Int Microbiol (2002) 5: 161–167
DOI 10.1007/s10123-002-0084-x

REVIEW ARTICLE

R.M. Atlas

Responding to the threat of bioterrorism: a microbial ecology perspective – the case of anthrax

Received: 15 March 2002 / Accepted: 20 April 2002 / Published online: 20 August 2002

Abstract Anthrax is a disease of herbivores caused by the gram-positive bacterium *Bacillus anthracis*. It can affect cattle, sheep, swine, horses and various species of wildlife. The routes for the spread among wildlife are reviewed. There are three kinds of human anthrax – inhalation, cutaneous, and intestinal anthrax – which differ in their routes of infection and outcomes. In the United States, confirmation of cases is made by the isolation of *B. anthracis* and by biochemical tests. Vaccination is not recommended for the general public; civilians who should be vaccinated include those who, in their work places, come in contact with products potentially contaminated with *B. anthracis* spores, and people engaged in research or diagnostic activities. After September 11, 2001, there were bioterrorism anthrax attacks in the United States: anthrax-laced letters sent to multiple locations were the source of infectious *B. anthracis*. The US Postal Service issued recommendations to prevent the danger of hazardous exposure to the bacterium. *B. anthracis* spores can spread easily and persist for very long times, which makes decontamination of buildings very difficult. Early detection, rapid diagnosis, and well-coordinated public health response are the key to minimizing casualties. The US Government is seeking new ways to deter bioterrorism, including a tighter control of research on infectious agents, even though pathogens such as *B. anthracis* are widely spread in nature and easy to grow. It is necessary to define the boundary between defensive and offensive biological weapons research. Deterring bioterrorism should not restrict critical scientific research.

Keywords *Bacillus anthracis* · Endospores · Bioterrorism · Biological weapons · Ciprofloxacin

R.M. Atlas
Department of Biology,
University of Louisville,
Louisville, KY 40292, USA
E-mail: r.atlas@louisville.edu
Tel.: +1-502-8526495
Fax: +1-502-8522365

Introduction

The post-September 11 anthrax attack on the United States has highlighted the importance of microbial ecology in responding to the threat of bioterrorism. Although anthrax is primarily a zoonotic disease that affects herbivores, it is transmissible to humans through handling or consumption of contaminated animal products. It is caused by the gram-positive, endospore-forming bacterium *Bacillus anthracis* (Fig. 1). The spores of *B. anthracis* can persist in soil, which is its natural reservoir, for many years. Inhalation of endospores by animals can lead to disease; spores can also enter via ingestion of contaminated foods or via wounds and are readily disseminated when carcasses of dead animals are scavenged. Anthrax is widespread in South and Central America, the Caribbean, Southern and Eastern Europe, Africa, Asia and the Middle East. An understanding of both the infectious process and the ecology of the causal agent can help to prevent the use of anthrax as a biological weapon.

Among livestock, anthrax most commonly affects cattle, sheep, swine, and horses. Anthrax also infects various species of wildlife. It is endemic in the Kruger National Park in South Africa, the Etosha National Park, Namibia, and probably in some of the other game parks in southern Africa, where sporadic small or larger outbreaks affect a wide variety of species of wildlife from time to time; significant cyclical outbreaks occurring about every 10 years. Anthrax affects baboon, lion, leopard, cheetah, elephant, hippopotamus, zebra, warthog, bushpig, giraffe, African buffalo, and all antelopes–especially kudu.

Among African wildlife, there are three distinct epidemiological routes for the spread of anthrax: (1) The kudu/blowfly cycle. Blowflies feed on the body fluids of infected carcasses of kudu and then alight on leaves of nearby plants, often at heights of 1–2 m above the ground, which is the same height at which kudu graze. Defecation and droplet deposition by the blowflies

