Chapter 1

HISTORICAL OVERVIEW: FROM POISONED DARTS TO PAN-HAZARD PREPAREDNESS

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INTRODUCTION

Humans have used technology for destructive as well as beneficial purposes since prehistory. Aboriginal use of curare and amphibian-derived toxins as arrow poisons anticipated modern attempts to weaponize biological toxins such as botulinum and ricin. The derivation of the modern term "toxin" from the ancient Greek term for arrow poison, τωξικον φαρμακον (toxicon pharmicon; toxon = bow, arrow)[1,2] underscores the historical link between weaponry and biological agents.

Multiple factors confound the study of the history of biological weapons, including secrecy surrounding biological warfare programs, difficulties confirming allegations of biological attack, the lack of reliable microbiological and epidemiological data regarding alleged or attempted attacks, and the use of allegations of biological attack for propaganda and hoaxes. A review of historical sources and recent events in Iraq, Afghanistan, Great Britain, and the United States demonstrates that interest in biological weapons by state-sponsored programs, terrorists, and criminal elements is likely to continue. Humankind is witnessing a "democratization in the life sciences," in which the field is becoming industrialized and therefore making biotechnology available to an ever increasing number of people, some of whom will undoubtedly have ill intent. In addition, there are growing concerns that well-intentioned life sciences research to advance medical defenses against biological weapons agents and other highly virulent pathogens may inadvertently provide information that could be deliberately misused for biological weapons proliferation.[3]

Numerous historical examples exist of military disasters resulting from failures to adapt policy, strategy, and doctrine to offset the impact of revolutionary advances in weapons technology.[4] Biological medical defense programs, begun as narrowly focused efforts to counter a limited number of biological weapons agents, are being expanded as versatile capabilities, with a shift in emphasis from pathogen-specific approaches to capabilities-based programs to enable rapid responses to novel, potentially genetically engineered biological weapons agents. The response to biological weapons has fueled robust enterprises in basic and applied medical research, product development, manufacturing, stockpiling, infrastructure, public health policy, planning, and response capacities at local, national, and international levels.[5] Medical capabilities and biomedical research are being linked to diplomacy, commerce, education, ethics, law enforcement, and other activities to enable pan-societal sector responses to both biological weapons and the inevitable and dynamic challenges of naturally occurring emerging infectious diseases.[3] Integration of biological defense and public health programs and their mutual development must be continuous to optimize outcomes and maximize efficient utilization of limited resources, because the challenges posed by both biological weapons agents and naturally emerging pathogens are open-ended.[5]

EARLY USE

The impact of infectious diseases on military forces has been recognized since ancient times.[6,7] The use of disease as a weapon was used long before microbial pathogenesis was understood. Military leaders only knew that a cause and effect relationship existed between certain activities, locations, or exposures to victims of disease that resulted in the spread of infections that ultimately provided a military advantage. For example, an early tactic was to allow an enemy to take sanctuary in locations endemic for infectious diseases in anticipation that its troops would be afflicted, thus allowing unimpeded access of opposing armies to areas where transmission of malaria was highly likely.

Numerous anecdotal accounts exist of the attempted use of cadavers, animal carcasses, plant-derived toxins, and filth to transmit disease during antiquity through the Napoleonic era into modern times. Several examples illustrate the complex epidemiologic issues raised by biological warfare, the difficulty in differentiating epidemics resulting from biological attacks from outbreaks of disease that occur due to disruptions of war, and the adverse psychological impact of biological attacks on military operations.

During a naval battle against King Eumenes of Pergamum in 184 BCE, Hannibal ordered earthen pots filled with snakes to be hurled onto the decks of enemy ships. The pots shattered on impact, releasing live serpents among the enemy sailors. The Carthaginian victory is attributed to the ensuing panic rather than envenomation[8]; this illustrates that the psychological contagion of biological weapons may amplify their impact beyond their potential to cause organic disease.

