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Bioterrorism 12

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Bioterrorism, broadly defined as the deliberate and malicious deployment of microbial agents or their toxins as weapons in a non-combat setting, represents perhaps the most overt example of human behavior impacting epidemic infectious diseases (Artenstein, 2004a). While most of the microbial threat agents of potential use in bioterrorism occur naturally in various ecological niches throughout the world, they are rare and sporadic causes of human disease in developed countries and urban environments. It is human behavior within the context of the extant geopolitical milieu that transforms these naturally-occurring organisms into potential weapons of mass terror.

There is historical precedent for the use of biological agents against both military and civilian populations. It is postulated that the fifth plague visited upon Pharaoh in approximately 1450 BC, "murrained carcasses… pestilence," signified cutaneous anthrax (Plaut, 1981). In the fourteenth century, Tartar invaders probably introduced the Black Death to Caffa by catapulting plague-infected corpses into the besieged Crimean city for that explicit purpose (Wheelis, 2002). British forces in mid-eighteenth century colonial America, under the command of Lord Jeffrey Amherst, distributed blankets and clothing used by smallpox victims to Native American tribes in an attempt to affect the balance of power during the French and Indian wars (Christopher *et al*., 1997); it remains unclear whether these fomites resulted in contact transmission of smallpox to naïve hosts or whether the Native Americans were infected by direct contact with infected colonists.

The use of biological (and chemical) agents as weapons of war has been well documented (Christopher *et al*., 1997). The German biological warfare program during World War I included covert infections of Allied livestock with anthrax and glanders. The Japanese army began conducting experiments on the effects of bacterial agents of biowarfare on Chinese prisoners in occupied Manchuria in 1932 at their infamous Unit 731; thousands of individuals were killed as a result of these experiments, which continued until 1945 (Harris, 1994). The United

States began its own offensive biological weapons program in 1942 and, during its 28-year official existence, weaponized and stockpiled lethal biological agents, such as anthrax, as well as incapacitating agents, such as the etiologic agent of Q fever (Christopher *et al*., 1997).

The US program was ended by two presidential executive orders in 1969 and 1970; stockpiled weapons were destroyed by mandate from 1971–1973 (Christopher *et al*., 1997). However, small quantities of pathogens were stored at Fort Detrick, Maryland, for biodefense research purposes. In 1972, under the auspices of the United Nations, the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (BWC) was ratified with more than a hundred signatory nations, including the US and the Soviet Union (Christopher *et al*., 1997).

Although a party to the BWC, the government of the Soviet Union apparently continued to weaponize biological agents at least through the mid-1990s (Alibek, 1999). There is direct evidence that the Soviets deployed weaponized ricin, a biological toxin, to carry out covert assassinations during the 1970s (Christopher *et al*., 1997). Additionally, the corroborated statements of multiple high-level government defectors confirm decades of persistent Soviet violation of the BWC. Perhaps the most egregious example of these violations arose from the revelation, years after the event occurred, that an epidemic of inhalational anthrax in Sverdlovsk in 1979, responsible for the deaths of at least 66 people, resulted from the accidental release of weaponized spores from a biological weapons plant (Guillemin, 1999).

Other more recent examples of bioterrorism, though not necessarily resulting in attacks causing morbidity or mortality, may serve as harbingers of future events. Saddam Hussein's regime in Iraq developed and deployed anthrax- and botulinum-laden warheads in the years leading up to the Gulf War (Zilinskas, 1997); the reasons that these weapons were never used in an actual attack probably had more to do with the implicit threat of overwhelming US retaliation and Iraqi technological deficiencies rather than the regime's reluctance to violate any moral principles. Biological agents have also been used to forward political ideologies: in 1984 a religious cult, intent on influencing voter turnout during a local election, contaminated restaurant salad bars in The Dalles, Oregon, with *Salmonella*, resulting in over 750 cases of gastroenteritis among patrons, employees, and their contacts (Torok *et al*., 1997). This event, coupled with revelations that the Japanese cult Aum Shinrikyo had attempted, multiple times, to release weaponized anthrax before their successful release of sarin nerve agent in the Tokyo subway system in 1995 (Olson, 1999), provides compelling evidence of the terrorist potential of these agents.

The catastrophic events of 11 September 2001 clearly ushered in a new era of global terrorism. The massive, simultaneous, and dramatic attacks on unarmed citizens in New York and Washington illustrate, convincingly, the mounting

boldness of terrorists and their willingness to commit "unthinkable" acts. The anthrax attacks that followed 9/11 in the US killed 5 and sickened 17 additional people, and served to underscore the shifting sands of terrorism (Jernigan *et al*., 2001). While these bioterror attacks have never been directly linked to the events of 9/11, their temporal connection reinforces the persistent global threat posed by bioterrorism.

Social determinants of bioterrorism: the concept of "risk"

Any discussion of bioterrorism, and certainly one that involves mitigation strategies, hinges on the concept of "risk." "Risk" refers to the likelihood that exposure to a hazard will lead to a negative consequence; therefore, it is essential to understand both the threat and the potential range of consequences associated with bioterrorism in order to accurately assess risk in this regard (Ropeik and Gray, 2002). When applied to cause-specific mortality, risk can be viewed in a purely statistical sense: the risk of dying from cardiovascular disease in the US in the year 2000 was approximately 1 in 400, while the risk of succumbing in a lightning strike was approximately 1 in 4.5 million (Table 12.1). In the arenas of human biology and medicine, however, risk assessment is based on the complex interplay of genetics, environmental factors, and chance. Risk as it relates to bioterrorism is difficult to quantify; while the probability of exposure to a biologic attack is statistically low, it is not zero, and the consequences are potentially catastrophic. This, coupled with the fact that the likelihood of actual

Table 12.1 US mortality risk analysis for selected public health concerns

Heart disease	1 in 397
Cancer	1 in 511
Stroke	1 in 1699
Alzheimer's	1 in 5.752
Motor vehicle accident	1 in 6745
Homicide	1 in 15,440
Drowning	1 in 64,031
Fire	1 in 82,977
Bicycle accident	1 in 376,165
Lightning strike	1 in 4,478,159
Bioterrorism (anthrax)	1 in 56,424,800

Source: Artenstein, 2006; Harvard Center for Risk Analysis, http://www.hcra.harvard.edu/ © 2004 CBEP.

hazard exposure is dependent on the whims of terrorists (and therefore an unpredictable variable), renders accurate risk assessment impossible.

Geopolitics and the "psyche" of terrorists

The opening act of the modern era of terrorism dates from 1972, when the Palestinian terrorist group Black September murdered 11 members of the Israeli Olympic team and a German police officer in Munich (Post, 2005). As the event played out, the enormous amplifying effect of international media coverage was recognized and serves as a legacy for today's terrorists. Three types of terror organizations have since been recognized: social-revolutionary groups, nationalist-separatist groups, and, more recently, religious fundamentalists. Social-revolutionary groups, as exemplified by the Red Brigades in Italy and the Red Army Faction in Germany, are leftist groups with strong ties to Communist parties seeking to overthrow the extant capitalist economic and social order. With the collapse of Communism in Europe and the end of the Cold War, their activity has dramatically declined.

Nationalist-separatist terrorism organizations are one of the two types seen commonly today. These groups are fighting to establish a new political order or state based on ethnic identity. They are influenced by the struggle of earlier generations to gain independence from a perceived oppressive regime, and their acts of terrorism are focused on this regime or its allies. Examples of such organizations include the Provisional Irish Republican Army of Northern Ireland (PIRA), the Basque separatist group Euskadi ta Askatasuna (ETA), the secular Palestinian organization al-Fatah, and the Liberation Tigers of Tamil Eelam (LTTE) in Sri Lanka (Arena and Arrigo, 2005).

The most influential type of organization with regard to US foreign policy appears to be religious fundamentalist terrorists, illustrated by organizations such as Al-Qaeda and Islamic Jihad. The goal of these organizations is broader in scope, in that they want not only to change the local political situation but also to expel representatives of the secular world from their lands. In the case of Islamic fundamentalist terrorists, their aim is to rid their society of Western influences. Islam is considered to be a comprehensive system that guides all aspects of life and gives meaning and direction to social, legal, and political systems (Wiechman, *et al*., 1994). Western global influence, particularly the development of Western-style secularism in Islamic countries, is seen as an affront to the existence of Islamic societies.