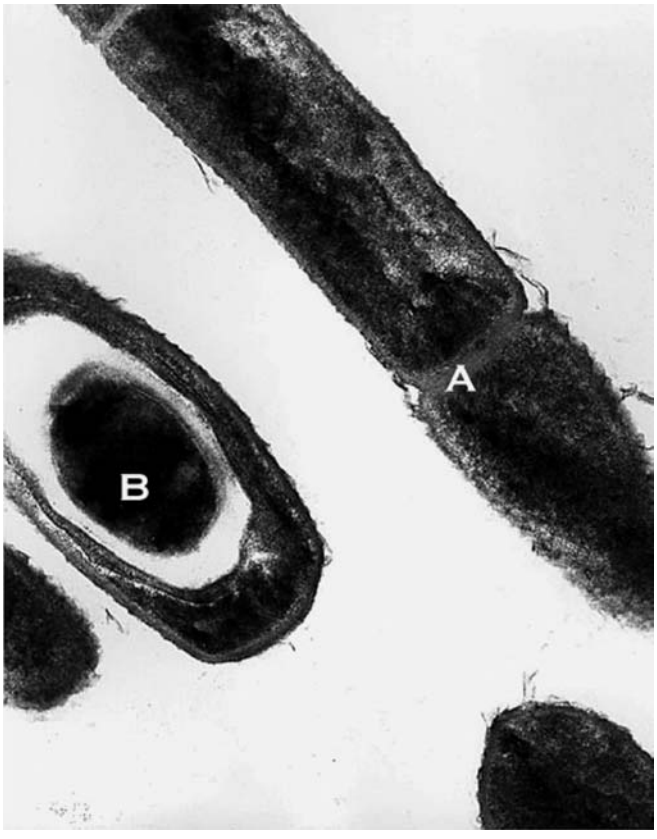

Fig. 1 Transmission electron micrograph of *Bacillus anthracis* from an anthrax culture, showing cell division (**A**), and spores (**B**)

contaminate the leaves and lead to transmission of *B. anthracis* to grazing kudu. Blowflies also lay eggs in the decaying carcasses of kudu so that as the pupae develop they also acquire spores of *B. anthracis*. Thus, the cycle of transmission of anthrax continues and amplifies. (2) The vulture/water hole route. Vultures that have fed on contaminated carcasses in turn contaminate watering holes. Vultures actually kill vegetative forms of *B. anthracis* as the bacterial cells pass through the vulture's digestive system, but spores survive and are disseminated by fecal deposition and via contaminated feet and feathers of the vulture. Thus, there is continuous contamination of the water holes with spores of *B. anthracis*. Any wildlife drinking the contaminated water can then become infected. African buffalo and elephants are especially susceptible to this route of transmission as they frequent watering holes in large numbers and often stir up the sediment. Many infected animals die near the watering hole, increasing the likelihood of transmission via this route. (3) Direct carcass-predator cycle of transmission. Lions, leopards, jackals, and wild dogs can ingest billions of spores of *B. anthracis* while feeding on infected prey. Therefore, epidemics of anthrax can impact a variety of wildlife animals. Seasonal and regional differences in rates of anthrax-associated mortalities reflect the underlying ecological distribution of spores of *B. anthracis*. The widespread natural distribution of *B. anthracis* endospores means that this deadly bacterium can readily be acquired from nature.

Facts about anthrax

Bacillus anthracis produces three toxin components, protective antigen, lethal factor, and edema factor [21], and a capsule that are critical for its high virulence [14]. Vegetative bacteria have poor survival expectancies outside an animal or human host, colony counts declining to undetectable within 24 h following incubation into water [27]. This contrasts with *B. anthracis* spores, which can survive for decades [Friedlander AM (2001) Anthrax. http://www.armymedicine.army.mil/history/borden/cwbw].

The three forms of human anthrax are: inhalation anthrax, cutaneous or skin anthrax, and intestinal anthrax. They differ entirely by the route of infection and have very different outcomes. Cutaneous anthrax, which is the most common form (95%), results from inoculation of spores under the skin. After incubation for a few hours to 7 days, a small papule forms that gives rise to an ulcer surrounded by vesicles (24–28 h). The formation of a painless eschar with edema follows; the death rate in untreated cases is less than 20% and almost all individuals treated with antibiotics recover. Ingestion of contaminated meat results in gastrointestinal anthrax, which is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea. The rate of fatality is estimated to be 25–60%. Inhalation of spores from animals or wool from infected animals, resulting in inhalation anthrax, is highly fatal even when treated with antibiotics. After incubation of 1–43 days (maybe longer), initial influenza-like symptoms including fever, cough, myalgia, and malaise develop; these are followed by high fever, dyspnea, cyanosis, hemorrhagic mediastinitis/pleural effusion and rapid progression to shock/death. Anthrax is not a contagious disease. Person-to-person transmission of inhalation anthrax is highly improbable, thus no quarantine procedures are necessary. There is no need to immunize or treat contacts of persons ill with anthrax, such as household contacts, friends, or coworkers, unless they were also exposed to the same source of infection.