One of the most notorious early biological warfare attacks was the hurling of cadavers over the walls of the besieged city of Caffa, a Genoese colony in the Crimea, in 1346.[9,10] After war broke out between the Genoese and the Mongols in 1343 for control of the lucrative caravan trade route between the Black Sea and the Orient, the Mongols laid siege to Caffa. The plague, later known as the Black Death, was

spreading from the Far East and reached the Crimea in 1346. The Mongols were severely afflicted and forced to abandon their siege. As a parting shot, they hurled "mountains of dead" over the city wall, probably with the use of a trebuchet, in the hope that "the intolerable stench would kill everyone inside." An outbreak of plague in the city followed. A review by Wheelis[10] suggests that the introduction of plague into the city by the cadavers—as a result of a tactically successful biological attack—may be the most biologically plausible of several competing hypotheses on the source of the outbreak. Although the predominant mode of plague transmission has been attributed to bites from infected fleas (which leave cadavers and carcasses to parasitize living hosts), modern experience (United States 1970–1995)[11] has implicated transmission from contact with infected animal carcasses in 20% of instances in which the source of the infection could be attributed. Contact with tissue and blood would have been inevitable during the disposal of hundreds or possibly thousands of cadavers. Alternatively, plague could have been introduced by imported human cases or infected rodents brought into the city through maritime trade, which was maintained during the siege. The importation of plague by a rodent-flea transmission cycle across the city wall is considered less likely because rats are sedentary and rarely venture far from their nests; it is unlikely that they would have traversed an open distance of several hundred meters between the Mongol encampment and the city walls.[10] Transmission from sylvatic to urban rodents is infrequent, at least under current ecological conditions.[12] Regardless of the portal of entry, the epidemic may have been amplified under siege conditions due to deteriorating sanitation and hygiene resulting in expansions of rats and fleas.

Smallpox was particularly devastating to Native Americans. The unintentional yet catastrophic introduction of smallpox to the Aztec empire during 1520, and its subsequent spread to Peru in advance of Pizarro's invasion of the Inca empire, played a major role in the conquest of both empires.[13] During the French and Indian Wars (1754–1763), British forces provided Native Americans with handkerchiefs and blankets contaminated with scabs from smallpox patients to transmit disease.[14–18] An epidemic of smallpox followed among the Native Americans of the Ohio River Valley. It is difficult to evaluate the tactical success of these biological attacks in retrospect because smallpox may have been transmitted during other contacts with colonists, as had previously occurred in New England and the South. Smallpox scabs are thought to have low infectivity due to the binding of virions in a fibrin matrix, and transmission by fomites has been considered less efficient than respiratory droplet transmission.[13]

THE WORLD WARS

The birth of scientific bacteriology during the 19th century provided the scientific and technical basis for modern biological weapons programs. The Hague Conventions of 1899 and 1904 outlawed the use of "poison or poisoned arms," although bacteriological weapons were not specifically addressed.[19–20] During World War I, German espionage agents reportedly infected draft animals intended for military use with *Burkholderia [Pseudomonas] mallei* and *Bacillus anthracis*.[21–23] Covert operations were reportedly conducted in Argentina, Norway, Mesopotamia, Romania, Russia, and the United States. Unsuccessful attempts were also made to cripple grain production in Spain using wheat fungus.[21]

The German biowarfare program of World War I is of special interest because it was the first program with a scientific basis; it conducted a large-scale (strategic) biological campaign, which targeted neutral nations as well as belligerents, and it targeted crops and animals instead of humans. Although German operatives thought the program was successful, confirmatory data are not available.[21]

In response to chemical warfare during World War I, the 1925 Geneva Protocol, an international protocol (for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare), was formulated by the League of Nations' Conference for the Supervision of the International Trade in Arms and Ammunition. It had no verification mechanism and relied on voluntary compliance. Many of the original signatory states reserved the right to retaliatory use, making it effectively a no first-use protocol. Signatories that began research programs to develop biological weapons between World War I and II included Belgium, Canada, France, Great Britain, Italy, The Netherlands, Poland, and the Soviet Union.[24]

