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15 Bioterrorism: An Overview

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Although deliberate attempts to induce infectious disease among adversaries date back to at least the Roman Empire, concerns about the possible use of microbes by terrorists or by countries with developed biological weapons programs have increased significantly over the past several decades.[1-3] In the 1990s in response to this growing unease, biological agents of concern were provisionally grouped by the Centers for Disease Control and Prevention (CDC) into three tiered categories (A, B, and C).[4] Tier-specific assignment of an organism was based on several factors, including dissemination or transmissibility characteristics, anticipated associated morbidity and mortality, and/or special preparedness needs, including laboratory preparedness (Table 15-1). More recently, and complementary to the CDC categories, the Department of Homeland Security (DHS), using additional criteria, has developed a systematic framework to assess the risk of a number of organisms.[5] As a result of this assessment, a subset of organisms is deemed to pose a material threat to the national security of the United States (Table 15-2).[6] The havoc that could be generated by an attack with one of these agents was illustrated in 2001 when a small number of letters containing *Bacillus anthracis* spores were disseminated via the U.S. postal system.[7] Although only 22 people became ill at five sites in different states, fear and apprehension extended across the country and internationally.[8-10]

There is a general consensus among those who are most knowledgeable of bioterrorism and biological warfare that the potential use of biotechnology for subversive goals poses a serious and growing threat, and that the release of one or more biological agents is inevitable.[11-14] The release and subsequent spread of a contagious agent such as smallpox virus could prove catastrophic if measures for control are not promptly and effectively applied. Equally serious could be a large-scale release of a highly lethal but nontransmissible agent such as anthrax. The possible use of genetically modified agents offers an additional dimension to the threat.[15]

Serious concerns about the potential use of what are commonly referred to as weapons of mass destruction (WMD) arose in the context of the Cold War and focused originally on nuclear weapons and the potential of these to result in the ultimate scenario of a "nuclear winter."[16] Chemical weapons remained on the agenda of concerns given their extensive use during World War I. Concern about biological weapons waned significantly during the 1970s, coincident with President Nixon's initiative in 1969 to terminate the U.S. offensive biological weapons program and the subsequent endorsement by many countries of the 1972 Convention on the Prohibition, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (usually referred to as the Biological Weapons Convention [BWC] or the Biological and Toxin Weapons Convention [BTWC]).[17,18] The Convention called for the destruction of all stocks of biological weapons and the cessation of research on their use as offensive agents.

Among those responsible for national policy and by the public health and medical communities, three points of view predominated until about 1995 that served to discourage consideration of biological weapons as more than a theoretical possibility:

1. That biological weapons had been deployed so rarely that precedent would suggest they would not be used;
2. That their use is so morally repugnant that no nation state or organized group would deign to use them; and
3. That it is technologically so difficult to produce organisms in quantity and to disperse them that the science is beyond the reach of any but the most sophisticated laboratories.

Each of these arguments has now been shown to be invalid. It is now known that there are nations and dissident groups who have both the motivation and access to skills to cultivate successfully some of the most dangerous pathogens, as well as deploy them as agents in acts of terrorism or war. This was borne out in the anthrax attacks of late 2001 during which letters containing anthrax spores were sent to media and political figures.[7] Methods for transforming biological agents into weapons are publicly available, and the skills and equipment necessary to produce them are modest.

Some have assumed that because the likely pathogens to be used as biological weapons are comparatively rare, it would be difficult for a prospective terrorist to acquire the organisms. With the exception of smallpox and multidrug-resistant (MDR) anthrax, all of the pathogens deemed to pose a material threat to the national security of the United States exist in nature and periodically cause human and animal disease.[19] Furthermore, many of these pathogens exist in diagnostic and research laboratories.

In contrast to the challenges of acquiring functional nuclear weapons, the production of biological weapons is easier and far less expensive. For many of the organisms, production is reasonably straightforward, especially for those with expertise. Those without such expertise can obtain it from the Internet and through academic courses, including sophisticated methods that could be used for genetic engineering of pathogens. Existing or new biomedical production facilities or industries could be converted to the production of microorganisms for bioweapons due to the dual-use nature of manufacturing equipment and supplies. Notably, comparatively little space is required and—for most agents—comparatively small quantities need to be aerosolized to produce large numbers of casualties. For example, in 1999 a small team of scientists without prior training in biological weapons development built a clandestine laboratory in Nevada under a Defense Threat Reduction Agency (DTRA) effort to assess whether non–state actors could manufacture biological weapons in the United States using materials purchased on the open market and whether such manufacture could be detected.[20,21] The scientists produced enough simulated anthrax—without being detected—to kill at least 10,000 people (had they actually produced anthrax spores) with materials purchased on the open market, mostly from a local hardware store, with a budget of less than $1.5 million.[20]

Various methods might be used for dispersing biological weapons. The most likely would be direct contamination of food or water supplies and aerosol dispersion. There is a general consensus that aerosols pose the most serious threat. Organisms dispersed by other means could cause disease outbreaks, but they would be much less likely to cause disease on a scale great enough to threaten the integrity of civil government. Each of the organisms of greatest concern could be disseminated in a fine particle aerosol in the range of 1 to 5 microns. Such particles are inhaled and penetrate deeply into the lung. Larger-sized particles, in contrast, are trapped in the upper airways and usually do not succeed in initiating infection. A fine particle aerosol is invisible to the naked eye and behaves much like smoke in that it is able to penetrate most interior air spaces. In the 1979 Sverdlovsk anthrax outbreak, for example, human cases occurred in individuals who were as much as 4 km from the point of purported unintentional release of a spore-contaminated plume from an unfiltered exhaust pipe in a biological weapons production facility; animals who were 50 km away also developed anthrax.[22]

Generating an aerosol is comparatively straightforward using any of a number of off-the-shelf devices such as paint sprayers, fogging machines that disseminate insecticides, purse-size perfume atomizers, and hand-held drug delivery devices such as used by asthma patients. Even small releases of an agent would, almost certainly, result in

KEYWORDS

anthrax; bioterrorism; medical countermeasures; public health preparedness; risk assessment; smallpox; Strategic National Stockpile; threat assessment

TABLE 15-1 Centers for Disease Control and Prevention Bioterrorism Agents and Disease Categories

Category	A	B	C
Priority	1	2	3
Characteristics	Easily disseminated or spread person to person Highly lethal Serious public health effects May cause great panic and social disruption	Moderately easy to disseminate Moderate morbidity Less lethal than category A agents Require fewer special public health preparations	Includes emerging infectious diseases Potential for wide dissemination in the future because of availability, ease of production/dissemination, and potential to result in high morbidity, lethality, and major public health effects
Disease (agent)	Anthrax *(Bacillus anthracis)* Botulism (*Clostridium botulinum* toxin) Plague *(Yersinia pestis)* Smallpox (variola) Tularemia *(Francisella tularensis)* Hemorrhagic fever viruses	Brucellosis (*Brucella* species) Epsilon toxin of *Clostridium perfringens* Food safety threats (e.g., salmonella) Glanders *(Burkholderia mallei)* Melioidosis *(Burkholderia pseudomallei)* Psittacosis *(Chlamydia psittaci)* Q fever *(Coxiella burnetii)* Ricin toxin from *Ricinus communis* (castor beans) Staphylococcal enterotoxin B Typhus fever *(Rickettsia prowazekii)* Viral encephalitis (e.g., Venezuelan equine encephalitis) Water safety threats (e.g., *Vibrio cholerae*)	Emerging infectious disease threats such as Nipah virus and hantavirus

From Centers for Disease Control and Prevention. Bioterrorism Agents/Diseases. Available at http://www.bt.cdc.gov/agent/agentlist-category.asp. Accessed July 3, 2013.

TABLE 15-2 Biological Agents with Material Threat Determinations

Bacillus anthracis
Multidrug-resistant *B. anthracis*
Botulinum toxins
Burkholderia mallei
Burkholderia pseudomallei
Ebola virus
Francisella tularensis
Marburg virus
Rickettsia prowazekii
Variola virus
Yersinia pestis

*Material threat determinations have also been issued for classes of chemical agents, radiologic materials, and nuclear detonation effects. See reference 5 for more information.

From U.S. Department of Health and Human Services. 2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy. Available at http://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf. Accessed July 18, 2013.

serious public concern as was witnessed during the anthrax release in the United States in 2001. Repeated releases in different parts of the country could be devastating, especially if the public health response were seen as deficient. A large-scale release of agents could be as devastating as a nuclear weapon. For example, a 1993 Office of Technology Assessment report estimated that if 100 kg of anthrax spores were released upwind of Washington, DC, using a crop-duster aircraft, there would be between 130,000 and 3 million deaths.[23]

It is clear that preventing the proliferation and use of biological weapons or countering them will be extremely difficult. Detection or interdiction of those intending to use biological weapons is next to impossible. Thus, the first evidence of intent to use such weapons will likely be the appearance of sick people in hospital emergency departments. The rapidity with which those front-line health care workers and others, such as infectious disease specialists and laboratory scientists, can reach a proper diagnosis and the speed with which preventative and/or therapeutic measures are applied could well spell the difference between thousands and, perhaps, tens of thousands of casualties.

HISTORY OF BIOLOGICAL WEAPONS

Recorded attempts to deliberately use microbial agents as weapons date back to the Roman Empire.[3] Attempts that pre-date the 19th century and the development of the field of microbiology were generally focused on using infected people, animal carcasses, or other vectors (e.g., fomites) to spread disease (Table 15-3).[17,24-29] The effectiveness of these efforts is not clear.