In the mid-1800s, inhalation anthrax related to the textile industry became known as wool-sorters' disease (in England) and rag-pickers' disease (in Germany and Austria) because of the frequency of infection in mill workers exposed to imported animal fibers contaminated with *B. anthracis* spores. In the early 1900s, human cases of inhalation anthrax occurred in the United States in conjunction with the textile and tanning industries. Of the 18 cases of inhalation anthrax reported in the United States in the twentieth century [5–8, 10, 16, 18–20,23], most were related to exposure to animal products, primarily in textile mills processing goat hair,

goatskins, or wool. In the last decades of the twentieth century, with improved industrial hygiene practices and restrictions on imported animal products, the number of cases fell dramatically [3].

According to the Centers for Disease Control and Prevention (CDC), a confirmed case of anthrax is defined as a clinically compatible case of cutaneous, inhalational, or gastrointestinal illness that is laboratory-confirmed by isolation of *B. anthracis* from an affected tissue or site, or other laboratory evidence of *B. anthracis* infection. Regarding the detection of anthrax spores, a variety of methods are being employed. At its simplest level, a number of clinical laboratories are screening samples by microscopy for the presence or absence of structures resembling the spores of *Bacillus* species. This can help rule out the possible presence of *B. anthracis*. Additional culture methods are being used in which swabs of environmental samples and human nasal swabs are used to inoculate media that permit the growth of *B. anthracis*. After 24 h the media are examined for the presence of colonies typical of *B. anthracis*. This bacterium is non-motile, so the colonies do not spread, and also non-hemolytic, so blood cells included in the medium do not lyse and thus there is no zone of clearing around the colonies. Clinical laboratories use additional conventional biochemical tests for the identification of pathogens, including *B. anthracis* (Fig. 2).

The CDC has issued interim guidelines for the management of exposed individuals and antimicrobial therapy regimes for those with cutaneous and inhalation anthrax. For both inhalation and cutaneous anthrax, ciprofloxacin and doxycycline are the first-line therapies [3, 14, 17]. The inappropriate use of antibiotics, however, can produce adverse reactions and be worse than the actual threat of anthrax.

Anthrax vaccine

Vaccination of livestock, often with the non-capsulated, avirulent Sterne strain, is used to prevent the spread of anthrax. As long as vaccination is carried out, there is effective control of this disease. But because of the environmental persistence of *B. anthracis*, the danger always exists that anthrax will occur if adequate vaccination is not carried out. This became evident in Zimbabwe in the late 1970s when war interrupted the vaccination program and a major epizootic of anthrax occurred among cattle.

Many grazing animals are protected against anthrax by vaccination, but the vaccine used for livestock is not the same as the human vaccine. Vaccination against anthrax is not recommended for the general public to prevent disease and is not available. The anthrax vaccine licensed for human use in the United States is a cell-free filtrate that contains protective antigen and alum. The vaccine is reported to be 93% effective in protecting against cutaneous anthrax. Animal studies have