After defeating Russia in the 1905 Russo-Japanese War, Japan became the dominant foreign power in Manchuria, and seized full military control between September 1931 and the end of 1932. Major Shiro Ishii, a Japanese army physician, established a biological weapons laboratory in Harbin, but soon realized that his controversial involuntary human research could not be conducted freely there. Ishii moved to a secret facility at Beiyinhe, 100 km south of Harbin, and began large-scale experimentation. All research study subjects died of either experimental infection or live vivisection. These studies continued until a prisoner

riot and escape, which resulted in the closing of the facility in 1937. However, larger and more extensive facilities were subsequently built.[24]

In 1936 Ishii built Unit 731, a massive research facility 24 km south of Harbin, where a census of 200 prisoners was kept as expendable subjects of experimentation. Ultimately, more than 3,000 Chinese prisoners were killed during these experiments. Most of the evidence was destroyed at the end of the war, and in all likelihood the actual number was much greater.[24] Additional facilities included Unit 100 at Changchun, and Unit Ei 1644 in Nanking. Unit 100 was primarily a veterinary and agricultural biowarfare research unit for developing biological weapons for sabotage. Although animals and crops were the focus of most of the research, numerous human studies were also conducted, similar to those conducted by Unit 731. In addition to conducting human experimentation, Unit Ei 1644 supported Unit 731's research efforts with bacterial agent production and flea cultivation.[24]

Eleven Chinese cities were allegedly attacked during "field trials" using agents including *Yersinia pestis*, *Vibrio cholerae*, and *Shigella spp*. These attacks may have backfired because up to 10,000 Japanese soldiers reportedly contracted cholera after a biological attack on Changde in 1941.[25] The field trials were terminated in 1943, yet basic research and human experimentation continued until the end of the war.[24–26] Despite the enormously expensive program (both in terms of national treasure and human lives) and the weaponization of many agents, Japan never developed a credible biowarfare capability, mainly because of the failure to develop an effective delivery system.[17]

In contrast to Japanese efforts during World War II, a German offensive biological weapons program never materialized. Hitler reportedly issued orders prohibiting biological weapons development. Unethical experimental infections of prisoners were done primarily to study pathogenesis and develop vaccines and sulfonamides, rather than to develop biological weapons. With the support of high-ranking Nazi party officials, however, scientists began biological weapons research, but their results lagged far behind those of other countries.[27]

Polish physicians used a vaccine and a serologic test in a brilliant example of "biological defense." Knowing that inoculation with killed Proteus OX-19 would cause false-positive Weil-Felix typhus test results, physicians inoculated local populations with formalin-killed Proteus OX-19 to create serologic pseudoepidemics of typhus. Using serologic surveillance, the German army avoided areas with epidemic typhus; consequently, residents of these areas were spared deportation to concentration camps.[28] Unconfirmed allegations indicate that Polish resistance fighters used letters contaminated with *B anthracis* to cause cutaneous anthrax among Gestapo officials[21,29] and used typhus against German soldiers.[21] Czechoslovakian agents reportedly used a grenade contaminated with botulinum toxin, supplied by British Special Operations, to assassinate Reinhard Heydrich, the Nazi governor of occupied Czechoslovakia[30,31]; however, the veracity of this claim has been challenged.[23]

