not to have been caused by bioterrorist activity. Instead, SARS was another example of how infections may be triggered by agents originating in animals when they adapt to new hosts in whom they may cause dangerous diseases [21].

#### Monkeypox virus

Another virus so far limited to the Old World recently entered the Americas: In summer 2003, 72 humans were infected with monkeypox in the United States [27]. These cases were quickly linked to contact with pet animals, mostly prairie dogs, obtained from pet shops. While being held prior to sale to the public, these animals appear to have been infected through contact with Gambian giant rats and other animals originating in Ghana that were carrying the monkeypox virus [16]. Thus, the obviously badly conducted and poorly regulated international trade in wild animals was responsible for the introduction of a potentially very harmful pathogen from West Africa into the United States—at a time when mass vaccinations against smallpox were undertaken in military personnel and were (albeit with little success due to wide-spread refusal) envisaged for large numbers of civilians! Again, there is no evidence that anything but human ignorance and greed were at play, but this event again shows the potential for a bioweapon attack [12].

---

### Modified pathogens

To date, most discussions regarding the creation of a national biodefense strategy have focused largely on addressing existing threats posed by naturally occurring pathogens and toxins. With the advent of recombinant DNA technology, however, researchers have techniques at their disposal for altering an organism’s genetic makeup and thus biological properties. This might allow enhancing the usability of “traditional” biological warfare agents [31]. Therefore, genetically modified bioweapon agents have been classified as a separate category (advanced biological warfare agents, ABW) [25]. In addition to increasing a pathogen’s virulence [23], its ability to survive under different environmental conditions such as high temperature, ultraviolet radiation and desiccation could potentially be improved (Table 2); by enhancing dissemination, this might make some hitherto rather unsuitable candidate agents such as filoviruses more likely to be utilized.

**Table 2** Classification and characteristics of various biological agents of potential biowarfare interest, compiled from various sources, e.g. CDC, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), WHO, American Public Health Association (APHA). Ability to survive is given as: ↓ low, ← → moderate, ↑ high, ↑↑ very high, ↑↑↑ extremely high; infectiousness as: ↓↓ no transmission, ↓ transmission rare, ← → moderate, ↑ high, ↑↑ very high

Agent	CDC group	Ability to survive	Infectiousness
Alphaviruses	B	↓	↓
Arenaviruses	A	↓	↑↑
<i>Bacillus anthracis</i>	A	↑↑↑	↓↓
<i>Brucella species</i>	B	↑↑↑	↓
<i>Burkholderia mallei</i>	B	↑↑	↑↑
<i>Coxiella burnetti</i>	B	↑↑	↓
Filoviruses	A	↓	↑↑
<i>Francisella tularensis</i>	A	← →	↓↓
Yellow fever virus	C	↓	↓
Hantavirus	C	↓	← →
Nipahvirus	C	← →	↑
<i>Salmonella species</i>	B	← →	↑
<i>Mycobacterium tuberculosis</i> (MDR)	C	↑↑	↓
Variola major virus	A	↑↑	↑↑
<i>Vibrio cholerae</i>	B	← →	↑
<i>Yersinia pestis</i>	A	← →	↑↑

Not only will advances in biotechnology facilitate novel agents engineered to attack specific human biological systems at the molecular level, but they will permit modification of existing agricultural pathogens and the development of new anti-agricultural and even anti-material agents. Likewise, technology targeted towards development of transgenic plants and insects that produce a desired protein could also be diverted toward nefarious ends.

### The role of scientists

The more sophisticated the biowarfare agent to be developed, the more it requires in terms of highly skilled scientific staff and other personnel. But will such individuals be available? A study concerning the willingness of physicians to participate in the death penalty [14] is interesting in this context. It showed that one in five American physicians would be prepared to give the deadly injection to prisoners sentenced to death, 36% would establish the death of the offender, and 41% agreed to participate in the procedure in a subordinate way. It should therefore not come as a surprise if there were enough scientists to develop deadly and poisonous weapons, not only in the former USSR.

### Strategies for defense

Following the recent developments outlined above, the Center of Competence for Highly Contagious Diseases in Hesse, Germany, developed a catalogue listing fac-

tors to facilitate the detection of a biological attack. These include: unusual, unexpected clusters of cases (large numbers of patients with similar symptoms, a large number of unclear illnesses, unexplained increase in incidence of an endemic disease), an unusual distribution (appearance of the same agent from different geographical and temporal sources, clusters occurring in geographically distinct areas, etc.), unusual modes of spread (absence of typical vectors or reservoirs, unusual spread of an agent through water, air, food, or a vector), atypical clinical courses (unusually high morbidity and mortality for a given illness, failure of normally adequate therapy, etc.), unknown or atypical infectious agents (genetically modified, atypical, or currently non-endemic strain, etc.), indirect evidence for increases in disease incidence (e.g., increase in requests for certain laboratory tests or in prescriptions for certain antibiotics, etc.), and non-medical criteria (threats, intelligence information, etc.) [34].