State Actors

In the early part of the 20th century, the advent of microbiology provided the scientific basis for the development of biological weapons and programs began to be developed by some countries, so-called state actors, as part of their warfare armamentarium. For example, Germany instituted a biological weapons program during World War I and conducted attacks of unknown effectiveness against animals (i.e., horses, mules, sheep, cattle) being shipped by neutral countries to the Allies.[30]

The use of chemical weapons by both sides of the conflict during World War I was considered appalling and led to the Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases and of Bacteriological Methods of Warfare (Geneva Protocol).[31] This treaty was drawn up and signed under the auspices of the League of Nations in 1925 and entered into force in 1928. Although the Geneva Protocol (which has been ratified, acceded to, or succeeded to by 137 State Parties as of March 15, 2013[32]) banned the use of biological weapons, it did not proscribe the research, production, or possession of biological weapons, and many of the State Parties to the treaty reserved the right to retaliate in kind should they or their allies be attacked. In addition, no provision was made for verification and compliance was voluntary. A number of countries agreeing to the Geneva Protocol began or continued biological weapons programs after becoming treaty signatories. These included Belgium, Canada, France, Germany, Italy, Japan, the Netherlands, Poland, the United Kingdom, and the Soviet Union.[17] The United States did not ratify the Geneva Protocol until 1975 after it had ended its biological weapons program.[25]

Despite the list of countries agreeing to the Geneva Protocol, biological weapons are known to have been used during World War II by some who had signed the treaty, including Japan and possibly the Soviet Union.[17] The Japanese biological weapons program was a vast enterprise. It consisted of a major center in Pingfan, Manchuria, termed Unit 731 with more than 3000 scientists plus smaller units at a number of other sites in China. Another center (Unit 100) worked primarily with animal and plant diseases, including glanders, sheep and cattle plague, red rust, and mosaic plant diseases. More than 10,000 prisoners died as a result of experimental infections or execution after experimentation.[25,33] At least 11 cities in China were attacked during World War II using, variously, anthrax, cholera, *Shigella, Salmonella,* and plague organisms to contaminate food and water supplies. For example, fleas were infected with plague bacteria and released by aircraft over cities. Data regarding the success of Japan's efforts to infect civilian populations is sketchy. Large outbreaks of cholera and plague are known to have occurred, but it is believed that transmission in any given area was not long sustained. The extent and sophistication of the Japanese program came to be known after the war when Japanese scientists were offered amnesty from war crimes prosecution for the

TABLE 15-3 Summary of the History of Use of Biological Weapons

PERIOD	SETTING OF USE	AGENT(S) USED	COMMENTS	REFERENCES
Pre-20th Century				
Roman Empire	Warfare	Unknown	Roman armies used bodies of animals to contaminate water supplies	3, 17
14th Century	Caffensistera (also known as Caffa or Kaffa)	*Yersinia pestis*	Cadavers flung by Mongols besieging the Genoese city using trebuchets. However, cadavers not efficient vector. Likely disease present beforehand and fleeing civilians carried plague to other European cities	17, 24, 25
Early Colonial North and South America	French and Indian War American Revolution	Variola major	British took blankets from smallpox patients and gave to the American Indians with intent to infect British sent infected civilians among revolutionary troops	17, 26, 27, 28
Early to Mid-20th Century				
World War I	Animals being shipped from the United States to Europe before the United States entry into the conflict	*Bacillus anthracis* *Burkholderia mallei*	German saboteurs dispersed 2 agents in eastern coastal port areas to infect horses, mules, and sheep being shipped to the Allies in an effort to impact transport and cavalry operations in Europe. Unclear if it was successful	17, 29, 30
World War II	Against civilian populations and opposing troops	*B. mallei* *B. anthracis* *Coxiella burnetii* *Francisella tularensis* *Vibrio cholera* *Yersinia pestis*	Japan had a vast biological weapons research and development program. Attacked 11 cities in China with various organisms Polish resistance fighters Soviets possibly used *F. tularensis* against German Panzers at Stalingrad in 1942; *C. burnetii* against German troops in Crimea in 1943 Unclear if any attacks were successful	17, 25, 33, 38
Late 20th Century				
1984	Against civilians	*Salmonella enterica* subsp. *enterica* serovar Typhi	Members of the Rajneesh religious cult deliberately contaminated salad bar contents in restaurants along an Oregon interstate highway in an effort to influence an election; 751 ill, 45 hospitalized, no deaths	2, 17, 49
Early 21st Century				
2001	Against civilians	*B. anthracis*	Several letters laced with anthrax spores sent via the U.S. mail processed via high-speed sorting machines with aerosolization of the organism; 22 persons ill (in 5 geographic areas) among whom there were 5 deaths	7, 17

information provided. This information served as an impetus for the expansion of biological weapons programs in a number of countries, including the United States, United Kingdom, Australia, France, and Canada.

In the United States, the principal biological weapons research site was located at Fort Detrick, Maryland; a production facility was constructed at Pine Bluff, Arkansas.[25] The studies conducted were wide-ranging. Examples of human disease–associated organisms or toxins that were weaponized and stockpiled include *B. anthracis;* botulinum toxins; *Francisella tularensis; Brucella suis; Coxiella burnetii*; staphylococcal enterotoxin B; and Venezuelan equine encephalitis. In conjunction with these activities, medical countermeasures were developed, including vaccines and antibiotics, to protect scientists and military personnel; technical advances were made that permitted large-scale fermentation and storage of agents. Studies of animal responses to infection were conducted at Fort Detrick, in atolls in the Pacific, and at desert sites in the United States. Experiments using aerosolized simulant organisms were conducted in a number of cities to study survival time of organisms and patterns of dispersal.[34]

Over time there was increasing international concern that the Geneva Protocol did not ban the research, production, or possession of biological weapons and lacked the means to verify adherence by signatory countries. Accordingly, in 1969, draft proposals for a new protocol were submitted to the Committee on Disarmament of the United Nations.[17] Meanwhile, President Nixon unilaterally terminated the U.S. offensive biological weapons program in 1969 by National Security Decision Memorandum (NSDM) 35, followed by the toxin weapons program in 1970 by NSDM 44.[35,36] Then in 1972, the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological and Toxin Weapons and on their Destruction—commonly referred to as the Biological Weapons Convention or the BWC—was opened for signature.[18] State Parties to the BWC—which entered into force in 1975—are obligated to not develop, produce, stockpile, or otherwise acquire or retain microbial or other biological agents or toxins of types and in quantities that have no justification for prophylactic, protective, or other peaceful purposes. They may not use any means of delivery of such agents or toxins for hostile purposes and must take necessary measures to prohibit or prevent such activities in their territories. Further, State Parties should destroy or divert to peaceful purposes all agents, toxins, weapons, equipment, and means of delivery and not transfer to any recipient or in any way assist, encourage, or induce to manufacture or otherwise acquire biological agents, toxins, weapons, equipment, or means of delivery.

The BWC—which has 169 State Parties[37]—has no formal verification protocol to monitor compliance. Accordingly, verifying adherence to and compliance with the BWC by State Parties has proven challenging. For example, the Soviet Union became a State Party to the BWC in 1975. However, in the late 1980s and early 1990s serious concerns arose regarding the biological weapons capability of the Soviet Union.[17] Through defectors, it was learned that the Soviet Union maintained a biological weapons program that was far more extensive and sophisticated than any had imagined at the end of the Cold War.[38-40] After the establishment of the BWC in 1972, the Soviet Union created a civilian research program called Biopreparat to conduct—under the guise of legitimate research—offensive biological weapons–related research not permitted under the BWC. The program included a system of 18 research laboratories and centers employing up to approximately 60,000 staff at its height. One of the larger and more sophisticated of its facilities, the Vector State Research Center of Virology and Biotechnology, referred to as VECTOR, was a 4000-person, 30-building complex with high-security biological facilities for laboratories and isolation of human cases. It was at VECTOR where, during the 1980s, the technical problems were solved for the large-scale production of smallpox virus intended to be used as an offensive weapon.

Another facility of concern was the Soviet Union's principal production center for smallpox virus located near Moscow, at Sergiev Posad. It was reportedly able to produce upwards of 20 tons of smallpox virus annually, primarily for delivery via intercontinental ballistic missile (ICBM) as a strategic weapon.[39] Currently, the site houses the Russian Federation's Ministry of Defense Microbiology Scientific Research Institute, a laboratory research complex known to maintain a national collection of dangerous pathogens, including Ebola, Marburg, and Lassa viruses.[42] In 1992, Russian officials confirmed the existence of a biological weapons program it had inherited from the Soviet Union and committed to dismantling it.[43] The dissolution of the Soviet Union in 1991 and the halting of the inherited Soviet offensive biological weapons program by Russian President Yeltsin in 1992 resulted in profound reductions in Biopreparat funding and personnel raising concerns that former biological weapons scientists may sell the expertise to states or groups seeking such knowledge.[44] In 2000 it was estimated that approximately 15,000 Biopreparat scientists remained employed within the system, which could pose a proliferation risk.[45]