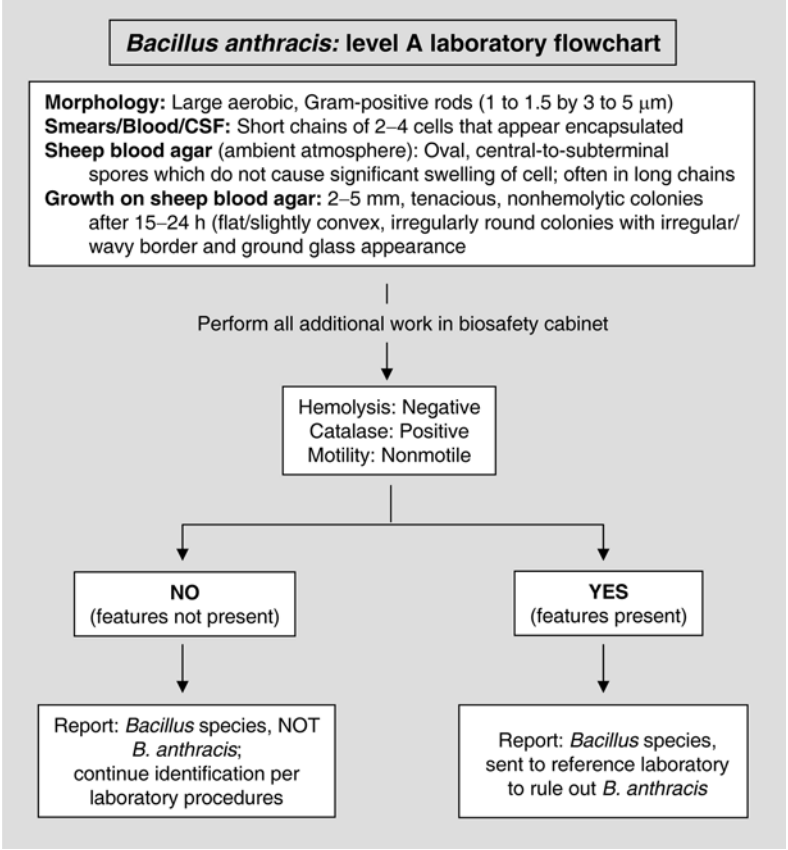

Fig. 2 *Bacillus anthracis* identification flowchart. From clinical samples, such as blood, CSF, or lesion material: encapsulated gram-positive rods with spores that are non-swelling and oval shaped, as well as the ground-glass appearance of colonies that are non-motile and non-hemolytic yields a presumptive identification of *B. anthracis*

suggested vaccine may also be protective against aerosol challenge. The anthrax vaccine is distributed by BioPort Corporation (Lansing, Michigan). Because *B. anthracis* is considered a potential biological warfare threat agent, the US Department of Defense recommends anthrax vaccination of all US active duty military personnel. According to the Advisory Committee for Immunization Practices (ACIP), civilians who should receive anthrax vaccine include people who, in their workplaces, come in contact with imported animal hides, furs, bonemeal, wool, animal hair (especially goat hair) and bristles, as well as people engaged in diagnostic or research activities that may put them in contact with anthrax spores. The vaccine should be administered only to healthy men and women aged 18–65 years since all studies to date have been conducted exclusively in that population. Pregnant women should not be vaccinated, because it is not known whether the anthrax vaccine can cause fetal harm.

The anthrax vaccination protocol consists of three subcutaneous injections given 2 weeks apart followed by three additional subcutaneous injections given at 6, 12, and 18 months. Annual booster injections of the vaccine are required to maintain immunity. Approximately 30% of recipients have mild local reactions consisting of slight tenderness and redness at the injection site of the skin. A moderate local reaction can occur if the vaccine is given to anyone with a past history of anthrax. Severe local reactions consisting of extensive swelling of the forearm in addition to the local reaction can occur infrequently. Systemic reactions characterized by flu-like symptoms occur from less than 0.2% of vaccinations [3, 15, 28].

Bioterrorism after September 11

After the first September 2001 anthrax attacks, many felt that increased acts of terrorism coupled with the easy acquisition and mass-production of many lethal microorganisms and toxins meant that bioterrorism was an inevitable reality [1, 4, 11, 12, 13, 26]. In the wake of these bioterrorist anthrax attacks, there has been a need to provide information to the public and the medical community about anthrax. The following is taken largely from several previous reports on the etiology, pathology, epidemiology, and identity of anthrax [9, 22, 25] and from CDC releases about the disease that were posted at the CDC Web site http://www.bt.cdc.gov during October 2001 [3]. The CDC has been made responsible for controlling the shipment of pathogens and toxins that were deemed most likely for potential misuse as biological weapons Table 1 lists those agents whose transport and manipulation are regulated by the CDC [2].