The perceived threat of biological warfare before World War II prompted Great Britain to stockpile vaccines and antisera, establish an emergency public health laboratory system, and develop biological weapons. "Cattle cakes" consisting of cattle feed contaminated with *B anthracis* spores were designed to be dropped from aircraft into Axis-occupied Europe to cause epizootic anthrax among livestock,[32,33] which would in turn induce famine. The cattle cakes were intended as a strategic economic weapon rather than as a direct cause of human anthrax. In addition, explosive munitions designed to aerosolize and disperse *B anthracis* spores as antipersonnel weapons were tested on Gruinard Island near the coast of Scotland in 1942. These experiments successfully caused anthrax in targeted sheep.[34] The antipersonnel weapons were not mass produced, and neither the cattle cakes nor the explosive munitions were used.[21] Great Britain continued its offensive biological warfare program during the early Cold War era in conjunction with the United States and Canada, and it performed secret open-air tests using pathogens in off-shore ocean sites near the Bahamas and Scotland.[21] Great Britain's offensive program was terminated between 1955 and 1956[35] because of budgetary constraints and reliance on nuclear deterrence.[32,33] Gruinard Island, which had been quarantined because of focal soil contamination by *B anthracis* spores following munitions testing, was decontaminated in 1986 using 2,000 tons of seawater and 280 tons of formaldehyde.[36] The United Kingdom conducts research to develop medical countermeasures at the Defence Science and Technologies Laboratories at Porton Down.

THE US PROGRAM

The US military recognized biological warfare as a potential threat after World War I. Major Leon Fox of the Army Medical Corps wrote an extensive report concluding that improvements in health and sanitation made biological weapons ineffective. In 1941, before the US entry into World War II, opinions differed

about the threat of biological warfare. Consequently, the Secretary of War asked the National Academy of Sciences to appoint a committee to study the issue. The committee concluded in February 1942 that biowarfare was feasible and the United States should reduce its vulnerability.

President Franklin D Roosevelt established the War Reserve Service (with George W Merck as director) to develop defensive measures against biological weapons. By November 1942 the War Reserve Service asked the Army's Chemical Warfare Service to assume responsibility for a secret large-scale research and development program, including the construction and operation of laboratories and pilot plants. The Army selected a small National Guard airfield at Camp Detrick in Frederick, Maryland, for the new facilities in April 1943. By summer of 1944 the Army had testing facilities in Horn Island, Mississippi (later moved to Dugway, Utah), and a production facility in Terre Haute, Indiana. No agents were produced at the Terre Haute plant because of safety concerns; simulant tests disclosed contamination after trial runs. In the only reported US offensive use of a biological weapon, the Office of Strategic Services (predecessor of the Central Intelligence Agency) used staphylococcal enterotoxin in a food-borne attack to cause an acute but self-limited illness in a Nazi party official.[37,38] Cattle cakes using *B anthracis* spores were produced at Camp Detrick and shipped to Great Britain, but were never used. The War Reserve Service was disbanded after the war and the Terre Haute plant was leased for commercial pharmaceutical production.[31] In January 1946 Merck reported to the Secretary of War that the United States needed a credible capability to retaliate if attacked with biological weapons. Basic research and development continued at Camp Detrick.

The United States learned of the extent of Japanese biological weapons research after World War II. In an action that has become controversial, Ishii and his fellow scientists were given amnesty for providing information derived from years of biological warfare research.[24]

When war broke out on the Korean peninsula in June 1950, concerns about Soviet biological weapons development and the possibility that the North Koreans, Chinese, or Soviets might resort to biological warfare resulted in an expansion of the US program. A large-scale production facility in Pine Bluff, Arkansas, was established. The plant featured advanced laboratory safety and engineering measures enabling large-scale fermentation, concentration, storage, and weaponization of microorganisms. In 1951 the first biological weapons, anticrop bombs, were produced. The first antipersonnel munitions were produced in 1954 using *Brucella suis*. The United States weaponized seven antipersonnel agents and stockpiled three anticrop agents (Table 1-1) over 26 years.[39]

Field tests using surrogate agents were conducted in the United States between 1949 and 1968, in which the general public and test subjects were uninformed. At least 239 open-air tests were conducted at several locations including the Dugway Proving Ground, Utah; remote Pacific Ocean sites; and populated areas including Minneapolis, St. Louis, New York City, San Francisco, and Eglin Air Force Base, Florida. These studies tainted the history of the offensive biological warfare program. The Special Operations Division at Camp Detrick conducted most of the field tests to study possible methods of covert attack and to examine aerosolization methods, the behavior of aerosols over large geographic areas, and the infectivity and rates of decay of aerosolized microbes subjected to solar irradiation and climatic conditions. Most tests used simulants thought to be nonpathogenic, including *Bacillus globigii*, *Serratia marcescens*, and particulates of zinc cadmium sulfide.[39,40]

In conjunction with the US Department of Agriculture (USDA), several open-air tests were conducted using anticrop agents at sites selected for safety.