Western colonization was responsible for the early development of Islamic fundamentalism. This movement is in large part traced to Hasan al-Banna, who came to believe that the nineteenth- and twentieth-century colonialism in the Middle East and the subsequent diffusion of secular ideas and Western values in the region had served to erode the fabric of Islam (Abu-Amr, 1993; Mitchell,

1993). As a response he formed the Egyptian Muslim Brotherhood in 1928, dedicated to re-establishing an Islamic state in which the tenets of the religion and the precepts of Islamic *shariah* (holy law) were both firmly established (Moussalli, 1998). As the movement evolved, the scope broadened to the establishment of a fundamentalist Islamic world-view (Davidson, 1998). In this way, a movement that began as predominantly Arab and anti-colonial has now become pan-Islamic, drawing from the entire, diverse, global Muslim population, in excess of 1 billion people. Al-Qaeda has emerged as the leading proponent of this new ideology, with its focus on both the local and worldwide struggle for influence.

Unique to these groups is the decision-making role of a pre-eminent leader who is generally thought to have insight to God's will. Actions sanctioned by the leader are thereby endowed with sacred significance, thus explaining the fervor with which group members kill innocent non-believers. Because their motivation is to expel Western secular values and create a pure Islamic state, they believe their actions are sanctioned by the *Koran* and not constrained by Western morals; they are willing to do the "unthinkable," including the use of biological agents as weapons (Post *et al*., 2003). Their enemies are anyone who is opposed to their worldview. While the primary goal is to attack symbolic targets that reflect the secular decadence of Western life and attract media attention, many attacks are conducted against smaller secondary targets, due to greater accessibility. A novel aspect of these terrorist's tactics is the focus on killing as many innocent people as possible. As illustrated by the 1998 US embassy bombings in Tanzania and Kenya, an additional objective appears to be the influencing of geopolitics through the induction of widespread fear in communities throughout the world where Western interests are present (Borum and Gelles, 2005).

Threat assessment: bioterrorism in the overall terrorism context

Biologic agents are considered to be "weapons of mass destruction" (WMD) because, as with nuclear and chemical weapons, their use may result in potential mortality on a massive scale. Bioterrorism occupies a unique niche among WMD (Table 12.2); exposure to biologic agents entails a clinical incubation period of days to weeks during which time recognition of an attack is problematic (assuming a covert attack), detection of a specific agent is difficult, and infection may disseminate widely among a population. This is in contradistinction to other forms of WMD, where recognition of an actual "event" occurs with the deployment, allowing mitigation strategies to begin nearly immediately. The difference is important, as specific therapeutic or prophylactic measures may be available in bioterrorism, as opposed to simply general decontamination and supportive measures used in other arenas of terrorism response.

Table 12.2 A comparison of weapons of mass terror

	Conventional	Biological	Chemical	Nuclear
Area involved	Limited	Moderately large	Moderate	Large
Rapid detection	Easy	Difficult	Moderate	Easy
Clinical incubation	Immediate	Days to weeks	Minutes to hours	Varies with dose
Medical Rx	Limited	Effective v some	Limited	Limited
Cost	High	Low	Low	Very high
Terror potential	High	Very high	Very high	Very high

Multiple factors likely contribute to the attractiveness of biological agents as tools of terrorism: they are relatively inexpensive, available, and the technology for their production is generally accessible (Bhalla and Warheit, 2004); these agents can be aerosolized, deployed in occult fashion, and cause lethal or disabling disease in exposed individuals, and their impact may be amplified by long distance travel of aerosols (depending on extant environmental conditions) and the potential for person-to-person transmission. Perhaps of greatest utility from a terrorist perspective is that the specter of bioterrorism provokes fear and anxiety – "terror" – that is disproportionate to that seen with other forms of WMD. For this reason, it may be more fitting to consider these agents as "weapons of mass terror."

Vulnerability to bioterrorism is invariable in nations adhering to democratic principles. This is largely because of the freedom of movement and the access to public institutions that is afforded in such societies; terrorists intent on committing malicious acts can exploit these liberties.

The Center for Nonproliferation Studies has identified at least 11 nations with either known (e.g. former Soviet states, pre-war Iraq) or probable (e.g. Iran, China, North Korea) offensive bioweapons programs (Center for Nonproliferation Studies at the Monterey Institute of International Studies, 2002). Much of the underlying technical expertise for such programs may have derived from freelance scientists who became available for hire after the dissolution of the Soviet Union (Alibek, 1999). Because the technology needed for bioterrorism is "dual use," in that it can serve legitimate functions such as vaccine or pharmaceutical production, rogue states may either resist or be insulated from international scrutiny, as occurred in pre-Gulf War Iraq (Zilinskas, 1997).

The aims of bioterrorism are similar to those of other forms of terrorism: morbidity and mortality among civilians, disruption of social fabrics through panic and fear, and exhaustion or diversion of resources (Artenstein, 2006). However, a successful outcome from a terrorist's standpoint may be achieved without

furthering all of these aims. The anthrax attacks in the United States in 2001 disrupted society and diverted scarce resources from other critical public health activities despite a limited number of casualties.

To be used in large-scale events, bioterrorism agents must undergo complex processes of production, chemical modification, and weaponization. Thus, state sponsorship or the support of organizations with significant resources and infrastructure would likely be necessary for the execution of substantial or multifocal attacks. However, recent revelations suggest the availability of bioweapons on the global black market (Miller *et al*., 2001), and their relative simplicity, availability, and portability may make them preferable to expensive conventional or nuclear weapons for small, well-resourced terrorist organizations or even isolated terrorist cells. As demonstrated by the US anthrax attacks in 2001, bioterrorism attacks can be successful using only low-technology delivery methods such as the postal system.

The prospect of bioterrorism has been fueled by progress in the fields of molecular biology and biotechnology. While these advances have led to the possibility of new vaccines, medications, diagnostics, and genetic therapies to alleviate human disease, they have also introduced the potential to modify biological agents for malicious intent (Franz and Zajtchuk, 2002). Therefore the dissemination of information on developments in molecular biology, considered to be necessary to advance science, can serve the unintended dual purpose of providing terrorists with a virtual blueprint for developing genetically altered "designer" bioweapons, including hybrid organisms or drug-resistant mutants (Rappert, 2003). For example, publication of the genetic sequence of the 1918 influenza virus (Taubenberger *et al*., 2005), and its reconstruction from viral RNA using reverse genetics (Tumpey *et al*., 2005), while important to understand the pathogenesis of pandemic influenza, has raised concerns that terrorists might recreate the virus. Finally, our advancing knowledge of human genetics may have a dark side: the potential opportunity for terrorists to engineer biological agents targeted against our genomic vulnerabilities (Petro *et al*., 2003).

Epidemiologic principles as applied to bioterrorism

A World Health Organization (WHO) model based on the hypothetical effects engendered by the intentional release of 50 kilograms of aerosolized anthrax spores upwind from a population center of 500,000, a moderate-sized city, estimated that the agent would disseminate in excess of 20 kilometers downwind and that between 84,000 and 210,000 people would be killed or injured by the event, depending on whether the area was in a developed or developing country (WHO, 1970). The complete WHO theoretical analysis showed that casualty estimates depend on the properties of specific pathogens, the environmental setting, and the host population.

Numerous attributes contribute to the selection of a pathogen as a biologic weapon: availability of seed material; ease of cultivation; feasibility of large-scale production; capacity for aerosolization; stability of the product in storage, as a weapon, and in the environment (biologic entities differ in their physical properties); technology for dissemination; cost; and clinical virulence (Artenstein, 2004a). The latter refers to the consistency with which a biological agent causes high mortality, morbidity, and social disruption, and its intrinsic transmission characteristics. The Centers for Disease Control and Prevention (CDC) have prioritized biologic agent threats based on the aforementioned characteristics (CDC, 2000); the major purpose of this classification is to direct and focus public health preparedness strategies (Table 12.3). Category A agents, considered the highest priority, are those associated with high mortality and the greatest potential for major impact on the public health. Additionally, category A agents have been demonstrated to be capable of wide dissemination or person-to-person transmission. Category B agents are moderately high priority concerns. They may be considered "incapacitating" agents because of their potential for moderately high morbidity, but relatively low mortality. Most of the category A and B agents were experimentally weaponized and tested by the former Soviet Union, and are thus of proven feasibility (Alibek, 1999). Category C agents include emerging threats and pathogens that may be available for development into bioweapons in the future. As previously discussed, the potential exploitation of scientific progress by terrorists should prompt innovative thinking as it pertains to risk assessment and public health response. It is critical to be cognizant of future novel threats based upon engineered emergent or re-emergent pathogens (Madsen and Darling, 2006). Towards this end, the current authors have added a miscellaneous grouping of potential threat agents to the extant CDC categories (Table 12.3).