There are indeed possibilities to defend society against attacks with suspected biological agents [37]. Besides assuring an heightened awareness among health care workers to increase the likelihood of early detection, letters can be humidified, for instance, to decrease the risk of aerosolization of the content, or they can be irradiated as done in some US post offices. In case of a real or doubtful contamination, there are pharmaceuticals, vaccines and therapeutic regimens available to treat exposed individuals [33].

It should not be forgotten either that efficient public health systems are able to fight epidemics successfully even in the absence of specific preventative measures such as vaccines, just by applying “good basic public health measures” [13], as was recently shown with SARS.

### Conclusions

Attacks with biological weapons are indeed a real threat and the responsible government agencies need to be aware of this. However, the actual likelihood of such attacks currently seems to be low compared to that of naturally emerging agents. An effective implementation of a national biosecurity strategy will require a variety of independent efforts across federal and public health organizations as well as bioscience research. There has to be a discussion whether the current cost-intensive smallpox vaccination programs are efficient. While the above-mentioned unwanted side effects were acceptable when there was still the danger of a smallpox epidemic, this is no longer true after its eradication. Neither does the immunity induced against the closely related cowpox or monkeypox viruses justify widespread vaccination with vaccinia virus, so that it should only be considered in case of an acute smallpox threat.

It is certainly beneficial to allocate grants for investigations into the ways in which microbiological agents change hosts and into virulence factors. On the



other hand we have to ensure that scientists comply with regulations and accept the ethical constraints of their activities, as well as apply the necessary safety precautions in their work [19]. Increased funding of bioweapon research programs will lead to more individuals with training and skills in this area and might thus have paradox effects [28]. Therefore, new initiatives to deal with broader threats that may result from misuse of technology need to be pursued, in parallel with existing and planned programs.

Ultimately, whenever novel infectious agents appear suddenly, it is probably inevitable that there will be speculations and rumors: that they were designed in biowarfare laboratories or emerged from biomedical research (as was argued for HIV), that they came from space (as suggested for SARS), or that they represent a bioterrorist attack. However, reality is more banal but nevertheless painful: Nature itself is the best bioreactor for apocalyptic biological agents and, through evolution, has at the same time developed the best defense strategies against them [30].