TABLE 1-1

BIOLOGICAL AGENTS PRODUCED BY THE US MILITARY (DESTROYED 1971–1973)*

Lethal Agents	Incapacitating Agents	Anticrop Agents
Bacillus anthracis	*Brucella suis*	Rice blast
Francisella tularensis	*Coxiella burnetii*	Rye stem rust
Botulinum toxin	Venezuelan equine encephalitis virus	Wheat stem rust
	Staphylococcal enterotoxin B	

*Lethal and incapacitating agents were produced and weaponized. Anticrop agents were produced but not weaponized.

Open-air releases of human pathogens (*Coxiella burnetii*, *Francisella [Pasturella] tularensis*) were performed at the Dugway Proving Ground, Eglin Air Force Base, and remote Pacific Ocean sites to study viability and infectivity using animal challenge models.[21,39,40] Controversial studies included environmental tests to determine whether African Americans were more susceptible to *Aspergillus fumigatus*, as had been observed with *Coccidioides immitis*. These studies included the 1951 exposure of uninformed workers at Norfolk Supply Center in Norfolk, Virginia, to crates contaminated with *Aspergillus* spores. In 1966 the US Army conducted covert experiments in the New York City subways. Light bulbs filled with *Bacillus subtilis var niger* were dropped from subway platforms onto the tracks to study the distribution of the simulant through the subway system.[39–41] Similar tests were conducted using the ventilation system of the New York City subways and the Pentagon.

The first large-scale aerosol vulnerability test conducted in San Francisco Bay in September 1950 using *B globigii* and *S marcescens* demonstrated the public health issues of such testing.[41] An outbreak of 11 cases of nosocomial *S marcescens* (*Chromobacterium prodigiosum*) urinary tract infection occurred at the nearby Stanford University Hospital; one case was complicated by fatal endocarditis. Risk factors included urinary tract instrumentation and antibiotic exposures.[42] No similar outbreaks were reported by other San Francisco area hospitals. A panel of civilian and academic public health experts secretly convened by the Army in 1952 failed to reach a conclusion regarding the possible link between the Stanford outbreak and the testing program, but recommended that other microbes be used as simulants.[41] Public disclosure of the testing program in the *Washington Post* on December 22, 1976, and in US Senate hearings in 1977[43] resulted in harsh criticism of the continued use of *S marcescens* as a simulant after the Stanford epidemic. However, a 1977 report from the Centers for Disease Control and Prevention (CDC) concluded that in 100 outbreaks of *S marcescens* infection, none was caused by the 8UK strain (biotype A6, serotype O8:H3, phage type 678) used by the Army testing program.[44] Other reports from the 1970s postulated a link between *S marcescens* infection and the testing program; however, all clinical isolates available for strain typing were antigenically distinct from the Army test strain. In all likelihood, the 1950 Stanford *S marcescens* epidemic represents an early example of a nosocomial outbreak caused by opportunistic pathogens of low virulence complicating the use of medical devices and surgical procedures in the setting of antibiotic selection pressure.[44]

The US program developed modern biosafety technologies and procedures including protective equipment, engineering and safety measures, and medical countermeasures, including new vaccines. There were 456 occupational infections and three fatalities (two cases of anthrax in 1951 and 1958 and a case of viral encephalitis in 1964) reported at Fort Detrick during the offensive program (1943–1969).[39] The infection rate of fewer than 10 infections per million hours of work was within the contemporary National Safety Council standards; the morbidity and mortality rates were lower than those reported by other laboratories. There were 48 infections and no fatalities at the production and testing sites.[39]

In 1954 the newly formed Medical Research Unit at Fort Detrick began studies to develop vaccines and therapy to protect against biological agents. Researchers began using human volunteers in 1956 as part of a congressionally approved program called "Operation Whitecoat." This use of volunteers set the standard for ethics and human use in research. Active duty soldiers with conscientious objector status served as research subjects, and participation was voluntary with informed consent. The program concluded with the end of conscription in 1973.