By definition, bioterrorism is insidious; absent of advance warning or specific intelligence information, clinical illness will be manifest before the circumstances of a release event are known. For this reason, health-care providers are likely to be the first responders to this form of terrorism, as symptomatic individuals present for medical attention. This contrasts with the more familiar scenarios in which police, firefighters, paramedics, and other emergency services personnel – traditional first responders – are deployed to the scene of a conventional attack or natural disaster. Physicians and other health-care workers must therefore maintain a high index of suspicion of bioterrorism and recognize suggestive epidemiologic clues and clinical features in order to enhance early recognition, optimize the initial management of casualties, and minimize the amplifying effect on the population (Artenstein *et al*., 2002a).

Early recognition is hampered for multiple reasons. As discussed above, it is likely that the circumstances of any event will only be known in retrospect; therefore it may prove problematic immediately to discern the extent of exposure. Terrorists have an unlimited number of targets in most open, democratic

Table 12.3 Agents of concern for use in bioterrorism

Highest priority (Category A)	
Microbe or toxin	Disease
Bacillus anthracis	Anthrax
Variola virus	Smallpox
Yersinia pestis	Plague
Clostridium botulinum	Botulism
Fracisella tularensis	Tularemia
Filoviruses	Ebola hemorrhagic fevers, Marburg disease
Arenaviruses	Lassa fever, South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever, Congo-Crimean hemorrhagic fevers
Moderately high priority (Category B)	
Coxiella burnetti	Q fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Alphaviruses	Viral encephalitides
Ricin	Ricin intoxication
Staphylococcus aureas enterotoxin B	Staphylococcal toxin illness
Salmonella spp., *Shigella dysenteriae, Escherichia coli* O157:H7, *Vibrio cholerae, Cryptosporidium parvum*	Food- and water-borne gastroenteritis
Category C	
Hantavirus	Viral hemorrhagic fevers
Flaviviruses	Yellow fever
Mycobacterium tuberculosis	Multi-drug resistant tuberculosis
Miscellaneous	
Genetically engineered vaccine- and/or antimicrobial-resistant category A or B agents	
HIV-1	
Adenoviruses	
Influenza	
Rotaviruses	
Hybrid pathogens (e.g. smallpox–plague, smallpox–ebola)	

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societies; it is unrealistic to expect that, without detailed intelligence data, all of these can be secured at all times. Government institutions, historic landmarks, or large social events may be predictable targets, but there are other, less predictable possibilities. US Department of State data reveal that businesses and other economic interests were the main targets of global terrorism during the period from 1996 to 2001 (US Department of State, 2002). Metropolitan areas are considered vulnerable, but, owing to the expansion of suburbs, commuters, and the clinical latency period between exposure and symptoms inherent with biologic agents, casualties of bioterrorism are likely to present for medical attention in diverse locations and at varying times after common exposures. A covert bioterrorism attack in New York City on a Wednesday morning may result in clinically ill persons presenting for medical attention over the ensuing weekend to a variety of emergency departments, urgent care centers, and physician offices within a 60-mile (~100-km) commuter radius. Additional cases may be seen hundreds or thousands of miles away at both national and international locations as infected, mobile individuals make use of modern modes of transportation during the clinical incubation period. This adds layers of complexity to an already complicated setting, and illustrates the critical importance of surveillance and real-time communication in this setting.

Further hindering the early recognition of bioterrorism is that the initial symptoms of many of the high priority agents may be non-diagnostic. In the absence of a known exposure, many symptomatic persons may either not seek medical attention early, or if they do they may be misdiagnosed as having a flu-like or other benign illness. Once beyond the early stages many illnesses related to bioterrorism progress rapidly, and treatment may be less successful. Because most of the diseases caused by agents of bioterrorism are rarely (if ever) seen in clinical practice, physicians are likely to be inexperienced with their clinical characteristics; physicians were only able to correctly diagnose diseases due to category A agents 47 percent of the time in one multicenter study (Cosgrove *et al*., 2005). Additionally, these agents will by definition have been manipulated in a laboratory, and those affected may not present with the classic clinical features seen in naturally occurring infection. This was dramatically illustrated by some of the inhalational anthrax cases in the United States (Jernigan *et al*., 2001).

Early recognition of bioterrorism is facilitated by the recognition of epidemiologic and clinical clues. Clustered presentations of patients with common symptoms and signs may suggest a common exposure source, and should prompt expeditious notification of local public health authorities. Aside from capturing the low-probability event of bioterrorism, this approach will also lead to enhanced recognition of outbreaks of naturally occurring disease, or those due to emerging pathogens. The recognition of a single case of a rare or non-endemic infection, in the absence of an appropriate travel history or other potential natural exposure, should raise the suspicion of bioterrorism and should prompt notification of public health authorities. Finally, unusual patterns of disease, such as

an acute, fulminant febrile illness in an otherwise healthy young individual, or concurrent illness in human and animal populations, should raise suspicions of bioterrorism or another novel, emerging infection. Since multifocal attacks are expected, attention must be paid to effective, ongoing communication between public health jurisdictions to ensure that a single unusual case is not viewed in a vacuum, as it may not represent an isolated event. An effective response to bioterrorism requires coordination of the medical system at all levels, from the community physician to the tertiary care center, with public health, emergency management, and law enforcement contributions.

Threat agents

CDC category agents are those biologic threat agents thought to be of major public health concern. Extensive coverage of these and other pathogens of concern in bioterrorism can be found elsewhere (Sidell *et al*., 1997). Data concerning clinical incubation periods, transmission characteristics, and infection control procedures for selected agents of bioterrorism are provided in Table 12.4. Syndromic differential diagnoses for select clinical presentations are detailed in Table 12.5.

Table 12.4 Infection control issues for selected agents of bioterrorism

Disease	Incubation period	Person-to-person transmission	Infection control practices
Inhalation of anthrax	2–43* days	No	Standard
Botulism	12–72 hours	No	Standard
Primary pneumonic plague	1–6 days	Yes	Droplet
Smallpox	7–17 days	Yes	Contact and air-borne
Tularemia	1–14 days	No	Standard
Viral hemorrhagic fevers	2–21 days	Yes	Contact and air-borne
Viral encephalitides	1–14 days	No	Standard
Q fever	2–14 days	No	Standard
Brucelloses	5–60 days	No	Standard
Glanders	10–14 days	No	Standard

*Based on limited data from human outbreaks; experimental animal data support clinical latency periods of up to 100 days
Source: Artenstein (2003), reproduced with permission.

Table 12.5 Syndromic differential diagnoses of selected bioterrorism agents

Clinical presentation	Disease	Differential diagnosis
Non-specific flu-like symptoms with nausea, emesis; cough with or without chest discomfort, without coryza or rhinorrhea, leading to abrupt onset of respiratory distress with or without shock; mental status changes, with chest radiograph abnormalities (wide mediastinum, infiltrates, pleural effusions)	Inhalational anthrax	Bacterial mediastinitis, tularemia, Q fever, psittacosis, Legionnaires' disease, influenza, *Pneumocystis carinii* pneumonia, ruptured aortic aneurysm, superior vena cava syndrome, histoplasmosis, coccidioidomycosis, sarcoidosis
Pruritic, painless papule, leading to vesicle(s), leading to ulcer, leading to edematous black eschar with or without massive local edema and regional adenopathy and fever, evolving over 3–7 days	Cutaneous anthrax	Recluse spider bite, plague, staphyloccal lesion, atypical Lyme disease, orf, glanders, tularemia, rat-bite fever, ecthyma gangrenosum, rickettsial pox, atypical mycobacteria, diphtheria
Rapidly progressive respiratory illness with cough, fever, rigors, dyspnea, chest pain, hemoptysis; possible gastrointestinal symptoms; lung consolidation with or without shock	Primary pneumonic plague	Severe community-acquired bacterial or viral pneumonia, inhalational anthrax, inhalational tularemia, pulmonary infarct, pulmonary hemorrhage
Sepsis, disseminated intravascular coagulation, purpura, acral gangrene	Septicemic plague	Meningococcemia, Gram-negative, streptococcal, pneumococcal or staphylococcal bacteremia with shock; overwhelming postsplenectomy sepsis, acute leukemia, Rocky Mountain spotted fever, hemorrhagic smallpox, hemorrhagic varicella (in immunocompromised patients)

(*Continued*)

Table 12.5 (Continued)