Another example that illustrates the challenges of verifying compliance to the BWC is the case of Iraq, which signed the BWC in 1972. After the first Gulf War (Operation Desert Storm) in 1991, U.N. Security Council Resolution 687 established, among other things, the U.N. Special Commission (UNSCOM) to carry out on-site inspections of Iraq's biological, chemical, and missile capabilities and to oversee their destruction, removal, or procedures to render them harmless.[46] In April 1991 under its initial declaration (as required under U.N. Resolution 687), Iraq declared that it did not have a biological weapons program and in August 1991 declared to the first biological weapons inspection team only that it had conducted "biological research activities for defensive military purposes."[47] It was not until July 1995, after 4 years of UNSCOM investigations and "in the light of irrefutable evidence" that Iraq admitted for the first time that it had an offensive biological weapons program.[47] However, Iraq initially denied weaponization. It took a defector to begin to uncover the full extent of the Iraqi program. In August 1995 General Hussein Kamel, who had responsibility for all of Iraq's weapons programs, defected to Jordan and began cooperating with UNSCOM. Subsequently, Iraq admitted to "a far more extensive biological warfare programme" than previously admitted including weaponization."[47] U.N. Resolution 687 invited Iraq to ratify the BWC, which it did in 1991.[48]

Verifying adherence to the BWC remains a challenge. A 2011 assessment by the U.S. Department of State found that China, Iran, and Russia—all State Parties to the BWC—engaged in biological research activities in 2011 with potential dual-use applications; however, available information did not establish that any of these countries is engaged in activities prohibited by the BWC.[43] In addition, it remains unclear if Russia has fulfilled its obligations under the BWC with respect to the items specified in Article I of the BWC that it inherited from the former Soviet Union. Furthermore, the State Department noted that the United States has judged that North Korea—also a State Party to the BWC—might still consider the use of biological weapons an option and continues to develop its research and development capabilities without declaring relevant developments as part of the BWC confidence-building measures. Finally, the State Department noted the United States' concern that Syria—a signatory but not State Party to the BWC—may be engaged in activities that would violate its obligations under the BWC if it were a State Party.

Non–State Actors

Non–state actors, including individuals and groups (e.g., terrorist groups, criminal networks), present a unique, complex, and growing challenge with respect to the development and use of biological weapons. For example, there were 185 documented cases of biological weapon use by non–state actors during the 20th century—85% of which occurred from 1990-1999.[2] Twenty-seven of these cases were by terrorists, 56 by criminals, and 97 were by other/uncertain actors. A notable case occurred in September 1984, when members of a religious cult, the Rajneeshees, deliberately contaminated salad bars located along a stretch of an Oregon interstate highway with *Salmonella typhimurium* (now *Salmonella enterica* subsp. *enterica* serovar Typhi). Although there were no deaths among the 751 persons who became ill, 45 were hospitalized.[49] The public health investigation of this incident initially failed to determine how the salad bars became contaminated. It was not until 1 year after the outbreak that dissension among the perpetrators led law enforcement officials to discover the contamination was deliberate with the ultimate goal of disrupting a local election.[2] This episode illustrates the difficulty in differentiating an ordinary foodborne outbreak from a small-scale biological weapons attack conducted by non–state actors.

In late 2001 multiple letters containing anthrax spores were sent through the U.S. mail, resulting in 22 cases of anthrax—11 inhalational and 11 cutaneous.[7] Five of the victims died. A lengthy investigation by the Federal Bureau of Investigation (FBI), the U.S. Postal Inspection Service, other law enforcement agencies, and federal prosecutors from the District of Columbia and the Justice Department's Counterterrorism Section determined that the late Dr. Bruce Ivins acted alone in planning and executing the 2001 anthrax attack.[50] A review of the scientific approaches used in the investigation was conducted by a committee of the National Research Council (at the request of the FBI). It determined, among other things, that the available scientific evidence was insufficient to reach a definitive conclusion as to the origins of the anthrax spores used in the attack, leading some to continue to question whether Dr. Ivins was the culprit.[51,52]

In response to increasing concerns regarding the risk that non–state actors might acquire and use biological, chemical, and nuclear weapons and the fact that the BWC does not explicitly address non–state actors, U.N. Security Council Resolution 1540 was appended to Chapter VII of the U.N. Charter by unanimous vote on April 28, 2004.[53] Chapter VII sets out the U.N. Security Council's powers to maintain peace. Resolution 1540 adds the requirement that all member states develop laws with regulatory enforcement measures aimed at preventing the creation, proliferation, delivery, and spread of chemical, biological, and nuclear weapons by non–state actors. The desired intended outcome is to reduce the threat of non–state actors gaining access to and disseminating these weapons. The objectives of this Resolution were reiterated, and the mandate was extended under U.N. Security Council Resolutions 1673, 1810, and 1977 with the 1540 Committee mandate extended to 2021 to ensure full implementation of the original resolution through capacity building and technical assistance.[54]

ASSESSING THE THREAT AND RISK OF BIOLOGICAL WEAPONS

The prospects of preparing for and responding to an attack involving the dissemination of a biological weapon are daunting. Determining how to focus limited resources is a key to such efforts. Two critical elements are used to assess and estimate which biological organisms are of greatest concern: threat assessment and risk assessment. Threat assessment is the process of assessing the likelihood that a particular intentional hazard will occur by estimating potential adversaries' capabilities and intentions.[55] This is a particularly difficult task with respect to biological weapons. Potential adversaries pursuing a biological weapons capability encompass a diffuse set of state and non–state entities (e.g., terrorist groups, criminal networks, individuals), which are difficult to identify and gather information on.[56] To achieve a tactical and strategic advantage, potential adversaries strive to maintain secrecy, making it difficult to gain insight into their specific intentions and capabilities. In addition, it is extremely difficult to differentiate biological weapons research and development from legitimate research and development efforts. These factors make it difficult to develop threat assessments that are accurate and actionable. In addition, the biological weapons threat continually evolves as a result of advances in science and technology and as a result of adversaries adjusting their strategies and tactics in response to a nation's perceived vulnerabilities. Accordingly, there are substantial difficulties in identifying potential aggressors, let alone estimating their intentions and capabilities.

Given the inherent uncertainties in threat assessment, risk assessment is used to inform activities and programs for addressing the biological weapons threat. Risk is the potential for an unwanted outcome from an incident, event, or occurrence, as determined by its likelihood and the associated consequences.[55] In the United States, the

Biological Terrorism Risk Assessment (BTRA)—conducted by DHS every 2 years—is used to identify and prioritize credible, high-impact biological threats; assess their risks; and inform the federal government's risk mitigation efforts.[5] The BTRA employs a quantitative analysis that uses currently available information about potential aggressors, biological agents, acquisition, production, dissemination methods, targets, and public health response measures to define a wide range of attack scenarios and identify those that present the greatest risk to the U.S. population. This information is used by federal departments and agencies to help guide response planning.

PATHOGENS OF GREATEST CONCERN

Given the large number of potential biological threat agents and the long time lines, risks, and high costs associated with implementing risk mitigation strategies (e.g., medical countermeasures, surveillance infrastructure, medical and public health response capabilities), the U.S. government must prioritize the biological threats for which risk mitigation strategies should be pursued. The initial step in this prioritization scheme involves the BTRA, which identifies the biological agents deemed to be the greatest risk to the U.S. population.[5] These agents are then further analyzed in the Material Threat Assessment (MTA) process whereby DHS employs the BTRA results and develops plausible high-consequence scenarios that estimate the number of people in the population who would be exposed to specified levels of a given threat agent in those scenarios. The MTA results, which are classified, are then provided to the Department of Health and Human Services (HHS), which conducts medical and public health consequence assessments using modeling tools to estimate the potential impact of the MTA scenarios.[57] DHS and HHS then collaborate to review these assessments and determine if a particular biological agent poses a threat to national security.[5] DHS then issues Material Threat Determinations (MTDs) for those agents determined to present a material threat against the U.S. population sufficient to affect national security.

As of this writing, biological agents that have MTDs are *B. anthracis,* MDR *B. anthracis,* botulinum toxins, *Burkholderia mallei, Burkholderia pseudomallei,* Ebola virus, *Francisella tularensis,* Marburg virus, *Rickettsia prowazekii,* variola virus, and *Yersinia pestis* (see Table 15-2).[6] Although each of these biological agents and their accompanying diseases are discussed in separate chapters, a brief contextual discussion of each follows here.

Smallpox

Smallpox, a disease caused by variola virus (see Chapter 135), was declared eradicated by the WHO in 1980.[58] The VECTOR laboratory and the CDC in Atlanta are the only two repositories designated by the World Health Organization (WHO) to maintain stocks of the smallpox virus. Both institutions continue to do research on smallpox, albeit under the close scrutiny of the WHO Advisory Committee on Variola Virus Research.[41] It is difficult to ascertain whether clandestine repositories exist. A release of smallpox today could result in a public health catastrophe. Smallpox spreads directly from person to person, causing death in approximately 30% of those infected; although there is no approved drug, an antiviral candidate, Arestvyr (USAN tecovirimat; aka ST-246), is in development and has been placed in the Strategic National Stockpile for use in an emergency.[59] Vaccination against smallpox, once widely practiced, stopped in 1980 coincident with the declaration that smallpox had been eradicated. Few persons younger than 35 years have been vaccinated; vaccine immunity among those who are older is waning. The United States now has a large stockpile of vaccine, but most countries have little or none and worldwide production capacity is minimal.