Numerous unsubstantiated allegations were made during the Cold War era. During the Korean War (1950–1953), North Korean, Chinese, and Soviet officials made numerous accusations of US biowarfare attacks. Many allegations appear to be based on Chinese experiences during World War II field testing conducted by the Japanese Unit 731. Polish medical personnel were sent to China to support the communist war effort, accompanied by eastern European correspondents, who made numerous accusations based on anecdotal accounts of patients. These allegations, however, were not supported by scientific evidence. Some stories, such as the use of insect vectors to spread cholera, had dubious scientific plausibility. The North Korean and Chinese governments ignored or dismissed offers from the International Committee of the Red Cross and the World Health Organization (WHO) to conduct impartial investigations. The Soviet Union thwarted a proposal from the United States and 15 other nations to the United Nations (UN) requesting the establishment of a neutral commission for investigation. The United States admitted to having biological weapons but denied using them. The credibility of the United States may have been undermined by the knowledge of its biological weapons program and its failure to ratify the 1925 Geneva Protocol until 1975. Although unsubstantiated, these accusations resulted in a loss of international goodwill toward the United States and demonstrated the propaganda

value of biological warfare allegations, regardless of veracity.[43] Reviews of documents from former Soviet archives provide evidence that the allegations were fictitious propaganda.[45–47]

The Soviet Union accused the United States of testing biological weapons on Canadian Eskimos, resulting in a plague epidemic,[48] and of collaborating with Colombia in a biological attack on Colombian and Bolivian peasants.[49] The United States was also accused of planning to initiate an epidemic of cholera in southeastern China[50] and of the covert release of dengue in Cuba.[51] Similarly, the US allegations that Soviet armed forces and their proxies had used "yellow rain," aerosolized trichothecene mycotoxins (inhibitors of DNA and protein synthesis derived from fungi of the genus *Fusarium*) in Laos (1975–1981), Kampuchea (1979–1981), and Afghanistan (1979–1981), are widely regarded as unsubstantiated. The remote locations of the alleged attacks made intelligence investigations difficult. Western intelligence operatives never witnessed these alleged attacks, and no samples of the aerosols were recovered. Confounding factors included:

- contradictory testimonies from survivors of alleged attacks;
- discrepancies in reported symptoms;
- low disease rates in the allegedly attacked populations;
- the recovery of mycotoxin in fewer than 10% of the clinical and environmental samples submitted;
- the presence of *Fusarium* organisms as environmental commensals;
- the possible decay of toxin under prevailing environmental conditions;
- conflicting results of toxin assays from different laboratories;
- the similarity of alleged yellow rain deposits recovered from environmental surfaces to bee feces in ultrastructural appearance and pollen and mold content; and
- the natural occurrence of showers of bee feces from swarms of honey bees in the rain forests of southeast Asia.[52]

The US offensive program resulted in an understanding of the strategic nature of biological weapons. By the late 1950s assessments of the potential utility of biological weapons were mixed. In a letter from one of Dwight D Eisenhower's President's Science Advisory Council members, George Kistiakowsky, to James Killian, the chair of the council, the author made it clear that developing highly concentrated formulations of biological agents, proper handling of pathogens, and appropriate weaponization would result in cases that did not act as "normal" disease.[53] At high concentrations and in a dried formulation, biological agents had the potential for causing high mortality and morbidity. Still, questions remained about the potential to successfully use biological weapons in a controlled and reliable manner. The follow-on testing authorized by President John F Kennedy under the umbrella program of Project 112 was designed to fill in these knowledge gaps.[40,54] In the Bay of Pigs operation of 1961, military planners had developed enough interest in biological weapons that their use was contemplated. The codenamed "Marshall Plan" called for releasing incapacitating agents to attack defenders on the beach. Ultimately, the plan was scrapped and biological weapons were not used.[55]