Clinical presentation	Disease	Differential diagnosis
Fever, malaise, prostration, headache, myalgias followed by development of synchronous, progressive papular leading to vesicular and then pustular rash on face, mucous membranes (extremities more than the trunk); rash may become generalized, with a hemorrhagic component and system toxicity	Smallpox	Varicella, drug eruption, Stevens-Johnson syndrome, measles, secondary syphilis, erythema multiforme, severe acne, meningococcemia, monkeypox, generalized vaccinia, insect bites, Coxsackie virus infection, vaccine reaction
Non-specific flu-like illness with pleuropneumonitis; bronchiolitis with or without hilar lymphadenopathy; variable progression to respiratory failure	Inhalational tularemia	Inhalational anthrax, pneumonic plague, influenza, mycoplasma pneumonia, Legionnaires' disease, Q fever, bacterial pneumonia
Acute onset of afebrile, symmetric, descending flaccid paralysis that begins in bulbar muscles; dilated pupils, diplopia or blurred vision; dysphagia; dysarthria; ptosis; dry mucous membranes leading to airway obstruction with respiratory muscle paralysis; clear sensorium and absence of sensory changes	Botulism	Myasthenia gravis, brain-stem cerebrovascular accident, polio, Guillain-Barrè syndrome variant, tick paralysis, chemical intoxication
Acute-onset fevers, malaise, prostration, myalgias, headache, gastrointestinal symptoms, mucosal hemorrhage, altered vascular permeability, disseminated intravascular coagulation, hypotension leading to shock with or without hepatitis and neurologic findings	Viral hemorrhagic fever	Malaria, meningococcemia, leptospirosis, rickettsial infection, typhoid fever, borrelioses, fulminant hepatitis, hemorrhagic smallpox, acute leukemia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, systemic lupus erythematosus

Source: Artenstein (2003), reproduced with permission.

Anthrax

Anthrax results from infection with *Bacillus anthracis*, a Gram-positive, spore-forming, rod-shaped organism that exists in its host as a vegetative bacillus and in the environment as a spore. In nature, anthrax is a zoonotic disease of herbivores that is ubiquitous in the soil of many geographic regions; sporadic human disease results from environmental or occupational contact with endospore-contaminated animal products (Dixon *et al*., 1999). The cutaneous form of anthrax is the most common presentation of naturally-occurring disease; gastrointestinal and inhalational forms are exceedingly rare. Cutaneous anthrax occurred regularly in the first half of the twentieth century in association with contaminated hides and wools used in the garment industry, but it is uncommonly seen in current-day industrialized countries due to importation restrictions. The last known case of naturally occurring inhalational anthrax in the US occurred in 1976 (Suffin *et al*., 1978).

It is ironic that, as American policies and regulations alleviated the risk of industrial outbreaks of anthrax, latter-day governmental policies may have shifted that risk to bioterror-related outbreaks. What was once an occupational disease of slaughterhouse workers, ranchers, and mill workers has now become an occupational hazard of politicians, journalists, postal workers, and the public at large (Witkowski and Parish, 2002). Prevailing wisdom had previously held that a large-scale bioterrorism attack with anthrax would employ aerosolized endospores and result in outbreaks of inhalational disease. The attacks in the US in 2001 illustrate the difficulties in predicting modes and outcomes in bioterrorism: the attacks were on a relatively small scale, and while endospores were used, the delivery method – envelopes – resulted in a significant proportion of cutaneous cases (Inglesby *et al*., 2002). However, as with the Sverdlovsk outbreak in 1979, the serious morbidity and mortality in the US attacks were related to inhalational disease. Thus, it still seems warranted to plan for larger-scale events with aerosolized agents.

The clinical presentations and differential diagnoses of cutaneous and inhalational anthrax are described in Table 12.5. The lesion of cutaneous anthrax may be similar in appearance to other lesions, including cutaneous forms of other agents of bioterrorism such as tularemia or glanders; however, it may be distinguished by epidemiologic as well as certain clinical features. Unless secondarily infected, anthrax is traditionally a painless lesion and associated with significant local edema. The bite of *Loxosceles reclusa*, the brown recluse spider, shares many of the local and systemic features of anthrax, but is typically painful from the outset and lacks such significant edema (Freedman *et al*., 2002). Cutaneous anthrax is associated with systemic disease and its attendant mortality in up to 20 percent of untreated cases, although with appropriate antimicrobial therapy mortality is less than 1 percent (Inglesby *et al*., 1999).

Once the inhaled endospores reach the terminal alveoli of the lungs, generally requiring particle sizes of 1–5μm, they are phagocytosed by macrophages and transported to regional lymph nodes, where they germinate into vegetative bacteria

and subsequently disseminate hematogenously (Dixon *et al*., 1999). Spores may remain latent for extended periods of time in the host, up to 100 days in experimental animal exposures (Henderson *et al*., 1956). This correlates with the potential for prolonged clinical incubation periods after exposure to endospores; cases of inhalational anthrax occurred up to 43 days after exposure in the Sverdlovsk experience (Meselson *et al*., 1994). The calculated incubation period based on the known dates of exposure in 6 of the 11 cases of inhalational anthrax from 2001 ranged from 4 to 6 days (Jernigan *et al*., 2001), and from 1 to 10 days for the cutaneous cases (Bell *et al*., 2002). Studies in non-human primates suggest the incubation period is influenced by exposure inoculum (Dixon *et al*., 1999; Inglesby *et al*., 2002).

Prior to the US anthrax attacks in October 2001, most of the clinical data concerning inhalational anthrax derived from Sverdlovsk – the largest previous outbreak recorded. Although there is much overlap among the clinical manifestations noted in both outbreaks, more detailed data are available from the recent US experience. Mailed letters containing anthrax spores in late September and early October of 2001 from a still-unidentified terrorist source(s) resulted in 22 cases of bioterrorism-associated anthrax (Lucey, 2005). Of these, 11 were of the cutaneous form; 11 were confirmed persons with inhalational anthrax, 5 (45 percent) of whom died. Although this contrasts with a case-fatality rate of greater than 85 percent reported from Sverdlovsk, the reliability of reported data from this outbreak is questionable (Inglesby *et al*., 2002).

Patients almost uniformly presented an average of 3.3 days after symptom onset, with fevers, chills, malaise, myalgias, non-productive cough, chest discomfort, dyspnea, nausea or vomiting, tachycardia, peripheral neutrophilia, and liver enzyme elevations (Jernigan *et al*., 2001; Barakat *et al*., 2002). Many of these findings are non-diagnostic and overlap considerably with those of influenza and other common viral respiratory tract infections, rendering clinical diagnosis problematic in the absence of a known outbreak. Recently compiled data suggest that shortness of breath, mental status abnormalities, nausea, and vomiting are significantly more common in anthrax, whereas rhinorrhea and sore throat are uncommonly seen in anthrax, but noted in the majority of viral respiratory infections (CDC, 2001; Hupert *et al*., 2003).

Other common clinical manifestations of inhalational anthrax, as informed by the 2001 outbreak, include abdominal pain, headache, mental status abnormalities, and hypoxemia. Abnormalities on chest radiography appear to be universally present, although these may only be identified retrospectively in some cases (Jernigan *et al*., 2001). Pleural effusions appear to be the most common abnormality; infiltrates, consolidation, and/or mediastinal adenopathy/widening are also noted in the majority. The latter is thought to be an early indicator of disease, but computed tomography was more sensitive than chest radiography for this finding.

Clinical manifestations of inhalational anthrax generally evolve to a fulminant septic picture with progressive respiratory failure and shock. *B. anthracis* is routinely isolated in blood cultures if obtained before the initiation of antimicrobials.

Pleural fluid is typically hemorrhagic; bacteria can either be isolated in culture or documented by antigen-specific immunohistochemical stains of this material in the majority of patients (Jernigan *et al*., 2001). The average time from hospitalization until death was three days (range 1–5 days) in the US series, consistent with other reports of the clinical virulence of this infection. Autopsy data typically reveal hemorrhagic mediastinal lymphadenitis and disseminated metastatic infection. Pathology data from the Sverdlovsk outbreak confirm meningeal involvement, typically hemorrhagic meningitis, in 50 percent of disseminated cases (Abramova *et al*., 1993). Meningitis was the presenting manifestation in the index anthrax case in 2001 (Bush *et al*., 2001).

The diagnosis of inhalational anthrax should be entertained in the setting of a consistent clinical presentation in the context of a known exposure, a possible exposure, or epidemiologic factors suggesting bioterrorism (e.g. clustered cases of a rapidly progressive illness). The diagnosis should also be considered in a single individual with a consistent or suggestive clinical illness in the absence of another etiology. The early recognition and treatment of inhalational anthrax is likely to be associated with a survival advantage (Jernigan *et al*., 2001); however, patients appear to evolve rapidly to a late stage of infection in which survival appears unlikely (Lucey, 2005). Therefore, prompt empiric antimicrobial therapy should be initiated if infection is clinically suspected.