Anthrax

Anthrax, caused by *B. anthracis* (see Chapter 209), was one of the principal biological weapons in the arsenal of former state-run programs, including the former Soviet Union and Iraq.[17,60] Non–state actors have also pursued anthrax for weapons purposes. For example, the Aum Shinrikyo cult's attempts to develop an anthrax weapon in Japan went undetected for 5 years until the cult's sarin gas attack in the Tokyo subway system in 1995 attracted the attention of authorities.[2] In addition, Al-Qa'ida was pursuing biological weapons capabilities, including anthrax, before the U.S. invasion of Afghanistan in 2001.[17,61,62] The organism, found in nature and responsible for enzootic disease (including in the United States), is reasonably readily available, easy to produce in large quantity with a minimum amount of technical skill and supplies, and extremely stable in its spore form. Methods to grow MDR anthrax have been published in the scientific literature.[63,64] Whether such strains maintain virulence is unknown.

Botulism

Botulinum neurotoxins, produced by *Clostridium botulinum* (see Chapter 247), were one of the principal weapons in the arsenal of the former Soviet Union and are known to have been produced as a weapon by Iraq.[65] These neurotoxins are among one of the most toxic substances known, posing a significant bioweapon threat due to their potency, potential lethality, and relative ease of production. Those exposed to these neurotoxins may require prolonged intensive care and ventilatory support while receiving treatment with antitoxin.

Glanders and Melioidosis

Glanders is caused by infection with the bacterium *Burkholderia mallei* (see Chapter 223), and melioidosis is caused by *Burkholderia pseudomallei* (see Chapter 223).[66] Melioidosis is endemic in Southeast Asia and northern Australia. The disease is associated with a high mortality due to the speed with which septicemia develops, particularly in immunocompromised hosts, and the inherent resistance of the bacteria to several classes of antibiotics. Prolonged courses of antibiotics are required to treat melioidosis. Despite prolonged antimicrobial therapy, recurrent disease is common. Glanders is primarily a zoonotic disease in Africa, Asia, the Middle East, and Central/South America. Although human susceptibility to *B. mallei* infection has not been studied in depth, the organism is highly infectious in the laboratory setting. As with melioidosis, prolonged antimicrobial therapy is required to treat it and to prevent its relapse.

Ebola and Marburg Hemorrhagic Fever

Ebola and Marburg hemorrhagic fever viruses (see Chapter 166) are considered to be a significant threat for use as biological weapons due to their potential for causing severe illness and death.[67] These viruses are highly infectious, spread easily from person to person, and are associated with high mortality. No treatments are available.

Tularemia

Tularemia is a zoonotic disease found in many countries, including the United States. It is caused by the bacterium *Francisella tularensis* (see Chapter 229).[68] It is a hardy organism capable of surviving for weeks in the environment.[69] The bacterium was developed into an aerosol biological weapon by several countries in the past. It is considered to be a serious potential bioterrorist threat because it is one of the most infectious pathogenic bacteria known—inhalation of as few as 10 organisms can cause disease—and may lead to serious illness and death.

Epidemic Typhus

Epidemic typhus is caused by *Rickettsia prowazekii* (see Chapter 191), a bacterium carried and transmitted by body lice.[70] Although naturally occurring disease is typically associated with war, famine, and other poor hygiene environment due to lice infestation, the bacterium is easily aerosolized. Mortality is low with prompt antimicrobial therapy, but diagnosis may be a challenge given the nonspecific clinical manifestations of the disease.

Plague

Plague is caused by *Yersinia pestis* (see Chapter 231), a bacterium that was developed as a bioweapon by several countries in the past.[71] Primary pneumonic plague would result from an aerosol exposure and lead to a rapidly progressive and lethal infection; this form is transmissible to others. A zoonotic infection in many areas of the world, including the United States, *Y. pestis* is relatively simple to grow and disseminate.

EVENT DETECTION AND EPIDEMIOLOGY

Event Detection

The early detection of a biological attack is one of the keys to minimizing morbidity and mortality. Ideally, early identification of a biological attack could come from sensitive and specific pattern recognition of illnesses or a surveillance system for identification of environmental pathogens. However, an effective system does not currently exist. This means that early detection of a biological attack will primarily rely on front-line clinicians and laboratorians. In the United States, federal, state, tribal, and territorial governments, as well as many health care systems, have taken steps to improve surveillance capabilities to detect unusual biological outbreaks and cases. And in recent years, improved surveillance systems at the international, national, and local levels—including an improved network of public health laboratories—have enabled the detection of outbreaks of novel infectious diseases with an exceedingly small number of cases.[72] Despite these improvements, it is still highly likely that the first identification of a biological attack will be the diagnosis of patients by an astute clinician. Clinically suspect cases require prompt laboratory confirmation, which is an essential step for any public health response. Thus, through a variety of educational approaches and training programs, emphasis has been placed on assuring that clinicians, particularly emergency medicine and infectious disease specialists, are knowledgeable of biological agents of greatest concern, know of the importance of prompt reporting to public health officials, and have access to laboratories that are prepared to provide rapid disease diagnosis.

Since 2001 most clinical professional societies have provided bioterrorism training opportunities through publications in peer-reviewed journals, on-line training modules, and symposia at professional meetings. The American Board of Internal Medicine includes questions on the diagnosis and management of patients with infections due to biological threat agents on its certifying examination in internal medicine, as well as its subspecialty examination in infectious diseases. In 2003 the American Association of Medical Colleges recommended integration of bioterrorism and public health preparedness and response topics in medical school curricula.[73]

Event Epidemiology

The challenges associated with responding to a biological attack are uniquely different from those associated with responding to an explosion or to the release of a chemical agent. The effects of the latter are readily apparent, allowing early approximations to be made as to the geographic extent of the problem and the number and nature of casualties to be expected. Needed response efforts can thus be gauged and initiated immediately. For biological weapons, however, the incubation period of biological agents means there is an inherent delay from the time a covert attack is launched until the realization that an attack has occurred—most likely by the identification of sick patients. The varying incubation periods of the disease inevitably mean a delay in gauging the magnitude and scope of the attack and deploying appropriate response efforts on the basis of the epidemiology of the ensuing outbreak. However, the epidemiology of a disease outbreak from a biological attack can differ greatly from a natural disease outbreak, which can complicate event investigation and response efforts. For example, simultaneous attacks with an aerosolized biological agent in several locations could generate a large, complex geographic distribution of cases complicating efforts to develop an epidemic curve. In addition, exposure to a large inoculum of aerosolized biological agents could result in atypical disease presentations and clinical courses (e.g., shorter incubation periods, compressed and severe disease course). Furthermore, on the basis of experiences after the anthrax attacks, it is to be expected that there will be widespread apprehension, fear, and concern about the possibility of further cases—either from the spread of a contagious agent and/or from sequential attacks. Many may live in fear that they or their families will be the next victims. Experience shows that this inevitably complicates event investigation and response efforts.[8,9,74,75] For example, in the 2001 anthrax attack it was not until more than 2 weeks after the initial anthrax-laden letters were sent through the U.S. Postal Service that the index case was diagnosed and reported.[7,76] By that time nine cases of anthrax had actually occurred (two inhalational and seven cutaneous). As health and law enforcement authorities subsequently worked to determine what had happened and to implement appropriate response measures, additional anthrax-laden letters were sent (3 weeks after the initial letters), resulting in an additional 13 cases of anthrax (nine inhalational and four cutaneous).

PREPARING FOR AND RESPONDING TO BIOLOGICAL WEAPONS

Before 9/11/2001

Most physicians and public health practitioners viewed the threat of biological weapons as negligible as recently as 1997. In most schools of medicine and schools of public health, biological weapons were regarded as being morally repugnant and not a subject that should be discussed, even from the standpoint of the threats they pose.

Events such as the 1995 terrorist attack in Tokyo using sarin gas, revelations about the former Soviet Union's bioweapons program, and the discovery of Iraq's considerable investment in biological weapons created the impetus for the U.S. Congress to take some definitive steps to strengthen the country's preparedness against WMD. However, before the terrorist attacks of September 11, 2001 and the subsequent anthrax attacks, U.S. government efforts were focused largely on preventing the development and use of such weapons; comparatively little focus was placed on improving capabilities to respond to and mitigate an attack.

In May 1998, President Clinton requested that Congress provide U.S. $133 million in funds to HHS for fiscal year 1999 in support of a new program of public health preparedness in HHS. A newly appointed Assistant Secretary of Health, Dr. Margaret Hamburg, formerly New York City Commissioner of Health, was given responsibility for developing a strategic plan for HHS. Most of the funds were allocated to the CDC. Of the funds provided, $51 million was earmarked for the development of an emergency stockpile of antibiotics (the National Pharmaceutical Stockpile), primarily antibiotics for anthrax and vaccine for smallpox. The balance, $82 million, was provided for the initial steps in rebuilding the long-neglected public health infrastructure at federal, state, and local levels. Some of the funds were used in 1999 to create a laboratory network, under the direction of the CDC, to provide laboratory surge capacity, emergency assistance, and support to state and local public health laboratories for the identification of biological threat agents and later chemical threats. Subsequently, veterinary, military, government food testing, and some international laboratories were added to the network.

After 9/11/2001

The anthrax letter attacks in the fall of 2001 exposed the inadequacy of the United States' ability to respond to a biological attack. Preparedness and response gaps were identified across all levels of government. To address the identified gaps in preparedness, widespread actions—including numerous laws and new appropriations—were implemented. For example, in October 2007 the White House released Homeland Security Presidential Directive-21 (HSPD-21) establishing a *National Strategy for Public Health and Medical Preparedness*. This strategy was created to specifically address preparedness for catastrophic health events, defined as "any natural or manmade incident, including terrorism that results in a number of ill or injured persons sufficient to overwhelm the capacities of immediate local and regional emergency response and health care systems."[77] Over time, broader preparedness for public health threats beyond those posed from biological agents was desired, leading to enactment in 2006 of the Pandemic and All-Hazards Act (PAHPA), with the stated mission "to improve the Nation's public health and medical preparedness and response capabilities for emergencies, whether deliberate, accidental, or natural."[78] One of the elements of this new law was the creation of the Biomedical Advanced Research and Development Authority (BARDA) within the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) with a focus on advanced product research and development, as well as the acquisition of vaccines, biologics, drugs, and diagnostics for use in public health emergencies.