What is known is that on September 18, 2001, one week after the hijacked airplanes crashed into the World Trade Center and the Pentagon, anthrax-laced letters were sent from Trenton, New Jersey, to the *New York Post* and NBC Broadcasting Studios in New York City. A letter may also have been sent at that time to American Media in Boca Raton, Florida and to other media outlets. By September 21, an editorial assistant at the *New York Post* showed signs of cutaneous anthrax. A day later, a worker at the Hamilton, New Jersey, postal distribution center, where letters from Trenton would

Table 1 Select agents whose shipment is regulated by the CDC under the Antiterrorism and Effective Death Penalty Act of 1996 [2]

Viruses[a]	*Yersinia pestis*
Crimean-Congo hemorrhagic fever virus	*Coxiella burnetiiRickettsia prowazekii*
Eastern equine encephalitis virus	*Ricketsia rickettsii*
Ebola virus	**Fungi**
Equine morbillivirus	*Coccidioides immitis*
Lassa fever virus	**Toxins**[c]
Marburg virus	Abrin
Rift Valley fever virus	Aflatoxins
South American hemorrhagic fever viruses (Junin, Machopa, Sabia, Flexal, Guanarito)	Botulinum toxins
Tick-borne encephalitis complex viruses	*Clostridium perfringens* epsilon toxin
Variola major virus (smallpox virus)	Conotoxins
Venezuelan equine encephalitis virus	Diacetoxyscirpenol
Viruses causing hantavirus pulmonary syndrome	Ricin
Yellow fever virus	Saxitoxin
Bacteria[b]	Shigatoxin
Bacillus anthracis	Staphylococcal enterotoxins
Brucella abortus, *B. melitensis*, *B. suis*	Tetrodotoxin
Burkholderia (*Pseudomonas*) *mallei*	T-2 toxin
Burkholderia (*Pseudomonas*) *pseudomallei*	
Francisella tularensis	

[a]Exemptions: vaccine strains of viral agents (Junin virus strain candid, Rift Valley fever virus strain MP–12, Venezuelan equine encephalitis virus strain TC–83, and yellow fever virus strain 17–D) are exempt
[b]Exemptions: vaccine strains as described in Title 9 CFR, 78.1 are exempt
[c]Exemptions: Toxins for medical use. Inactivated for use as vaccines, or toxin preparations for biomedical research use at an LD_{50} for vertebrates of more than 100 ng per kg of body weight are exempt. National standard toxins required for biologic potency testing as described in 9 CFR Part 113 are exempt

have passed, also showed the first signs of cutaneous anthrax. A few days later, a mail-room worker at American Media showed possible signs of inhalation anthrax. Robert Stevens of America Media also developed signs of inhalation anthrax; the diagnosis of anthrax was confirmed on October 4 and he died the following day, becoming the first tragic victim of the anthrax bioterrorism attack. Additional cases of cutaneous anthrax occurred among a few New Jersey postal workers and among several people associated with the news media in New York City.

These cases clearly showed the airborne spread of *B. anthracis* spores causing inhalation anthrax and that contact with contaminated surfaces was causing the less serious form of cutaneous anthrax. On October 9, additional anthrax-laced letters were sent to Senators Tom Daschle and Patrick Leahy at their Congressional Offices. Following the opening of the Daschle letter, numerous Senate office workers were placed on prophylactic ciprofloxacin or doxycycline treatment. The Hart Senate Office Building was closed for months and all Senate mail was sealed – including the letter to Senator Leahy, which was not discovered for many weeks. Still the impending risk to postal workers was not yet realized and postal workers were not given prophylactic antibiotics. A week later, several postal workers at the District of Columbia Brentwood postal facility developed inhalation anthrax– two died. Additional postal workers at the Hamilton, New Jersey, facility also developed anthrax but recovered. Subsequently, a woman in New York City, not associated with the media or postal facilities, developed a fatal case of inhalation anthrax, as did a 94-year old Connecticut woman. These individuals may have been exposed through cross-contaminated mail that had passed through the Hamilton, New Jersey, postal sorting facility.

By mid November, 17 cases of anthrax – seven of the cutaneous form and ten of inhalation anthrax, four of which were fatal – had been detected (Table 2). Of the ten inhalation anthrax cases, seven occurred in postal employees in New Jersey and the District of Columbia who had probably been exposed to letters known to be contaminated with *B. anthracis* spores. Of the affected people, two were employees of a media company in Florida: one is believed to have received contaminated mail, the other to have sorted and distributed that mail. The last case was a resident of New York city, and the nature of her exposure to *B. anthracis* remains unknown. Another fatal case subsequently occurred in Connecticut in which secondary contamination of a letter that passed through the New Jersey mail sorting center is suspected as the source of infection [3].