Combination parenteral therapy is appropriate in the ill person for a number of reasons – to cover the possibility of antimicrobial resistance, to target specific bacterial functions (e.g. the theoretical effect of clindamycin on toxin production), to ensure adequate drug penetration into the central nervous system, and perhaps to favorably affect survival (Jernigan *et al*., 2001; Lucey, 2005). In the future, it is likely that novel therapies such as toxin inhibitors or receptor antagonists will be available, in combination with antimicrobials, to treat anthrax (Artenstein *et al*., 2004; Opal *et al*., 2005; see also Friedlander, 2001). Detailed therapeutic and postexposure prophylaxis recommendations for adults, children, and special groups have been recently reviewed elsewhere (Inglesby *et al*., 2002; Lucey, 2005). Anthrax vaccine adsorbed has been proved to be effective in preventing cutaneous anthrax in human clinical trials, and in preventing inhalational disease after aerosol challenge in non-human primates (Friedlander *et al*., 1999). The current vaccine has generally been found to be safe, but requires six doses over 18 months with the need for frequent boosting. Its availability is currently limited, although it is hoped that second-generation anthrax vaccines, currently in clinical trials, will prove effective.

Smallpox

The last known naturally acquired case of smallpox occurred in Somalia in 1977; the disease was officially declared eradicated in 1980, the culmination of

a 12-year intensive campaign undertaken by the WHO (Fenner *et al*., 1988). At that time all laboratories involved in the global eradication effort were asked to voluntarily destroy or relocate their variola virus stocks to the CDC and the State Research Center of Virology and Biotechnology in Russia (Rotz *et al*., 2005). However, because of concerns that variola virus stocks may have either been removed from, or sequestered outside of, their officially designated repositories, smallpox is today considered to be a potential bioterror threat. It is a cruel irony of the modern world that perhaps mankind's greatest triumph over nature – the eradication of smallpox – could be undone, volitionally and maliciously, by man.

Multiple features make smallpox an attractive biologic weapon and ensure that its reintroduction into human populations would be a global public health catastrophe: it is stable in aerosol form with a low infective dose; case fatality rates are historically high, approaching 30 percent; secondary attack rates among unvaccinated close contacts are 37 percent to 88 percent and are amplified; and much of the world's population is susceptible, as routine civilian vaccination was terminated more than three decades ago, vaccine-induced immunity wanes over time, and there is no virus circulating in the environment to provide low-level booster exposures (Breman and Henderson, 2002). Additionally, vaccine supplies are currently limited, although this problem has begun to be addressed, and there are currently no antiviral therapies of proven effectiveness against this pathogen.

After an incubation period of 7–17 days (average 10–12 days), the patient experiences the acute onset of a prostrating prodrome of fever, rigors, headache, and backache that may last 2–3 days. This is followed by a centrifugally distributed eruption that generalizes as it evolves through macular, papular, vesicular, and pustular stages in synchronous fashion over approximately eight days, with umbilication in the latter stages (Fenner *et al*., 1988). Enanthema in the oropharynx typically precedes the exanthem by a day or two. The rash typically involves the palms and soles early in the course of the disease. The pustules begin crusting during the second week of the eruption; separation of scabs is usually complete by the end of the third week. The differential diagnosis of smallpox is delineated in Table 12.5. Historically, varicella and drug reactions have posed the most problematic differential diagnostic dilemmas (Breman and Henderson, 2002).

Smallpox is transmitted person-to-person by respiratory droplet nuclei and, less commonly, by contact with lesions or contaminated fomites. Historically, therefore, most transmission has resulted from prolonged face-to-face contact, such as within families or health-care settings. Air-borne transmission by fine-particle aerosols has, under certain conditions, been documented (Wehrle *et al*., 1970). The virus is communicable from the onset of the enanthema until all of the scabs have separated, although transmissibility is thought to peak during the first week of the rash due to high titers of replicating virus in the oropharynx (Henderson *et al*., 1999). Thus, hospitalized cases are placed in negative-pressure

rooms with contact and air-borne precautions; cases that do not require hospital-level care should remain isolated at home to avoid infecting others.

The suspicion of a single smallpox case should prompt immediate notification of local public health authorities and infection-control specialists. Containment of smallpox is predicated on the "ring vaccination" strategy, which was successfully deployed in the WHO global eradication campaign and mandates the identification and vaccination of all directly exposed persons, including close contacts, health-care workers, and laboratory personnel. Vaccination, if deployed within four days of infection during the early incubation period, can significantly attenuate or prevent disease and may reduce secondary transmission (Henderson *et al*., 1999). Because variola virus does not exist in nature, and legitimate stocks were confined to the two sites in the US and Russia, the occurrence of even a single case of smallpox outside of an accidental laboratory exposure would be tantamount to bioterrorism. An epidemiologic investigation would be necessary to ascertain the perimeter of the initial release, so that tracing of initially exposed persons could be accomplished.

Botulism

Botulism, an acute neurologic disease resulting from intoxication with *Clostridium botulinum*, occurs sporadically and in focal outbreaks throughout the world, related to wound contamination by the bacterium or ingestion of food-borne toxin (Bleck, 2005). Aerosol forms of the toxin, while a rare mode of acquisition in nature, have been weaponized for use in bioterrorism (Zilinskas, 1997). Botulinum toxin is considered to be the most toxic molecule known; it is lethal to humans in minute quantities. It acts by blocking the release of the neurotransmitter acetylcholine from presynaptic vesicles, thereby inhibiting muscle contraction (Arnon *et al*., 2001). Botulism therefore possesses a number of attributes of concern: it is lethal in small quantities; it has been successfully weaponized in the past; and its deployment by terrorists could paralyze a health-care system.

Botulism presents clinically as an acute, afebrile, symmetric, descending, flaccid paralysis. The disease manifests initially in the bulbar musculature, and is unassociated with mental status or sensory changes. Fatigue, dizziness, dysphagia, dysarthria, diplopia, dry mouth, dyspnea, ptosis, ophthalmoparesis, tongue weakness, and facial muscle paresis are early findings seen in more than 75 percent of cases (Arnon *et al*., 2001). Progressive muscular involvement leading to respiratory failure may ensue. The clinical presentations of food-borne and inhalational botulism are indistinguishable in experimental animals (Arnon *et al*., 2001).

The diagnosis of botulism is largely based on epidemiologic and clinical features and the exclusion of other possibilities (see Table 12.5). Clinicians should recognize that any single case of botulism could be the result of sporadic food-borne exposure, the sentinel case of a larger-scale "natural" outbreak, or a

bioterrorism attack. A large number of epidemiologically unrelated, multifocal cases should be clues to an intentional release of the agent, either in food or water supplies or as an aerosol.

The mortality from food-borne botulism has declined from 60 percent to 6 percent over the last four decades, representing progress in supportive care and mechanical ventilation more than specific therapies (Arnon *et al*., 2001). The prolonged need for ventilatory support would rapidly deplete the availability of limited resources, such as ventilators, in the event of a large-scale bioterrorism event involving botulism. Treatment with an equine antitoxin may ameliorate disease if given early, but this is available only in very limited supply from the CDC.

Plague

Plague, the disease caused by the Gram-negative pathogen *Yersinia pestis*, presents in a variety of clinical forms in naturally acquired disease. Pandemic plague has significantly impacted world history; its impact may have been so great in the Middle Ages as to have led to genetic selection within Europeans, thus possibly affecting the course of future epidemic diseases such as HIV through changes in one of the viral co-receptors (Galvani and Slatkin, 2003). Plague is endemic in parts of Southeast Asia, Africa, and the western United States, with nearly all of the 13 annual US cases occurring in four states of the desert southwest (CDC, 1996).

The allure of plague as an agent of bioterrorism is related to a number of factors: it can be mass produced and disseminated as an aerosol, as successfully accomplished experimentally by both the US (Christopher *et al*., 1997) and the Soviet (Alibek, 1999) bioweapons programs in the past; the pneumonic form of the disease is communicable from person-to-person and associated with a high mortality rate if untreated; drug-resistant mutants occur in nature (Galimand *et al*., 1997); and an effective vaccine is not widely available. Perhaps the greatest appeal to terrorists is the stigma attached to plague, largely based on its historical track record of social and economic devastation. While the outbreak in Surat, India, in 1994 resulted in only 52 deaths, hundreds of thousands fled the city and mass chaos followed in its wake (Ramalingaswami, 2001).