With new legislative mandates came funding for preparedness and response improvements in medicine, public health, and research and development. Civilian biodefense spending by the federal government from fiscal year 2001 through fiscal year 2011 is estimated to have been more than $55 billion, of which $39.4 billion (72%) has been to HHS.[79] This allotment does not include $5.6 billion placed in a Special Reserve Fund created in October 2003 for the purchase of medical countermeasures over a 10-year period (Project BioShield). However, this biodefense funding includes programs that have no expressly stated civilian biodefense program elements. When all hazards programs that do not have a stated biodefense goal or mission are excluded, as well as funding provided for pandemic influenza and Department of Defense (DoD) funds for troops, the total funding for civilian biodefense drops to approximately $11 billion. Of that amount, a total of $1.3 billion (11.8%) was allocated to HHS and $8.3 billion (75%) to DHS.[79] Among HHS agencies the CDC, the National Institutes of Health (NIH) (primarily the National Institute of Allergy and Infectious Diseases), and ASPR each received about 30% of budgeted funds and the Food and Drug Administration (FDA) received approximately 8%.[79]

Public Health Preparedness and Response

The CDC administers funds for preparedness to state and local public health systems through the Public Health Emergency Preparedness (PHEP) Cooperative Agreement.[80] Public health departments use their PHEP funds to strengthen their capabilities to respond to all types of public health emergencies, including emerging infectious diseases, natural disasters, and biological, chemical, nuclear, and radiologic events. Since 2002 the CDC has provided nearly $9 billion to public health departments across the United States for preparedness under the PHEP Cooperative Agreement. In 2011 the CDC issued a set of 15 public health preparedness capabilities to assist state and local planners in identifying preparedness gaps, determining priorities, and developing plans for improving capabilities that align with national priorities.[81]

In 2004 the CDC created the Cities Readiness Initiative (CRI) as part of the PHEP Cooperative Agreement.[82] The initiative initially sought to assist 21 major cities to develop plans to rapidly receive, distribute, and dispense medical countermeasures within 48 hours from the National Stockpile in the event of a large-scale public health emergency. The program was expanded to 72 metropolitan statistical areas (MSAs) encompassing 57% of the U.S. population with at least one MSA in each state. Each jurisdiction is assessed on its medical countermeasure distribution and dispensing capabilities; only 13 (18.8%) of the jurisdictions were in the unacceptable range in the period 2008-2009.

A major challenge to public health officials is that of instituting necessary measures to avoid panic in the face of an epidemic of a traditionally feared disease. Reviews of past epidemics indicate that the most essential factor is effective leadership and competent, frequent, and open communication with the public, the press, professionals, and others concerned in dealing with the epidemic. This is an area that is too often neglected. The 2001 anthrax outbreak illustrated the problems resulting from inadequate lines of communication.[83] Health departments at all levels were overwhelmed by requests for information from the public, from health professionals, and especially from the media. None had experienced an epidemic threat such as this, and none were prepared. Frequent, authoritative, up-to-date reports through the media to the public proved absolutely vital, but it took time before a pattern for these became established. The need for communication between and among professionals was clear, and this is now being addressed in part by the national Health Alert Network, which is financed by federal preparedness funds.[84] It was also apparent that command centers were required to coordinate and direct operations and to facilitate the flow of information, but these took time to become established and to begin to function well. Sophisticated centers are now in place in the Secretary's Office at HHS, the CDC, and in many states and cities; they are now staffed on a 24-hour-per-day, 7-day-per-week schedule. Information and education materials have been prepared with respect to Category A diseases and are available throughout the health system. Of importance is the fact that at federal, state, and local levels, exercises are being conducted to test response systems to determine how well they are actually functioning.

A second factor in muting the likelihood of panic is to do everything possible to keep the normal day-to-day activities of citizens and the city as minimally disrupted as possible. Public officials at all levels have often been prone to want to invoke quarantine measures, whether to close airports or other parts of the transportation network or to forbid entry or departure from cities or other large areas. This was the case in all countries that reported cases of severe acute respiratory syndrome (SARS) in 2003. Experience has shown that quarantine measures are seldom effective and, in fact, often lead to more serious problems as many seek to flee an area or deny the presence of possible cases in family or friends, thus precluding appropriate containment measures.[85]

Laboratory Systems

A network of national, reference, and sentinel laboratories define the Laboratory Response Network (LRN), which was established by HHS at the CDC in 1999 under Presidential Decision Directive 39.[86] The network includes a component that specifically addresses biological terrorism in collaboration with the Association of Public Health Laboratories and the FBI. It defines a tiered system of laboratories for the identification and verification of biological agents. At the base of the network are approximately 25,000 sentinel laboratories composed of hospital and commercial diagnostic laboratories. These form the base of the network providing routine diagnostic services and ruling out the presence of biological threat agents in Biosafety Level (BSL)-1 and BSL-2 environments. The American Society of Microbiology works closely with the CDC and sentinel laboratories to provide needed protocols and training for laboratorians. The sentinel laboratories refer questionable samples to the second tier of approximately 150 reference laboratories that function as high as BSL-3 for further identification and investigation. This tier includes state and local public health, military, veterinary, agriculture, food, and water testing laboratories. Additionally, certain countries, such as Australia, Canada, the United Kingdom, Mexico and South Korea, have their own reference laboratories. Final confirmation of a threat agent is done at national laboratories capable of functioning at BSL-4 if needed. These laboratories have capabilities to conduct specialized strain characterization and bioforensics and are found at the CDC, U.S. Army Medical Research Institute of Infectious Diseases, and Naval Medical Research Center.

Great improvements have been made since the start of the LRN, but there is current evidence of slowed or reversing progress. In 2011 cuts in funding resulted in 44% of state public health laboratories being unable to renew their equipment/instrument maintenance contracts: 40% were unable to send staff to continuing education courses, and 40% lost at least one full-time laboratory position.[87] In 2012, persisting funding cuts resulted in 13 state public health laboratories reporting that in the event of an infectious disease outbreak lasting 6 to 8 weeks, they did not have sufficient capacity to work five 12-hour-day work weeks.[88]

Biosurveillance Systems

A multicomponent interagency, Biosurveillance Initiative, was created and funded beginning in fiscal year 2004 to fill the gap in surveillance and early warning of a potential terrorist attack or infectious disease outbreak. The initiative has three integrated elements. The first component is BioSense, a multistate data-sharing program managed by the CDC, using existing health databases originally in near real time to identify possible bioterrorist events or epidemics using an experimental approach called syndromic surveillance.[89-92] The system receives input from approximately 2000 hospitals (government and private) and other health care facilities, nearly 2800 laboratories, and almost 50,000 pharmacies. BioSense was upgraded in 2011 to BioSense 2.0. This is now in the distributed cloud computing environment to provide real-time information.[93] Under a data use agreement, state and local health departments along with the CDC can share information across jurisdictional borders when enhanced surveillance is necessary in emergencies.

Initially the surveillance effort focused on the detection of possible bioterrorism events or infectious disease outbreaks. However, in time,

the system has evolved to attempt to detect and then monitor a range of public health hazards. Although intuitively attractive, it remains to be determined whether this or any other surveillance system can be satisfactorily sustained, and at what cost, in the absence of regularly occurring and valid alarms that test the system.[94] Furthermore, it appears that the system has been used primarily to monitor events once they have been identified by other means, suggesting failed use as a detection system.[93]

Expansion of quarantine stations at U.S. ports of entry and land-border crossings where international travelers arrive is the second Biosurveillance Initiative element to improve monitoring of travelers, imported foodstuffs, and research materials. By the end of 2007 the number of quarantine stations had increased to 20 stations from a low of 8. It is unclear as to what contributions of significance they have brought to better surveillance that warranted increasing the number of quarantine stations. The third component of the initiative expanded the LRN to include food safety and animal diagnostic laboratories. This recognizes that an early warning of an attack may be noted in contaminated food or new or unusual animal diseases that could be transmitted to humans.

In a separate but related activity funded by DHS, the LRN and the Environmental Protection Agency (EPA) participate in the BioWatch Program, consisting of air sampling devices located in previously existing EPA air sampling locations in more than 30 major U.S. cities. Its goal is to rapidly detect the presence of any of a targeted number of aerosolized biological agents. The original system, first deployed in 2003, used multiple air samplers in each city. In 2005 the system was expanded to increase outdoor air sampling in each city and to add indoor facility monitoring. The estimated 10-year cost of the current system is $0.6 billion with an annualized cost of $80 million. A proposed expansion of the program to include more cities with more detection devices per city would increase the annualized cost to $200 million.[95] Although the system has not reported any false-positive results, it has had several "BioWatch Actionable Results" due to detection of airborne, naturally occurring DNA in the environment. Such identification, if declared before further information was known, could have caused considerable public concern. Illustrative of the problem was an event in October 2003 when two air monitors in Houston, Texas, detected the presence of tularemia on 2 consecutive days. Area hospitals and infectious disease specialists were warned about the possibility that a release had taken place, but authorities refrained from taking more definitive action, such as the mass community-wide distribution of antibiotics.