There was widespread fear across the nation. Many people imagined they had been exposed, and numerous hoaxes fueled the hysteria as fear of the mail spread. The US Postal Service issued recommendations to try to reduce the dangers:

- Do not handle the mail piece or package suspected of contamination.
- Damaged or suspicious packages should be isolated and the immediate area cordoned off.
- All persons who have touched the mail piece should wash their hands with soap and water.
- Notify local law enforcement authorities.
- List all persons and their contact information who have touched the letter and/or envelope for the authorities.
- Place all items worn when in contact with the suspect mail piece in plastic bags for law enforcement agents.
- As soon as practical, shower with soap and water.
- Contact CDC Emergency Response with any questions.

Bioterrorists do not need to rely upon culture collections to supply potential bioweapons. In the post-September 11 anthrax bioterrorism events in the United States, however, it appears that a bioterrorist acquired the Ames strain, which had been initially cultured from a dead cow in Texas and deposited with the US Army Lab in Maryland. The strain was subsequently transferred to the US Army Infectious Disease Research Laboratory (USAMRIID), which distributed it to other government laboratories within the United States and Britain. The British laboratory at Porton Down also sent it to Louisiana State University, so that at least five laboratories were known to have received the Ames strain. Somehow, a bioterrorist also acquired the Ames strain. (At the writing of this article, both the identity of the bioterrorist and the source of the Ames strain are unknown.)

The powerful contamination by spores

Clearly, biological weapons have the potential for causing mass casualties. The estimation of casualties from a hypothetical biological attack with several microorganisms is shown in Table 3 [3].

In retrospect, it is clear that spores of 1–2 μm can pass directly through an envelope. This apparently was

Table 2 Number of cases of anthrax, by site, September-October 2001 [Center for Disease Control and Prevention (2001) Update: Investigation of bioterrorism-related anthrax and adverse events from antimicrobial prophylaxis, 50:973–976]

	Florida	New York City	District of Columbia	New Jersey	Connecticut	Total
Inhalation confirmed	2	1	5	2	1	11
Cutaneous confirmed	0	6	0	5	0	11
Total	2	7	5	7	1	22

Table 3 Estimates of casualties from a hypothetical biological attack based upon the release of 50 kg of various agents by an aircraft flying along a 2-km path upwind of a city of half a million people [WHO Group of Consultants (1970) Health aspects of chemical and biological weapons. WHO, Geneva]

Diseases	Casualties	Fatalities
Brucellosis	125,000	500
Q fever	125,000	150
Tularemia	125,000	30,000
Anthrax	125,000	95,000

known to some within the bioweapons research community. Canadian researchers had warned as early as October 4, 2001, that spores of *B. anthracis* could pass through the walls of tightly sealed envelopes. But this risk was not recognized within the public health community as the CDCs and others responded to the anthrax attack. Nor was it known to the broader scientific community that the spores in the Daschle and Leahy letters had been refined to produce "weaponized anthrax," with reduced electrostatic charge so that the spores acted more like a gas than a particle. As the postal sorting machines pressed against the envelopes, clouds of spores spread through the postal facility and also contaminated machinery and subsequent letters. Later investigations indicated that the spores did not adhere to surfaces in an irreversible manner as had previously been thought. Thus, months after contamination at the Hart Senate Office Building spores still readily became airborne and spread with minimal disturbance.

Given the threat posed by contaminated mail and buildings, investigations were quickly carried out to determine effective decontamination procedures. Studies at the British bioweapons defense facility at Porton Down had shown that 41.5 kGray of irradiation could kill 99.9% of the spores of *B. anthracis*. The US postal system turned to electron-beam technology to irradiate mail and eliminate any threat of viable anthrax spores. This has proven difficult, in part because of the geometry of electron-beam technology for generating sufficient radiation energy and in part because of the heat generated in the process; some mail has caught fire and burned. Also, given the bulk of US mail that is processed daily, there is no sufficient electron-beam capacity. Thus, most mail is untreated.