Aerosolized preparations of the agent, the expected vehicle in bioterrorism, would be predicted to result in cases of primary pneumonic plague outside of usual endemic areas. As was the case with the anthrax attacks in 2001, however, additional forms of the disease, such as bubonic and septicemic plague, might also be expected to occur. Primary pneumonic plague classically presents as an acute, febrile, pneumonic illness with prominent respiratory and systemic symptoms; gastrointestinal symptoms, purulent sputum production or hemoptysis occur variably (Artenstein and Lucey, 2000). Chest roentgenogram typically shows patchy, bilateral, multilobar infiltrates or consolidations. In the absence of

appropriate treatment, there may be rapid progression to respiratory failure, vascular collapse, purpuric skin lesions, necrotic digits, and death. The differential diagnosis, as noted in Table 12.5, is largely that of rapidly progressive pneumonia. The diagnosis may be suggested by the characteristic small Gram-negative coccobacillary forms in stained sputum specimens with bipolar uptake – the "safety pin" appearance – of Giemsa or Wright stain (Inglesby *et al*., 2000). Culture confirmation is necessary to confirm the diagnosis; the microbiology laboratory should be notified in advance if plague is suspected, because special techniques and precautions must be employed to avoid inadvertent exposures.

Treatment recommendations for plague have been reviewed elsewhere (Inglesby *et al*., 2000). Pneumonic plague can be transmitted from person-to-person by respiratory droplet nuclei, thus placing close contacts, other patients, and health-care workers at risk. Prompt recognition and treatment, appropriate deployment of postexposure prophylaxis, and early institution of droplet precautions will interrupt secondary transmission of plague.

Tularemia

Francisella tularensis, the causative agent of tularemia, is another small Gram-negative coccobacillus that would likely cause a primary pneumonic presentation if delivered as an aerosol agent of bioterrorism. The agent is associated with a high attack rate due to its virulence: as few as 10 organisms can cause a pneumonic infection (Dennis *et al*., 2001). Inhalational tularemia presents with the abrupt onset of a febrile, systemic illness with prominent upper respiratory symptoms, pleuritic chest pain, and the variable development of pneumonia, hilar adenopathy, and progression to respiratory failure and death in excess of 30 percent of those who do not receive appropriate therapy (Dennis *et al*., 2001). The diagnosis is generally based on clinical features after other infectious etiologies are ruled out. Laboratory personnel should be notified in advance if tularemia is suspected, because the organism can be very infectious under culture conditions.

Viral hemorrhagic fevers

The agents of viral hemorrhagic fevers (VHF) are members of four distinct families of ribonucleic acid viruses that cause clinical syndromes with overlapping features: fever, malaise, headache, myalgias, prostration, mucosal hemorrhage, and other signs of increased vascular permeability and circulatory dysregulation, leading to shock and multiorgan system failure in advanced cases (Borio *et al*., 2002). Specific agents of VHF may also be associated with specific target organ effects. These pathogens include the agents of Ebola, Marburg, Lassa fever, Rift Valley fever, and Congo-Crimean hemorrhagic fever.

Hemorrhagic fever viruses have been viewed as emerging infections in nature due to their sporadic occurrence in focal outbreaks throughout the world; they are thought to be the results of human intrusion into a viral ecologic niche. They are, however, potential weapons of bioterrorism because they are highly infectious in aerosol form, are transmissible in health-care settings, cause high morbidity and mortality, and are purported to have been successfully weaponized (Alibek, 1999). Additionally, VHF frequently produce dramatic clinical pictures that have received worldwide attention, thus fulfilling another terrorist goal – to induce maximum fear and panic in the civilian population.

Blood and other body fluids from infected patients are extremely infectious, and person-to-person air-borne transmission may occur; therefore, strict contact and air-borne precautions should be instituted in these cases (Borio *et al*., 2002). Treatment is largely supportive, and includes the early use of vasopressors as needed. Ribavirin is effective against some forms of VHF, but not those caused by Ebola and Marburg viruses. Nonetheless, this drug should be initiated empirically in patients presenting with a syndrome consistent with VHF until the etiology is confirmed.

Genetically modified weapons

While modern-day terrorists may be constrained by the physics of aerosols, dispersion clouds and pulmonary alveolar dimensions, advances in molecular genetics and biotechnology have afforded them the possibility of manipulating the genetic composition of biologic organisms in order to enhance their threat potential. Theoretically, at least, such science could result in a Cold War-style "arms race" between bioterrorist states and biodefense organizations, since the molecular technology would serve dual purposes (Fraser, 2004).

The application of genomic science to bioterrorism may include the insertion of select genes for heightened infectivity, virulence, enhanced aerosol stability or antibiotic resistance into the agent's genome; it may also involve modification of the sequences recognized by detection devices or the host immune response (Petro *et al*., 2003). One example is the concept of a multi-drug resistant anthrax strain created by the insertion of plasmids carrying multiple antibiotic-resistant genes. There is evidence that the Soviets had some success in developing such variants (Alibek, 1999); the STI-1 strain was engineered with plasmid-based resistance to penicillin, rifampicine, tetracycline, chloramphenicol, macrolides, and lincomycin (Stepanov *et al*., 1996). This strain was purportedly developed as a live bacterial vaccine for prophylaxis and treatment purposes in a bioterrorism setting, thus illustrating a dramatic example of dual-use technology.

More ominous is the concept of genetic or genomic warfare, in which biological threat agents are tailored in the laboratory to attack populations of specific genetic backgrounds. The initial draft of the human genome has identified many

essential genes that may be targets for future pharmaceuticals; conceivably, specific genomic segments may also be exploited as targets for custom-designed biological threat agents (Black, 2003). Potential weapons may include infectious agents, toxins, or small molecules targeted to subjects who display select genetic profiles. There is evidence that the Iraqi Government was working on weaponizing the camelpox virus prior to 1990 specifically for use as a possible "ethnic weapon," as it is most toxic to populations reared in areas without camels and therefore immunologically inexperienced with this organism (Zilinskas, 1997).

Bioterrorism and the public health response: problem areas

The response to bioterrorism is unique among weapons of mass destruction, because it necessitates the consequence management that is common to all disasters as well as the application of basic principles of infectious disease: disease surveillance, infection control, antimicrobial therapy and prophylaxis, and vaccine prevention. For these reasons, and factors related to the epidemiology of bioterrorism (see above), physicians and other clinicians are the likely first responders to bioterrorism and are expected to be reliable sources of information for their patients, colleagues, and public health authorities (Artenstein *et al*., 2002b).

There remain a number of potential pitfalls regarding bioterrorism that must be identified and managed to optimize the public health. As discussed above, emergencies involving conventional threats, natural disasters, or even chemical attacks, have immediate consequences; assessments of casualties can begin as can containment and mitigation strategies. In bioterrorism, the clinical latency period between exposure to an agent and the manifestation of signs and symptoms is in the order of days to weeks with most of the CDC category A, B, or C agents, other than pre-formed, pathogen-derived toxins. For this reason, early diagnoses of the first cases are likely to prove problematic; heightened clinical vigilance is required to recognize presentations of diseases that are rarely seen in clinical practice (Artenstein, 2003). The fear of the unknown, exacerbated by the "stealth" property of biologic attacks, may result in a panicked society and paralyzed economy.

Even after the initial victims have been diagnosed, communications among hospitals and other health-care institutions on local, regional, national, and global levels will be essential to define the epidemiology and possibly to identify exposure sources. Given the extent and ease of transit within our world, clinical presentations from a point-source, unifocal biologic attack could occur in widely disparate geographic locations. Additionally, it is likely that a terrorist attack would be multifocal, thus further confounding efforts to delineate extents and sources of exposure. A classic epidemiologic approach using case definitions,

case identification, surveillance, and real-time communications is necessary whether the event is a malicious attack, emergent from nature, or of unknown source (Artenstein *et al*., 2002b).

Other potential pitfalls reside in the arena of diagnostic techniques, treatment, and prevention of disease related to biologic agents. Although an active area of research, the development of field-ready, highly predictive, rapid screening tests for agents of bioterrorism has not, as yet, progressed to the point at which such assays are approved by the US Food and Drug Administration and available for deployment. Treatment and prevention issues – such as the absence of effective treatments for many forms of viral hemorrhagic fevers, shortages in the availability of multivalent anti-toxin for botulism, projected shortages in the availability of mechanical ventilators to manage a large-scale attack using botulism, lack of human data regarding the use of antiviral agents in smallpox, and the unfavorable toxicity profiles of currently available smallpox vaccines – remain unresolved but active areas of research. The fact that modern molecular biologic techniques have been used to produce genetically altered pathogens with "designer" phenotypes, such as antimicrobial or vaccine resistance, adds additional layers of complexity to an already complex problem. Finally, as has been vividly illustrated during the recent epidemic of severe acute respiratory syndrome (Svoboda *et al*., 2004) and had been well recognized when epidemic smallpox occurred with regularity (Breman and Henderson, 2002), transmission of infection within hospitals is common. Health-care workers, our first line of defense against an attack using biologic agents, remain at significant occupational risk.