In its 2011 evaluation report of BioWatch, the Institute of Medicine noted that other public health system–based surveillance systems are more flexible and broader than BioWatch and are more experienced in surveillance because it is fundamental to their activities. With this in mind, the Institute recommended that HHS lead efforts to enhance DHS's surveillance capabilities with BioWatch. Furthermore, the Institute stated that BioWatch needs to overcome significant technical and operational testing challenges, improve its usefulness greatly through better collaboration with public health systems, and engage an external advisory panel of experts with technical and operational expertise.[95]

Clinician and Health Care System Preparedness and Response

Deliberate or naturally occurring infectious disease threat may quickly overwhelm even the well-resourced health care system and disrupt delivery of medical care. To improve preparedness and increase resilience, HHS established the National Bioterrorism Hospital Preparedness Program (NBHPP) in 2002 to provide funding and guidance to hospitals to enhance their ability to respond to a biological attack.[96] The program was administered by the Health Resources and Services Administration (HRSA) until 2006, when it was transferred to ASPR by PAHPA and renamed the Hospital Preparedness Program (HPP). Under PAHPA, HPP has expanded its scope to improve community and hospital preparedness for all-hazards public health emergencies. Since 2002, HHS has provided more than $2 billion to states, territories, and eligible municipalities through grants, partnerships, and cooperative agreements under HPP.[97]

In 2009 the Institute of Medicine constituted a committee to develop guidance for health care systems to establish and implement standards of care during disasters when resources were severely constrained.[98] The committee defined "crisis standards of care" as a state where "a substantial change in health care operations and the level of care that can be delivered in a public health emergency is justified by specific circumstances."[98] The committee also developed templates to guide the efforts of professionals and organizations responsible for disaster planning and implementation and emphasized the need for integrated planning for a coordinated response with public health systems. In 2012, a survey of acute care hospitals determined that more than 94% of hospitals participated in a discrete entity, partnership, organization, coalition, planning group, consortium, or other agreement with other hospitals and community partners for emergency preparedness and response.[99]

The difficulties of sharing health care providers licensed in one state but not another was highlighted after the events of September 2001. In response, a mandated federal system of guidelines and standards was created to register, credential, and allow deployment of medical professionals across state jurisdictions in the event of a large-scale national emergency. The state-based system, called the Emergency System for Advance Registration of Volunteer Health Professionals, is implemented at the state level with federal assistance, initially from HRSA and, since December 2006, from ASPR.[100]

In the event of a large bioterrorist incident requiring supplementation of clinical response efforts, both the National Disaster Medical System (NDMS) and the Medical Reserve Corps (MRC) can be activated.[101,102] NDMS, a system coordinated by HHS, acts to temporarily supplement state and local medical care needs after a disaster of any kind. NDMS can provide personnel, supplies, equipment at the site or at definitive care sites in unaffected areas, and patient care movement. Disaster medical assistance teams (DMATs) are local units activated for 2-week deployments with sufficient supplies and equipment to be self-sustaining for at least 72 hours before resupply is necessary. In the event of a national disaster, DMATs may be moved from their local area, at which time they are made federal employees with medical credentials recognized in all states and protected under the Federal Tort Claims Act against any malpractice claim. Predisaster employment is protected under the Uniformed Services Employment and Reemployment Rights Act. The MRC was created in 2002 as community-based and locally organized groups of health care volunteers who donate their time and expertise to prepare for and respond to existing emergency medical and public health resources when needed. There are more than 300 units in the United States. Units have been active, for example, in providing services after hurricanes. The Office of Surgeon General acts as a clearinghouse for information and best practices in establishing and maintaining MRC units. Liability protection for individual MRC practitioners is determined by each state.

MEDICAL COUNTERMEASURES

Medical countermeasures include drugs, vaccines, diagnostic tests, and other equipment and supplies needed to respond to a public health emergency. HHS has the mission to protect the U.S. civilian population against biological threats by providing leadership in the research, development, regulation, procurement, stockpiling, maintenance, deployment, and utilization of medical countermeasures. As such, HHS is pursuing a unified, integrated approach to its mission through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), a coordinated, interagency partnership that fosters the medical countermeasure programs necessary to improve public health emergency preparedness, as well as to prevent and mitigate the adverse health consequences associated with biological threats.[103] Since its inception, PHEMCE has achieved significant success in developing and stockpiling medical countermeasures for several of the priority threat agents. Table 15-4 lists medical countermeasures available for biological agents for which there are MTDs.

Medical Countermeasure Research and Development

Before the anthrax letter attacks in late 2001, research specifically directed at problems posed by biological weapons was principally

TABLE 15-4 Medical Countermeasures (MCMs) for Biological Agents with Material Threat Determinations

MTD AGENT	CATEGORY	MCMS[a] DIAGNOSTICS	PREEXPOSURE PROPHYLAXIS	POSTEXPOSURE PROPHYLAXIS (PEP)	TREATMENT
Gram-Positive Organisms					
Bacillus anthracis (anthrax)	A	Conventional microbiology and culture methods Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	Vaccine • BioThrax[b] Antitoxin • Raxibacumab[f]	Antimicrobials[c] • Quinolones ◦ Ciprofloxacin ◦ Levofloxacin • Tetracyclines ◦ Doxycycline • Penicillins[d] ◦ Penicillin G ◦ Amoxicillin [IND or EUA][e] Vaccine (in combination with antimicrobials)[c] • BioThrax [IND or EUA][b] Antitoxin (in combination with antimicrobials) • Raxibacumab[f]	Antimicrobials[g] • Quinolones ◦ Ciprofloxacin [IND or EUA] • Tetracyclines ◦ Doxycycline • Penicillins ◦ Penicillin G Antitoxin (in combination with antimicrobials) • Raxibacumab[f]
Multidrug-resistant *B. anthracis* (MDR anthrax)	A	Microbial culture with antimicrobial susceptibility testing Rapid antimicrobial susceptibility testing available at specialized reference laboratories	Vaccine • BioThrax[b] Antitoxin • Raxibacumab[f]	Antimicrobials[c] • Selection of antimicrobial agents for PEP based on susceptibility testing Vaccine (in combination with antimicrobials)[c] • BioThrax [IND or EUA][b] Antitoxin (in combination with antimicrobials) • Raxibacumab[f]	Antimicrobials[g] • Selection of antimicrobial agents for treatment based on susceptibility testing Antitoxin (in combination with antimicrobials) • Raxibacumab[f]
Gram-Negative Organisms					
Burkholderia mallei (glanders) and *Burkholderia pseudomallei* (melioidosis)	B	Microbial culture and biochemical methods Serologic and nucleic acid based diagnostics available at specialized reference laboratories	N/A	Antimicrobials[h] • Sulfonamides ◦ TMP-SMX [IND or EUA] • Penicillin ◦ Amoxicillin/clavulanic acid (co-amoxiclav) [IND or EUA]	Antimicrobials *IV intensive phase*[i] • Cephalosporins ◦ Ceftazidime [IND or EUA] • Carbapenems ◦ Meropenem [IND or EUA] *Oral eradication phase*[i] • Sulfonamides ◦ TMP-SMX [IND or EUA] • Penicillin combination ◦ Amoxicillin/clavulanic acid (co-amoxiclav) [IND or EUA]
Franciscella tularensis (tularemia)	A	Conventional microbiology and culture methods Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	N/A	Antimicrobials[k] • Quinolones ◦ Ciprofloxacin [IND or EUA] • Tetracyclines ◦ Doxycycline	Antimicrobials *Contained casualty*[j] • Aminoglycosides ◦ Streptomycin ◦ Gentamicin [IND or EUA] *Mass casualty*[m] • Quinolones ◦ Ciprofloxacin [IND or EUA] • Tetracyclines ◦ Doxycycline
Rickettsia prowazekii (typhus)	B	Conventional serologic testing and microbial culture Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	N/A	N/A[n]	Antimicrobials[o] • Tetracyclines ◦ Doxycycline
Yersinia pestis (plague)	A	Conventional microbiology and culture methods Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	N/A	Antimicrobials[p] • Quinolones ◦ Ciprofloxacin ◦ Levofloxacin • Tetracyclines ◦ Doxycycline	Antimicrobials[q] • Quinolones ◦ Levofloxacin • Aminoglycosides ◦ Streptomycin ◦ Gentamicin
Toxins					
Botulinum toxins (botulism)	A	Conventional serologic testing Rapid diagnostic tests for nucleic acid and antigen/toxin detection available at specialized reference laboratories	N/A	N/A	Antitoxin • hBAT (botulism antitoxin heptavalent (A, B, C, D, E, F, G)[r] • BabyBIG [Botulism Immune Globulin Intravenous (Human) BIG-IV)][s]

TABLE 15-4 Medical Countermeasures (MCMs) for Biological Agents with Material Threat Determinations—cont'd

MTD AGENT	CATEGORY	MCMS[a] DIAGNOSTICS	PREEXPOSURE PROPHYLAXIS	POSTEXPOSURE PROPHYLAXIS (PEP)	TREATMENT
Viruses					
Ebola virus (hemorrhagic fever)	A	Serologic testing and virus isolation Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	N/A	N/A	N/A
Marburg virus (hemorrhagic fever)	A	Serologic testing and virus isolation Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	N/A	N/A	N/A
Variola virus (smallpox)	A	Serologic testing Rapid diagnostic tests for nucleic acid and antigen detection available at specialized reference laboratories	Vaccine • ACAM2000[t] • IMVAMUNE [IND or EUA][u]	Vaccine[v] • ACAM2000[t] • IMVAMUNE [IND or EUA][u]	Antivirals • Arestvyr (USAN tecovirimat; aka ST-246) [IND or EUA][w] • CMX001[IND][x]

a. MCMs noted have approved/licensed indication unless otherwise noted as Investigational New Drug [IND] or Emergency Use Authorization [EUA].