Building contamination represented an additional problem. Several attemps to eliminate viable anthrax spores from the Hart Senate Office Building using chlorine dioxide fumigation initially failed. Eventually, by adjusting the humidity, the building was decontaminated and reopened. Nearly a year later, attempts are being made to decontaminate the postal facilities that were heavily contaminated by the letters sent to Senators Daschle and Leahy. Given that it may be nearly impossible to eliminate all viable spores, an important question remains – what is the concentration of anthrax spores needed to cause a fatal infection of inhalation anthrax? Based on animal studies and epidemiological investigation following the 1979 accidental release of anthrax spores from a bioweapons facility at Sverdlosk (currently, Ekaterinburg, Russia) in the former Soviet Union, it had been thought that exposure to 8,000–10,000 spores was necessary to cause inhalation anthrax. But the deaths in New York City and Connecticut suggest that a much lower concentration could suffice, especially in the elderly or in immuno-suppressed individuals. Thus, the level of decontamination necessary to protect fully the health of workers in contaminated buildings is unknown.

Measures to deter bioterrorism

Hence, at what seems to be the end of this wave of the anthrax attack, we can pause to ask what we know and what we have learned. Clearly, we are extremely vulnerable to bioterrorist attacks. Even a few contaminated letters and a relatively few cases can wreak panic across the nation. We have also learned that spores are easily spread and very persistent. There are means of disinfection, but these are difficult. There are also means of prophylaxis and treatment that can greatly reduce lethality. Early detection, rapid diagnosis, and a well-coordinated public health response are critical for minimizing casualties. Preparedness is key to protecting against bioterrorism.

Yet, even as the investigation to find who sent the anthrax-laced letters continues, the US Government is seeking new ways of deterring bioterrorism. Major research funding will be available to find vaccines and drugs that will ensure that the population is protected against the major biothreat agents, including anthrax and smallpox. Many of these vaccines and drugs will be stockpiled and used only in the event of a bioterrorist attack. New environmental detectors will be developed and deployed that will provide warning of a bioterrorist attack. Access to select agents will be much more carefully controlled in the United States. The Select Agent Rule already controls the shipment of 36 select agents. The US Patriot Act, signed into law on October 26, 2001, also restricts certain individuals from possessing select agents, including those from countries designated by the United States as supporting terrorism. Soon anyone possessing select agents in the United States will have to register and gain authorization for possession. Anyone in possession of a biological agent must have a legitimate reason – those possessing any biological agent for other than legitimate diagnostic or bona fide research activities face severe criminal penalties.

To be effective, these regulations for access to dangerous pathogens will need to be extended to other nations. Harmonization of shipping of select agents is a responsible means of lowering the risk of bioterrorism that can be accomplished without having a serious impact on legitimate research activities. Even though such measures will not eliminate totally the risk of bi-

oterrorism, because pathogens such as *B. anthracis* are widely distributed in nature, they are nevertheless appropriate responsible measures that scientists should support to reduce the risk of a repeat of the 2001 anthrax attacks on the United States.

Microbial ecologists need to extend the defenses against bioterrorism to protect water, plants, and animals. Future bioterrorist attacks could target a nation's agricultural and environmental resources rather than directly targeting humans. We need to strengthen the Biological Weapons Convention to ensure compliance with the edicts – never, under any circumstances, to develop, produce, stockpile, or otherwise acquire or retain microbial or other biological agents, or toxins in quantities that have no justification for peaceful purposes; not to transfer agents, toxins, weapons, equipment, or means of delivery of biological weapons to others; and to take necessary measures to prohibit and prevent the development or acquisition of biological weapons by a nation's military or citizens. We need to do so without impeding the necessary research for improving our scientific understanding of the environment and the world in which we live. We need to define the boundary between defensive and offensive biological weapons research. In addition, we must deal with claims, including those of the Sunshine Project, that oil and plastic biodegradation and bioremediation research as well as biological control of plant pests are forms of biological warfare that are banned under the Biological Weapons Convention. The Sunshine Project is particularly concerned about the biological control efforts that might be used to control illicit-drug plants. Members view efforts in the United States to find an effective means for biological control of coca plants as biological warfare against Columbia, and against poppy plants as biological warfare against Afghanistan that justified the September 11 attacks. We need to reject such radical claims against the efforts of microbial ecologists to find effective solutions to the world's pollution problems. We must strengthen the means of deterring bioterrorism without causing a chilling effect on critical scientific research.

Acknowledgements Figure 1 comes from The Public Health Image Library and the CDC/Dr. Sherif Zaki/Elizabeth White. Figure 2 is based on Fig. A1 of the "Basic diagnostic testing protocols for Level A laboratories for the presumptive identification of *Bacillus anthracis*" [http://www.bt.cdc.gov/Agent/Anthrax/LevelAProtocol/ban-la-cp-031802.pdf (downloaded March 18, 2002)].