Vaccines

Perhaps the most effective approach towards mitigation of the bioterrorist threat is the development of an effective, scaleable, technologically advanced vaccine platform that can not only respond to likely threat agents, but also has the flexibility to respond to novel and re-emergent pathogens. Vaccines will need to be designed for imminent threats and post-exposure settings; products targeted against the likeliest threats will need to be stockpiled for rapid, practical deployment. A brief review of the current state of vaccines for select Category A agents follows; smallpox vaccine is discussed on p. 342. More comprehensive reviews of biodefense vaccines can be found elsewhere (Cieslak *et al*., 2000; Ales and Katial, 2004).

Anthrax vaccine adsorbed (AVA) is currently the only licensed anthrax vaccine in the US, and consists of a cell-free filtrate derived from a non-encapsulated, attenuated strain of *B. anthracis* developed in the 1950s (Friedlander *et al*., 1999). It is licensed and beneficial for adults in both the pre- and post-exposure settings. It has a complicated dosing schedule and requires frequent boosting

(Nass, 1999). While generally safe, the vaccine is difficult to produce and is associated with significant local reactions. Recent work has focused on the development of a recombinant subunit vaccine targeted against the anthrax protective antigen (PA); antibodies to PA inhibit binding to its cellular receptor and correlate with protection against anthrax (Friedlander, 2001). Purified PA and DNA plasmids that express PA *in vivo* are in clinical trials as next-generation anthrax vaccines.

Although antibodies to PA address the initiation of anthrax infection, antibodies against additional virulence factors such as the capsule or somatic antigens in the spore may be needed to induce sterilizing immunity (Brey, 2005). DNA vaccines provide an attractive new platform, as they are thought to be relatively safe and easy to produce. A plasmid DNA vaccine encoding genetically detoxified PA and lethal factor, the latter a major component of anthrax lethal toxin, has been effective in protecting animals from aerosolized spore challenge, and is currently undergoing human clinical trials (Hermanson *et al*., 2004).

Francisella tularensis represents an example of an intracellular pathogen that requires the induction of a wide range of immune responses, in particular CD8+ T-cell activation, to achieve protective immunity. The existing vaccine, consisting of live attenuated strains of *F. tularensis*, has been used extensively in the former Soviet Union (Alibek, 1999). One strain, LVS, was produced by multiple passages of a fully virulent strain of *F. tularensis* subspecies *holarctica*, and was shown to protect against aerosol challenge in animal and human models of the disease (Saslaw *et al*., 1961; Isherwood *et al*., 2005). However, LVS vaccine licensure was recently revoked due to several problems: it affords incomplete protection against laboratory-acquired tularemia (Eigelsbach and Down, 1961; Saslaw, *et al*., 1961; Burke, 1977); the genetic and immunological basis for its attenuation and immunogenicity remains unknown (Oyston *et al*., 2004); and it provides suboptimal protection against aerosol challenge in animal and human studies (Eigelsbach *et al*., 1961; Hornick and Eigelsbach, 1966). To date, an incomplete understanding of correlates of protection in tularemia has hindered development of an effective subunit vaccine. Completion of the genetic sequence for the infective strain *F. tularensis* SCHU S4 and the vaccine strain LVS may further the discovery of proteins which are likely to induce protective immunity (Larsson *et al*., 2005; Oyston and Quarry, 2005; Twine *et al*., 2005).

Whereas anthrax and tularemia efforts demonstrate models for bacterial vaccines, *Clostridium botulinum* is an example of a vaccine effort directed against an important toxin agent of bioterrorism. Antitoxin remains a scarce resource, and is only useful in certain clinical settings; vaccines are an important approach to mass prophylaxis against this toxin (Artenstein, 2003). Botulinum toxin is expressed by *C. botulinum* in seven structural forms designated toxins A–G (Arnon *et al*., 2001). There is currently a pseudo-licensed US vaccine against serotypes A–E, developed in the early 1970s (Byrne and Smith, 2000). It consists of formalin-deactivated purified toxins (toxoids) combined to form a

pentavalent vaccine. An individual monovalent vaccine against serotype F has been developed in the United Kingdom (Hatheway, 1976). For purposes of mass production, DNA-based vaccines are under development. The carboxyl half of botulinum toxin appears to be the best vaccine candidate, and several vaccine expression systems in yeast and viral vectors are currently being tested in animal models (Lee *et al*., 2005; Middlebrook, 2005).

Bioterrorism in special populations

The public health approach to bioterrorism must be broadened to include special populations, including not only children, pregnant women, and immunocompromised persons, but also other at-risk vulnerable populations – disabled persons, non-English speakers, the homeless, substance abusers, mentally ill persons, and those that are geographically or culturally isolated. A general approach to the management of biothreat infections requires an assessment of the risk of certain drugs or products in select populations versus the potential risk of the infection in question, accounting for extent of exposure and the agent involved. While specific recommendations for treatment and prophylaxis have been recently reviewed (Inglesby *et al*., 1999, 2000; Dennis *et al*., 2001), these only address the biological part of the issue. A larger and more complex problem is ensuring that risk communication regarding bioterrorism and other emergencies is appropriately formulated and delivered in a fashion that is accessible and understandable by at-risk populations in our communities, and that these people have access to the public health system in a manner that optimizes health and minimizes the transmission of contagion (McGough *et al*., 2005).

Psychosocial issues

An often overlooked but vitally important issue in bioterrorism is that of psychosocial sequelae. These often take the form of acute anxiety reactions and exacerbations of chronic psychiatric illness during the stress of the event, or posttraumatic stress disorder (PTSD) in its aftermath. Nearly half of the emergency department visits during the Gulf War missile attacks on Israel in 1991 were related to acute psychological illness or exacerbations of underlying psychopathology (Karsenty *et al*., 1991). Data from recent acts of terrorism in the US suggest that PTSD may develop in as many as 35 percent of those affected by the events (Yehuda, 2002). In the early period after the 11 September 2001 attacks in New York, PTSD and depression were nearly twice as prevalent as in historical control subjects (Galea *et al*., 2002). Although close proximity to the events and personal loss were directly correlated with PTSD and depression, respectively, there was a substantial burden of morbidity among those only

indirectly involved. The psychological impact of these events and of persistent international concern over terrorism can be expected to be significant and sustained for society as a whole.

Public health response as informed by recent events: anthrax attacks, 2001

During October and November of 2001, beginning just weeks after the events of 11 September, the US experienced a series of biological attacks using weaponized anthrax spores deployed in mailed letters. In total there were 22 confirmed or suspected cases, 11 of inhalational anthrax and 11 of the cutaneous form (Jernigan *et al*., 2001); five of the inhalational cases were fatal. Although these attacks were small scale and employed a low-technology approach to anthrax delivery, their impact was substantial: two branches of the Federal Government were temporarily closed, postal operations were severely disrupted, thousands of potentially exposed persons received post-exposure prophylaxis, total mitigation costs approached US$3 billion, and scarce public health resources were diverted away from other concerns to manage the inordinate volume of false alarms that accompanied the actual exposures (Heyman, 2002). Not unexpectedly, a host of after-action reports and analyses have subsequently reviewed the salient features of the response to these significant acts of bioterrorism (Gursky *et al*., 2003; Lucey, 2005).

A number of important lessons, at all levels, were learned from the response to the anthrax attacks of 2001. First and foremost, they exposed the numerous deficiencies in the national and local public health infrastructures, including laboratory and diagnostic capabilities. Second, the events revealed significant knowledge gaps in the scientific community regarding biological threat agents – for instance, the finding of secondary spore aerosolization with experimental routine office activities in the US Hart Senate Office Building during the decontamination phase suggests an additional risk from anthrax weapons (Weis *et al*., 2002). Third, the attacks caused the public health community to question previously held assumptions regarding bioterrorism; the idea that such substantial social and economic disruption could result from such a small event represents a new potential paradigm for terrorists and planners alike (Artenstein, 2003).