## References

- Beeching NJ, Dance DAB, Miller ARO, Spencer RC (2002) Biological warfare and bioterrorism. *Br Med J* 324:336–339
- Berger A, Drosten C, Doerr HW, Stürmer M, Preiser W (2004) Severe acute respiratory syndrome (SARS)—paradigm of an emerging viral infection. *J Clin Virol* 29:13–22
- Bravata DM, Sundaram V, McDonald KM, Smith WM, Szeto H, Schleinitz MD, Owens DK (2004) Evaluating detection and diagnostic decision support systems for bioterrorism response. *Emerg Infect Dis* 10:100–108
- Bundesministerium für Gesundheit und Soziale Sicherung (BMGS) Pressemitteilung 4/2003. Available at: [http://www.bmgs.bund.de/deu/gra/aktuelles/pm/bmgs03/bmgs4\\_4340.cfm](http://www.bmgs.bund.de/deu/gra/aktuelles/pm/bmgs03/bmgs4_4340.cfm) (accessed 25 May 2004)
- Bush LM, Abrams BH, Beall A, Johnson CC (2001) Index case of fatal inhalational anthrax due to bioterrorism in the United States. *N Engl J Med* 345:1607–1610
- Casadevall A, Pirofski LA (2004) The weapon potential of a microbe. *Trends Microbiol* 12:259–263
- Centers for Disease Control and Prevention (1999) Outbreak of West Nile-like viral encephalitis—New York, 1999. *MMWR Morb Mortal Wkly Rep* 48:845–849
- Centers for Disease Control and Prevention (2001) Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR Morb Mortal Wkly Rep* 50:889–893
- Centers for Disease Control and Prevention (2003) Bioterrorism Agents/Diseases; last modification November 19, 2003. Available at: <http://www.bt.cdc.gov/agent/agentlist-category.asp> (accessed 25 May 2004)
- Centers for Disease Control and Prevention (2003) Smallpox vaccination and adverse reactions: guidance for clinicians. *MMWR Morb Mortal Wkly Rep* 52:1–28
- Centers for Disease Control and Prevention (2004) 2003 West Nile virus activity in the United States (reported as of May 21, 2004). Available from [http://www.cdc.gov/ncidod/dvbid/west-nile/surv&controlCaseCount03\\_detailed.htm](http://www.cdc.gov/ncidod/dvbid/west-nile/surv&controlCaseCount03_detailed.htm) (accessed 12 July 2004)
- Di Giulio DB, Eckburg PB (2004) Human monkeypox: an emerging zoonosis. *Lancet Infect Dis* 4:15–25
- Dye C, Gay N (2003) Epidemiology: Modeling the SARS epidemic. *Science* 300:1884–1885
- Farber NJ, Aboff BM, Weiner J, Davis EB, Boyer EG, Ubel PA (2001) Physicians' willingness to participate in the process of lethal injection for capital punishment. *Ann Intern Med* 135:884–888
- Fenner F, Henderson DA, Arita I, Ježek Z, Ladnyi ID (1988) Developments in vaccination and control between 1900 and 1966. In: Smallpox and its eradication, chapter 7. World Health Organization, Geneva
- Guarner J, Johnson BJ, Paddock CD, Shieh WJ, Goldsmith CS, Reynolds MG, Damon IK, Regnery RL, Zaki SR, the Veterinary Monkeypox Virus Working Group (2004) Monkeypox transmission and pathogenesis in prairie dogs. *Emerg Infect Dis* 10:426–431
- Jernigan DB, Raghunathan PL, Bell BP, et al (2002) Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* 8:1019–1028
- Jia XY, Briese T, Jordan I, Rambaut A, Chi HC, Mackenzie JS, Hall RA, Scherret J, Lipkin WI (1999) Genetic analysis of West Nile New York 1999 encephalitis virus. *Lancet* 354:1971–1972
- Kelley M, Coghlan J (2003) Mixing bugs and bombs. *Bull Atom Sci* 59:24–31
- Lancioti RS, Roehrig JT, Deubel V, et al (1999) Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. *Science* 286:2333–2337
- Ludwig B, Kraus FB, Allwinn R, Doerr HW, Preiser W (2003) Viral zoonoses—a threat under control? *Intervirology* 46:71–78
- Monaghan K (2003) SARS down but still a threat. National Intelligence Council Intelligence Community Assessment, August 2003. Available at: [http://www.cia.gov/nic/special\\_sarsthreat.html](http://www.cia.gov/nic/special_sarsthreat.html) (accessed 25 May 2004)
- Müllbacher A, Lobigs M (2001) Creation of killer poxvirus could have been predicted. *J Virol* 75:8353–8355
- Nash D, Mostashari F, Fine A, et al (2001) The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 344:1807–1814
- Petro JB, Plasse TR, McNulty JA (2003) Biotechnology: impact on biological warfare and biodefense. *Biosecur Bioterror* 1:161–168
- Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or other Gases, and of Bacteriological Methods of Warfare (Geneva Protocol, 1925). Opened for signature: 17 June 1925, entered into force: 8 February 1928. Available at: <http://www.sussex.ac.uk/spru/hsp/Genev-Prot.html> (accessed 21 June 2004)
- Reed KD, Melski JW, Graham MB, et al (2004) The detection of monkeypox in humans in the Western hemisphere. *N Engl J Med* 350:342–350
- Richardson L (2004) Buying biosafety—is the price right? *N Engl J Med* 350:2121–2123
- Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM (2002) Public health assessment of potential biological terrorism agents. *Emerg Infect Dis* 8:225–230
- Rumyantsev SN (2004) The best defence against bioweapons has already been invented by evolution. *Infect Genet Evol* 4:159–166
- Spencer RC, Lightfoot NF (2001) Preparedness and response to bioterrorism. *J Infect* 43:104–110
- Takahashi H, Keim P, Kaufmann AF, Keys C, Smith KL, Taniguchi K, Inouye S, Kurata T (2004) *Bacillus anthracis* incident, Kameido, Tokyo, 1993. *Emerg Infect Dis* 10:117–120
- The European Agency for the Evaluation of Medicinal Products (2002) EMEA/CPMP guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism. CPMP/4048/01. Available at: <http://www.emea.eu.int/htms/human/bioterror/bioterror.htm> (accessed 18 July 2004)
- Wirtz A, Gottschalk R, Weber HJ (2003) Management of an attack with biological agents. Reflections on the necessary infrastructure for states and towns. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 46:1001–1009

35. World Health Organization (2002) Smallpox eradication: destruction of variola virus stocks. Report by the Secretariat. Available at: [http://www.who.int/gb/ebwha/pdf\\_files/WHA55/ea5521.pdf](http://www.who.int/gb/ebwha/pdf_files/WHA55/ea5521.pdf) (accessed 25 May 2004)
36. World Health Organization (2003) Laboratory safety manual. Second edition (revised). WHO/CDS/CSR/LYO/2003.4. Interim guidelines. World Health Organization, Geneva 2003
37. World Health Organization (2004) Public health response to biological and chemical weapons: WHO guidance, 2nd edn. World Health Organization, Geneva 2004. Available at: <http://www.who.int/csr/delibepidemics/biochemguide/en/> (accessed 18 July 2004)