By the late 1960s domestic and international pressures were calling for the elimination of the US offensive biological warfare program. At Dugway Proving Ground, an incident involving chemical weapons testing caused the death of 3,000 sheep. Debates about chemical and biological weapons, both for and against the development of offensive capabilities, ensued between Congress, the administration, industry, and even private citizens. In Europe draft texts of what would later become the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological and Toxin Weapons and on their Destruction (1972 Biological Weapons Convention [BWC]) were being developed by Great Britain, Sweden, and the Soviet Union.

In May 1969 US President Richard Nixon called for an interagency review of chemical-biological warfare policies. The review was authorized as part of National Security Study Memorandum 59. The findings resulted in recommendations to President Nixon to eliminate the US offensive program and retain a defensive program.

To this end, on November 25, 1969, when visiting Fort Detrick, President Nixon announced a new US policy on biological warfare, unilaterally renouncing the development, production, stockpiling, and use of biological weapons. In explaining his decision, President Nixon stated, "Biological weapons have massive, unpredictable, and potentially uncontrollable consequences. They may produce global epidemics and impair the health of future generations."[56] Almost immediately after the statement, confusion and a potential loophole caused by the ambiguity concerning biologically derived toxins that were technically excluded from the renunciation were corrected through National Security Study Memorandum–85, "Review of Toxins Policy," which was issued on December 31, 1969.

The US Army Medical Unit was closed, and Fort Detrick and other installations in the offensive weapons program were redirected to solely develop defensive measures such as vaccines, drugs, and diagnostics. The US Army Medical Research Institute of Infectious Diseases (USAMRIID) was created with biosafety level 3 and 4 laboratories dedicated to developing medical defensive countermeasures. By May 1972 all antipersonnel agents had been destroyed, and the production facility at Pine Bluff, Arkansas, was converted into a research facility. By February 1973 all agriculture-targeted biological agents had been destroyed. Although staphylococcal entertoxin was used during World War II by Office of Strategic Services' espionage agents,[37,38] biological weapons have never been used by the US Armed Forces.[39] The Central Intelligence Agency developed weapons containing cobra venom and saxitoxin for covert operations; all records regarding their development and deployment were destroyed in 1972; all remaining toxin samples were destroyed per presidential orders after a US Senate investigation.[37] The United States signed and ratified both the 1925 Geneva Convention and the 1972 BWC, which outlaws all offensive biological weapons research, production, and possession, in 1975 (see Disarmament: The Biological Weapons Convention).

Although many welcomed the termination of the US offensive program for moral reasons, the decision was partly motivated by pragmatic considerations. Biological weapons were unnecessary for national security because of a formidable arsenal of conventional, chemical, and nuclear weapons. Although open-air simulant studies suggested that biological weapons would be effective, the potential effects of aerosols of virulent agents on targeted populations were still conjectural and could not be empirically validated for ethical and public health reasons. Despite evidence to the contrary from information obtained through the US offensive program, some still considered biological weapons to be untried, unpredictable, and potentially hazardous for the users. Field commanders and troops were unfamiliar with their use. Most importantly, the United States and allied countries had a strategic interest in outlawing biological weapons programs to prevent the proliferation of relatively low-cost weapons of mass destruction. Outlawing biological weapons made the arms race for weapons of mass destruction prohibitively expensive, given the cost of nuclear programs.[21,57]