Perhaps the most durable lesson resulting from the anthrax attacks revolves around the difficult yet important issue of communication. Local and federal authorities struggled with imparting appropriate crisis and risk communication, and at times were viewed as giving contradictory messages to the media and the public (Gursky *et al*., 2003). This uncertainty, along with a rapidly evolving situation on the ground and heightened public anxieties (no doubt magnified in the immediate post-9/11 period), led to inconsistent statements and actions by public

health authorities, which exacerbated the public's lack of confidence in its leaders. One such example was the recommended use of ciprofloxacin as post-exposure prophylaxis for the Senate Office workers, while the mostly African-American postal workers were given doxycycline. As both drugs are effective, a consistent message and recommendation would have gone a long way towards assuaging public concern. The overarching theme highlighted by the anthrax attacks of 2001 is that our public health response planning must be proactive, not reactive to future events.

Smallpox vaccination program, 2003

The terrorist attacks on the World Trade Center and the Pentagon on 9/11, and the anthrax attacks that followed shortly thereafter, served to focus attention on the threat of bioterror. Smallpox, for reasons delineated above, is widely considered to be a high priority threat agent, and one for which an effective vaccine exists, although not in sufficient quantity for broad application. In late 2002 the Federal Government authorized the implementation of a smallpox vaccination program for over half-a-million operational military personnel, and a second program, presided over by the states, to vaccinate civilian "smallpox response teams" comprising health-care workers and other emergency response personnel (Faden *et al*., 2003).

Routine use of smallpox vaccine ceased in 1972, at which point it was determined that the potential risk of vaccine-associated adverse events significantly outweighed the risk of smallpox (Fenner *et al*., 1988). Because smallpox vaccine may be associated with a number of potentially life-threatening toxicities, and at the time the programs were implemented there was no clearly definable risk of a smallpox exposure, the decision to proceed with pre-event vaccinations provoked a vocal national debate, raising a number of statistical, scientific, political, legal, and ethical issues that informed public health response planning in general.

Many of the issues were controversial and complex: whether vaccination of health-care workers is preferable to mass vaccination of the public (Kaplan *et al*., 2002; Bozzette *et al*., 2003); and the risk-to-benefit ratio for health-care workers, and how to compensate them in the event of vaccine-related injury (Faden *et al*., 2003). While these and other issues sparked useful discussion, the most significant development related to the smallpox vaccination program was probably the recognition of hitherto unrecognized toxicity information concerning the vaccine itself.

Smallpox vaccine has a well-described toxicity profile that includes such serious but predictable complications as post-vaccinial encephalitis, a rare, potentially fatal neurologic syndrome generally seen in young children; progressive vaccinia, frequently fatal and seen in immunocompromised hosts; generalized vaccinia; eczema vaccinatum, dissemination of the vaccine virus seen in hosts with

eczema or atopic disease; and contact transmission of vaccinia to an unvaccinated host (Artenstein, 2004b). Historically, 1 per million vaccinees developed a fatal complication (Lane *et al*., 1970). The vaccination program was designed to screen participants carefully in order to minimize the potential for serious sequelae (CDC, 2003); in general it was successful in this regard, with over 730,000 military personnel and 40,000 civilian volunteers vaccinated, and very low rates of predictable, serious adverse events noted (Grabenstein and Winkenwerder, 2003; Poland *et al*., 2005).

Because of the questions concerning risk outweighing benefit in the pre-event setting, the vaccine program was subjected to more rigorous scrutiny than historical smallpox mass vaccination. As may be seen with such large, well-studied datasets, novel and unanticipated effects were observed. Ischemic cardiac events occurred in 24 military and 9 civilian vaccinees; in retrospect, most had underlying coronary artery disease, and the incidence of ischemia did not exceed the level expected in an age-matched, unvaccinated population (Poland *et al*., 2005). On the other hand, 86 cases of myopericarditis in military vaccinees and 22 cases among civilians were recognized, leading an expert panel to conclude that smallpox vaccination is casually related to myopericarditis and increases the risk of this complication (Poland *et al*., 2005). Thus, data gleaned from preparations for a potential bioterrorist attack using smallpox will inform future vaccine efforts for smallpox (Artenstein *et al*., 2005) as well as other areas of biodefense.

Pandemic influenza

The public health response to the potential for pandemic influenza, although not a bioterror threat *per se*, represents an opportunity to implement some of the lessons learned from other, recent experiences in biodefense. While it is not clear that the cause of the current avian influenza epidemic, H5N1, will be the next pandemic strain (Bartlett and Hayden, 2005), the possibility of a future influenza pandemic appears to be all but certain (Mermel, 2005). H5N1 has met two of three criteria for a pandemic: it represents a novel subtype of influenza to which the population is immunologically naïve, and it is capable of infecting humans (albeit in limited fashion to date) and causing potentially lethal disease (WHO, 2005). The remaining pandemic hurdle for the virus is the ability for efficient human-to-human transmission (Fauci, 2006).

Given this, and the state of scientific knowledge that is currently available, we are in a much more favorable circumstance than our predecessors were at the time of the 1918 influenza pandemic. We are in a position to couple the recent public health lessons related to bioterror threats with our expanding databases of genetics, molecular biology, and biotechnology, and apply all of this knowledge to the immense challenge posed by the threat of pandemic influenza.

Challenges to global public health

The threat of bioterrorism will likely persist and continue to present challenges to global public health. Adding to the concern is the possibility that advances in biomedical research may be used for malicious purposes – a possibility that has recently resulted in the creation of the National Science Advisory Board for Biosecurity by the US Department of Health and Human Services, to counsel government agencies regarding the dissemination of results from "controversial experiments" (Steinbrook, 2005). While the overall risk of bioterrorism is probably low from a practical standpoint, the consequences are potentially quite high; thus it is essential that we continue to develop countermeasures and response plans. There is otherwise a tendency to move on in our thinking to "the next big thing" and to leave these threats incompletely addressed. This concept of "bioterrorism fatigue" can be quantified (Figure 12.1).

Bioterrorism represents the ecological niche that lies at the confluence of global geopolitics, sociology, biology, public health, and medicine. So too do

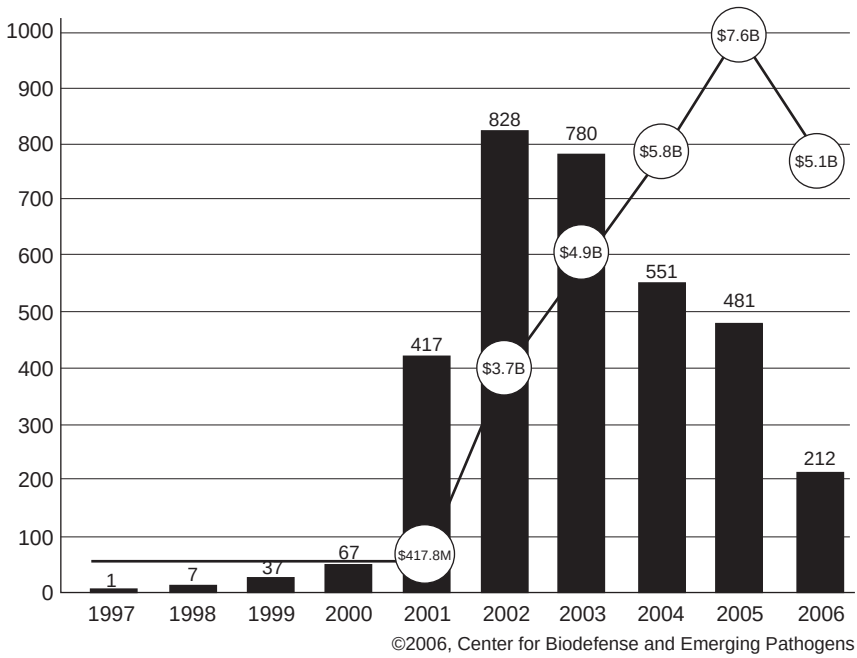

Figure 12.1 "Bioterrorism fatigue": declining volume of publications using the keyword "bioterrorism" as referenced in the PubMed database from 1997 through 2006 (the latter year represents an annualized number) with superimposed federal bioterrorism funding from 2001 through 2006 (©2006, Center for Biodefense and Emerging Pathogens).

emerging infectious disease threats, such as pandemic influenza. Fortunately, the resources, human and economic, and technology that must be allocated to a cogent biodefense strategy are similar to those that are needed to combat naturally occurring disease threats (Artenstein, 2003; Relman, 2006). The duality of biodefense offers society the luxury of not having to choose between the two; it instead speaks to the need for a nimble and robust approach that can be adapted to changing circumstances.

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