References

1. Atlas RM (1998) The medical threat of biological weapons. Crit Rev Microbiol 24:157–168
2. Atlas RM (1998) Biological weapons pose challenge for microbiology community. ASM News 64:383–389
3. Atlas RM (2001) Bioterrorism before and after September, 11. Crit Rev Microbiol 27:355–379
4. Barnaby W (1997) Biological weapons: an increasing threat. Med Confl Surviv 13:301–313
5. Brachman P, Pagano J, Albrink W (1961) Two cases of fatal inhalation anthrax, one associated with sarcoidosis, N Engl J Med 265:203–208
6. Brooksher W, Briggs J (1920) Pulmonary anthrax: report of a case JAMA 74:323–324
7. Cowdery J (1947) Primary pulmonary anthrax with septicemia. Arch Pathol 43:396–399
8. Fletcher J (2000) Human Anthrax in the United States: a descriptive review of case reports, 1955–1999. Rollins School of Public Health, Atlanta, Georgia
9. Franz DR, Jahrling PB, Friedlander A, et al. (1997) Clinical recognition and management of patients exposed to biological warfare agents. JAMA 278:399–411
10. Gold H (1955) Anthrax: a report of one hundred seventeen cases. Arch Intern Med 96:387–396
11. Hansen JE (1999) Viruses, bacteria, and toxins as biological warfare. Urgeskr Laeger 161:772–775 [In Danish]
12. Henderson DA (1998) Bioterrorism as a public health threat. Emerg Infect Dis 4:488–492
13. Henderson DA (1999) The looming threat of bioterrorism. Science 283:1279–1282
14. Inglesby TV, Henderson DA, Barylett JG, et al. (1999) Anthrax as biological weapon. Medical and public health management. Working group on civilian biodefense. JAMA 281:1735–1745
15. Ivins BE, Fellows PF, Pitt MLM, et al. (1996) Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol challenge in rhesus monkeys. Salisbury Med Bull 87(Suppl.):125–126
16. Krane S (1957) Cases from the medical grand rounds of the Massachusetts General Hospital, case 388: sinusitis due to anthrax. Amer Pract Dig Treat 8:1628–1636
17. Kelly DJ, Chulay JD, Mikesell P, Friedlander AM (1992) Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. J Infect Dis 166:1184–1187
18. Laforce F (1978) Woolsorter's disease in England. Bull NY Acad Sci 54:956–963
19. LaForce F, Bumford B, Feeley JC, Stokes SL, Snow DB (1969) Epidemiologic study of a fatal case of inhalation anthrax. Arch Environ Health 18:798–805
20. Levinsky W, Anderson T, Ricardson G (1954) Inhalation anthrax meningitis and bacillemia: a case report. In: Proceedings of the Symposium on Anthrax in Man. Philadelphia, Pennsylvania, pp 96–103
21. Liddingtong RC (2002) The crystal structure of the final component of the three part anthrax toxin using that molecule to stimulate its own activity. Nature 415:373–374
22. Pile JC, Malone JD, Eitzen EM, Friedlander AM (1998) Anthrax as a potential biological warfare agent. Arch Intern Med 158:429–434
23. Plotkin S, Brachman P, Utell M, Bumford F, Atchison M (1960) An epidemic of inhalation anthrax, the first in the twentieth century, I. Clinical features. Am J Med 29:992–1001
24. Schupp JM, Klevytska AM, Zinser G, Price LB, Keim P (2000) *vrrB*, a hypervariable open reading frame in *Bacillus anthracis*. J Bacteriol 182:3989–3997
25. Shafazand S, Doyle R, Ruoss S, Weinacker A, Raffin TA (1999) Inhalational anthrax: epidemology, diagnosis, and management. Chest 116:1369–1376
26. Slater MS, Trunkey DD (1997) Terrorism in America. An evolving threat. Arch Surg 132:1059–1066
27. Titball RW, Turnbull PC, Hutson RA (1991) The monitoring and detection of *Bacillus anthracis* in the environment. J Appl Bacteriol 70(Suppl.):S9–S18
28. Turnbull PC (1991) Anthrax vaccines: past, present and future. Vaccine 9:533–539