b. Licensed for active immunization for the prevention of disease caused by *B. anthracis*, in persons 18 through 65 years of age at high risk of exposure—http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/UCM074923.pdf.

c. Recommendation for postexposure prophylaxis is 60 days of oral antimicrobial therapy (based on susceptibility testing) in combination with a three-dose regimen of anthrax vaccine (BioThrax). Ciprofloxacin and doxycycline are considered equivalent first-line antimicrobial agents for postexposure prophylaxis; other antibiotics may be considered for off-label use in patients unable to tolerate approved antibiotics for postexposure prophylaxis (e.g., clindamycin, chloramphenicol, rifampin, vancomycin, and other quinolones—http://wwwnc.cdc.gov/eid/article/14/4/07-0969_article.htm).

d. Penicillins should not be initially used for postexposure prophylaxis because of concern for resistance.

e. Amoxicillin can be used for postexposure prophylaxis once the *B. anthracis* strain has been proven penicillin susceptible, when other antimicrobial agents are not considered safe to use, such as for pediatric patients and for nursing or pregnant women— http://wwwnc.cdc.gov/eid/article/14/4/07-0969_article.htm.

f. Raxibacumab is approved to treat inhalational anthrax and to prevent inhalational anthrax when alternative therapies are not available or not appropriate—http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125349s000lbl.pdf.

g. Recommendation for initial therapy is IV ciprofloxacin or IV doxycycline plus one or two additional antibiotics with adequate central nervous system penetration and in vitro activity against *B. anthracis* (e.g., ampicillin, penicillin, rifampin, vancomycin) based on susceptibility testing; ciprofloxacin is recommended over doxycycline as the primary antimicrobial agent unless ciprofloxacin use is contraindicated; clindamycin is strongly recommended for inclusion in the antimicrobial regimen because of its ability to inhibit protein synthesis; therapy should be continued for 60 days with a switch to oral antibiotics when clinically appropriate—http://wwwnc.cdc.gov/eid/article/14/4/07-0969_article.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm.

h. Recommended duration of postexposure prophylaxis is 21 days; if the organism is susceptible and the patient does not have a documented allergy, TMP-SMX is the agent of first choice; if the organism is resistant to TMP-SMX or the patient is intolerant, the second-line choice is co-amoxiclav—http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm.

i. Recommended duration of intensive therapy is generally 10 to 14 days; however, more than 4 weeks of parenteral therapy may be necessary in cases of more severe disease; ceftazidime is recommended if no complications; meropenem is recommended for patients with neuromelioidosis or persistent bacteremia or in intensive care unit—http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm.

j. Recommended duration of therapy is a minimum of 12 weeks. If the organism is susceptible and the patient does not have a documented allergy, oral TMP-SMX is the agent of first choice; if the organism is resistant to TMP-SMX or the patient is intolerant, the second-line choice is co-amoxiclav—http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm.

k. Recommended duration of postexposure prophylaxis is 14 days of oral doxycycline or ciprofloxacin—http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#2.

l. Recommended duration of parenteral antimicrobial therapy in a contained casualty setting is 10 days; streptomycin is recommended drug of choice; gentamicin is an acceptable alternative. Doxycycline, ciprofloxacin [IND or EUA], and chloramphenicol are recommended alternatives; relapses and primary treatment failures occur at a higher rate with these antimicrobials than with aminoglycosides; they should be given for at least 14 days to avoid relapse—http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#2.

m. Recommended duration of oral antimicrobial therapy in a mass casualty setting is 14 to 21 days for doxycycline and 10 days for ciprofloxacin—http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#2.

n. Antibiotics are not recommended for PEP for rickettsial diseases—http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/rickettsial-spotted-and-typhus-fevers-and-related-infections-anaplasmosis-and-ehrlichiosis.htm.

o. Recommended duration of oral antimicrobial therapy is 5 days of oral doxycycline; chloramphenicol is an alternative—Botelho-Nevers E, Socolovschi C, Raoult D, Parola P. Treatment of *Rickettsia* spp. infections: a review. *Expert Rev Anti Infect Ther*. 2012;10(12):1425-1437.

p. Recommended duration of postexposure prophylaxis is 7 days; doxycycline and ciprofloxacin are recommended antimicrobials; levofloxacin is also approved for postexposure prophylaxis—http://www.cdc.gov/plague/healthcare/clinicians.html; http://jama.jamanetwork.com/article.aspx?articleid=192665.

q. Recommended duration of treatment is 10 days or until 2 days after fever subsides; streptomycin and gentamicin are preferred antimicrobials; doxycycline, ciprofloxacin, and chloramphenicol are alternative agents; levofloxacin is also approved for treatment—http://www.cdc.gov/plague/healthcare/clinicians.html.

r. Approved for the treatment of symptomatic botulism after documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients—http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf.

s. Approved for infant botulism caused by toxin types A or B in patients younger than 1 year of age (1) —http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM117160.pdf.

t. Licensed for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection—http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142572.pdf.

u. IMVAMUNE is an investigational smallpox vaccine derived from modified vaccinia virus Ankara (MVA)—a highly attenuated pox virus that has lost the capacity to replicate in human cells—http://www.bavarian-nordic.com/pipeline/imvamune-smallpox-vaccine.aspx.

v. Vaccination within 3 days of exposure will completely prevent or significantly modify smallpox in the vast majority of persons. Vaccination 4 to 7 days after exposure likely offers some protection from disease or may modify the severity of disease—http://www.bt.cdc.gov/agent/smallpox/vaccination/faq.asp.

w. Investigational therapeutic agent active against orthopoxviruses including smallpox—http://www.siga.com/product-pipeline/.

x. Investigational therapeutic agent active against orthopoxviruses including smallpox—http://www.chimerix.com/therapeutic-programs/category/smallpox.

IV, intravenous; MDR, multidrug resistant; MTD, material threat determinations; PEP, postexposure prophylaxis; TMP-SMX, trimethoprim-sulfamethoxazole.

conducted by the U.S. Army Medical Research Institute for Infectious Diseases in Frederick, Maryland. Under the provisions of the BWC, research was focused on the development of medical countermeasures against validated threat agents.[18] The 2001 attack on the civilian population highlighted the need for research leading to medical countermeasures not only for a small number of healthy adults functioning on the battlefield but for the entire population, with special consideration being given to both the very young and very old and those with comorbid health conditions. Accordingly, the federal government expanded its efforts in this area and gave HHS the lead for developing medical countermeasures to protect the entire civilian population.

In the immediate aftermath of the 2001 anthrax attack, one of the most urgent challenges was to prepare to deal with the two agents that had received the most attention during the course of the Soviet biological weapons program and which presumably could have been acquired or developed by any of a number of countries—smallpox and anthrax. Routine smallpox vaccination had stopped in 1972 coincident with progress in the smallpox eradication program and a decreasing risk of importation of the disease. Only 15 million doses of smallpox vaccine remained in storage. It had been produced in 1978. This amount was woefully insufficient to cope with epidemic smallpox should the virus be released. The old vaccine had been a crude preparation produced on the skin of calves and would not meet the standards of a contemporary vaccine. After the 1980 declaration that smallpox had been eradicated, vaccination stopped everywhere and all production facilities were dismantled or converted to other uses. It was estimated then that 5 to 8 years would be required, after traditional vaccine development protocols, to develop, produce, and license a new vaccine, grown, as are contemporary vaccines, in tissue cell culture. The pathway from discovery through development, production, and final FDA approval of a new product is costly, as well as time consuming, with a price tag estimated to be between $800 million and $1.2 billion.[104]

The perceived need for enough smallpox vaccine for the nation led HHS in the autumn of 2001 to set the goal of securing—as soon as possible—sufficient vaccine for every American. In less than 18 months, the vaccine had been produced and tested for antigenicity and was delivered to the Strategic National Stockpile ready for use as an investigational new drug in the event of an emergency. However, it was recognized that under emergency conditions, it would be impossible to fulfill the formal requirements to satisfy an Investigational New Drug application. Accordingly, plans were made for the vaccine to be used before licensure when authorized by the HHS Secretary under an Emergency Use Authorization. Licensure was granted by the FDA on August 31, 2007.[105]

Having the vaccine was not enough. Definitive planning and training by state, city, and regional authorities were requisite if large-scale vaccination programs were to be conducted. Such preparations are still lacking as the nation's response to the influenza A/H1N1 pandemic in 2009-2010 highlighted. For example, despite more than 8 years of preparatory work, the public health response in providing timely access to vaccines and antiviral products would be unacceptable faced with a smallpox epidemic challenge.

A comprehensive review of all-hazards medical countermeasure preparedness was conducted by the National Biodefense Science Board (NBSB) in 2010. They identified seven advances made by the U.S. government since the terrorist attacks of 2001 that specifically encourage the research, development, acquisition, and use of medical countermeasures: (1) the establishment in 2003 of the BioShield Special Reserve Fund dedicated for the procurement of medical countermeasures; (2) the creation of BARDA in 2006 to facilitate advanced research and development of medical countermeasures; (3) the creation of the Emergency Use Authority established under the Project BioShield Act of 2004; (4) finalization of the FDA Animal Rule in May 2002, under which the FDA may grant marketing approval for drugs and biologics on the basis of adequate and well-controlled animal studies when human efficacy trials are not feasible and/or ethical; (5) establishment of the Portfolio Advisory Committee to align HHS and DoD medical countermeasure development activities and resources; (6) outreach mechanisms (stakeholder meetings and workshops) of the PHEMCE; and (7) adoption of common language (technology readiness levels [TRLs]) to identify the level of product development for medical countermeasures by HHS and DoD.[106]

A broad 5-year strategic plan (2011-2016) was published by BARDA outlining five goals and five strategies for the agency.[107] The overarching PHEMCE—which integrates all aspects of emergency preparedness and response across both the public and private sector, including medical countermeasures—strategic plan with a linked 5-year implementation plan incorporates the goals of BARDA in its plan.[6,108] Advanced development priorities in the biodefense sphere include diagnostic assays for biological threat agents, a new-generation anthrax vaccine, botulinum antitoxin, smallpox antivirals and a new vaccine with a lower adverse event profile, and viral hemorrhagic fever antivirals.[108]

Strategic National Stockpile

The Strategic National Stockpile (SNS) is an important part of the response armamentarium after a biological attack.[109] The stockpile is managed by the CDC and contains antibiotics, antitoxins, vaccines, life-support medications, and medical supplies that can be used to supplement state and local resources during a large-scale public health emergency. Within 12 hours of a request, a Push-Package containing an initial supplemental cache of medical countermeasures and supplies can be at the targeted destination. These packages have been prepositioned in strategically located secure warehouses to facilitate prompt delivery. If additional support is necessary, a vendor-managed inventory is called on to deliver ongoing needed medical countermeasures and supplies.

Emergency Use Authorization

During a public health emergency such as an attack involving a biological agent, medical countermeasures may be necessary before they have completed their development pathway to approval (drugs), licensure (vaccines and biologics), or clearance (diagnostics) by the FDA. Although individual physicians may engage in off-label use of an approved or licensed product, investigational products require a detailed informed consent. In a public health emergency during which large numbers of people would need to be given medical countermeasures, meeting this requirement in full could lead to delayed care with possible heightened morbidity and mortality. To address this issue, the FDA may issue an Emergency Use Authorization allowing the use of an unapproved medical product or the unapproved use of approved medical products during a declared emergency if there are no adequate, approved, and available alternatives and if other statutory criteria are met.[110]

DUAL USE: THE TWO-EDGED SWORD OF MODERN BIOLOGY

The rapidly accruing knowledge base of modern biology is making it possible to understand such factors as mechanisms for immune system or host restriction evasion. Furthermore, it is now possible to synthesize and manipulate genomes. Examples of microbial manipulations of greatest concern include the transfer of antibiotic resistance, modification of the antigenic properties, modification of the stability in the environment, and the transfer of pathogenic properties.[111,112] What once were the tools of exploration used only by the most sophisticated laboratories are now increasingly present in laboratories around the world and even in high school laboratories. Moreover, the de novo synthesis of entire organisms is now possible.[113-115] For those interested in biological weapons, a new world has opened.

Several scientists have reported in the open literature on the development of antibiotic-resistant strains of anthrax.[38,64,116] Apart from research dealing directly with biological select agents, unexpected and unintended results are possible when working with other microbes as happened with researchers at the John Curtin School in Australia.[117] In an effort to develop a virally vectored contraceptive vaccine, they added a single cytokine gene to the mousepox virus and found, to their surprise, that it suppressed the cell-mediated immune response resulting in high mortality—even in mice immunized against mousepox virus that would normally be fully protected. The question of whether the addition of this cytokine gene to the smallpox virus, which is closely related to mousepox virus, would suppress the immune defenses

of man resulting in increased virulence cannot be definitively answered. However, this event illustrates the risks posed by advances in biology. Certainly, one must anticipate the potential of many more experiments over the years ahead that might have unintended consequences, some of which could be catastrophic.

Such experiments comprise "dual-use research of concern"—commonly referred to as DURC—defined as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security."[118] Restricting access to known biological pathogens of concern to those with a legitimate need and ensuring effective control, or at least responsible stewardship, of knowledge and information are vexing challenges yet to be fully resolved. The problem is that the more extensive and restrictive the controls, the more difficult it will be to undertake studies that are necessary to produce better vaccines, drugs, and other products. For example, knowing precisely which gene of an organism causes damage and how it acts may permit a highly targeted vaccine or drug, but at the same time it identifies a gene that if inserted into another organism could potentially produce a devastating effect.

Appropriate restrictions are believed to be required, but determining what those should be, balancing security needs with the needs of freedom for inquiry, is not easy. In the United States, it is a federal crime to knowingly develop, produce, stockpile, transfer, acquire, retain, or possess any biological agent, toxin, or delivery system for use as a weapon or knowingly assist a foreign state or any organization to do so and to knowingly possess any biological agent, toxin, or delivery system that is not reasonably justified by a prophylactic, protective, bona fide research, or other peaceful purpose.[119]

In addition to criminal penalties related to the development, possession, or use of biological weapons, the United States employs a number of programs to prevent or limit access to the materials, information, and knowledge that could be used to create a biological weapon. For example, the U.S. Department of Commerce enforces export controls over certain biological agents, toxins, and dual-use equipment and technologies.[120] In addition, HHS and the U.S. Department of Agriculture (USDA) maintain a list of select biological agents and toxins that could threaten public health and safety and are subject to regulations regarding their possession, use, and transfer.[121] Under the Select Agent Program all persons possessing, using, or transferring select agents are required to register with HHS or USDA as appropriate and to meet established biosafety and security standards and procedures. The possession, transport, and receipt of select agents is prohibited by restricted persons, including individuals under indictment for or convicted of a crime punishable by imprisonment for more than 1 year; foreign nationals from countries determined by the Secretary of State to repeatedly supply support for acts of international terrorism; individuals dishonorably discharged from the U.S. Armed Services; individuals adjudicated as a mental defective or who have been committed to any mental institution; and unlawful users of controlled substances.

The direct and indirect costs and complexity of physical facilities and procedures that limit access under the Select Agent Program are consequential. For example, both the NIH and the CDC have undergone costly major infrastructure modifications to their respective campuses to enhance security and strengthen procedures to limit access to select agents. Some laboratories have had to abandon or forego studies on these threat agents simply because of the security requirements related to undertaking such research. The costs of registering and policing compliance are likewise substantial. More salient is the question of what efficacy these procedures may have in deterrence, recognizing that few other nations have implemented measures that are, in any way, comparable.

Although preventing access to biological agents, toxins, and dual-use equipment and technologies is challenging to say the least, preventing access to dual-use information is even more daunting. In 2003 the U.S. National Academy of Sciences' Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology issued a report (colloquially known as the Fink report) on ways to balance national security and scientific openness. The Committee recommended that a system of responsible oversight, consisting of voluntary self-governance by the scientific community and an expansion of existing regulatory processes, be developed for scientific experimentations in the life sciences in order to hinder their unintentional development as weapons.[122] In response to the Fink report, the National Science Advisory Board for Biosecurity (NSABB) was established to "provide advice to federal departments and agencies on ways to minimize the possibility that knowledge and technologies emanating from vitally important biological research will be misused to threaten public health or national security."[123] The Board's tasks include recommending strategies for enhancing the culture of responsibility among individuals with access to biological select agents and toxins; advising on polices governing publication, public communication, and dissemination of dual use research methodologies and results; and advising on policies regarding the conduct, communication, and oversight of dual-use research and research results.

Recently, two separate studies describing the successful genetic manipulation and rescue of mutant strains of highly pathogenic avian influenza A, subtype H5N1, with increased stability and enhanced transmissibility in mammals were published in the scientific literature.[124,125] Due to biosecurity concerns, the U.S. government was alerted by the journal editors before the publications. The Board was tasked with reviewing, assessing the impact, and recommending the most appropriate course of action regarding the unpublished manuscripts. After much deliberation, the Board recommended that the manuscripts be revised to not include the methodological details that could enable replication of the experiment by those who would seek to do harm. HHS provided the Board's nonbinding recommendations to the study authors and journal editors.[126] As a result, the original manuscripts were revised accordingly. After further careful deliberation, the Board recommended the publication of both revised manuscripts, noting that the data described in the revised manuscripts do not appear to be directly enabling and no longer posed an immediate threat to public health or national security.[127]

In light of the H5N1 controversy, the Board recommended that the federal government develop an oversight policy that would augment existing approaches to evaluating research that has the potential to be misused for harmful purposes. The White House Office of Science and Technology Policy (OSTP) released a policy statement entitled *Oversight of Life Sciences Dual Use Research of Concern*, which governs the way all federal departments and agencies track and maintain oversight on federally funded life sciences research with potential dual-use concerns.[128] Specifically, departments and agencies conducting or funding research that involves 1 or more of the 15 agents or toxins listed in the policy statement and produces, aims to produce, or is reasonably anticipated to produce one or more of the seven effects detailed in the policy statement will need to submit reports to the Assistant to the President for Homeland Security and Counterterrorism on a yearly basis.

Although proponents of this policy believe that it is necessary to increase scrutiny and oversight of DURC, many expressed concern that the unintended consequence will be the lack of transparent communication in the research field that can propel the development of medical countermeasures. The federal government is working diligently to develop a mechanism to allow secure access of the information to those with a legitimate need in order to achieve important public health goals. This path is difficult and may require legislative support and codification in order to achieve reasonable goals, but the need is real and urgent.

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