THE SOVIET PROGRAM

Although a signatory to the 1925 Geneva Convention, the Soviet Union began a weapons development program in 1928[58] under the control of the state security apparatus, GPU (the Unified State Political Administration of the Committee of People's Commissars of the USSR). Work was initially done with typhus, reportedly with experimentation on political prisoners at Slovetsky Island in the Baltic Sea and nearby concentration camps. The program subsequently expanded to include work with the agents of Q fever, glanders, and melioidosis, and possibly tularemia and plague. Outbreaks of Q fever and tularemia among German troops are two suggested, but unconfirmed, Soviet uses of biological warfare during World War II.[59] However, the origin of epidemic tularemia during the battle of Stalingrad as a consequence of biological warfare has been challenged and attributed to natural causes and a breakdown of public health.[60] Similar outbreaks of Q fever in Axis troops in Italy, Greece, Bulgaria, and the Ukraine[61]; in Allied troops in the Mediterranean Theater[62–64]; and more recently, among Czech peacekeepers in Bosnia-Herzegovina[65] and tularemia among civilians during the Kosovo conflict[66] have been attributed to amplification of natural transmission cycles during wartime.

Stalin was forced to move his biological warfare operations out of the path of advancing German forces. Laboratories were moved to Kirov in eastern European Russia, and testing facilities were eventually established on Vozrozhdeniya Island on the Aral Sea between the Soviet Republics of Kazakhstan and Uzbekistan. At the conclusion of the war, Soviet troops invading Manchuria captured many Unit 731 Japanese scientists and learned of their extensive human experimentation through captured documents and prisoner interrogations. Emboldened by the Japanese findings, Stalin put KGB (Committee of State Security) chief Lavrenty Beria in charge of a new biowarfare program. The production facility at Sverdlovsk was constructed using Japanese plans. After Stalin died in 1953, Beria was executed, and Nikita Khrushchev, the new Kremlin leader, transferred the biological warfare program to the Fifteenth Directorate of the Red Army. Colonel General Yefim Smirnov, a strong advocate of biological weapons who had been the chief of army medical services during the war, became the director.[67]

In 1956 Defense Minister Marshall Georgy Zhukov announced that the Soviet Union would be capable of deploying biological and chemical weapons in the next war. By 1960 numerous research facilities existed in the Soviet Union. Although the Soviet Union signed the 1972 BWC, it doubted US compliance, and subsequently expanded its program.[58,59,67] Various institutions under different ministries and production facilities were incorporated into an organization known as

Biopreparat to carry out offensive research, development, and production under the label of legitimate civil biotechnology research. Biopreparat conducted clandestine activities at 52 sites and employed more than 50,000 people. Production capacity for weaponized smallpox was 90 to 100 tons annually.[59]

The Soviet Union was an active participant in WHO's 1964 to 1979 smallpox eradication program. Soviet physicians participating in the program sent specimens to Soviet research facilities. For the Soviets, the program presented an opportunity not only to rid the world of naturally occurring smallpox, but also—reportedly—to obtain virulent strains of smallpox virus that could be used to develop biological weapons. WHO announced the eradication of smallpox in 1980, and the world rejoiced at this public health breakthrough. The bioweapon developers in the former Soviet Union had a more cynical reaction. Smallpox eradication would result in the termination of vaccination; eventually the world's population would again become vulnerable. It was this vulnerability that would inspire the former Soviet Union to develop smallpox as part of a strategic weapons system, with production of the virus on a massive scale and plans for delivery using intercontinental missiles.[59]

In addition to military biological weapons programs, the Soviets developed toxin weapons for use by Warsaw Pact intelligence services. An assassination using a biological weapon was executed in September 1978 when a Bulgarian secret service member attacked Georgi Markov, a Bulgarian exile living in London. A device concealed in an umbrella discharged a tiny pellet into the subcutaneous tissue of his leg. He died several days later. The pellet, which had been drilled to hold a toxic material, was found at autopsy. No toxin was identified, but ricin was postulated as the only toxin with the potency to kill with such a small dose.[68] Vladimir Kostov, a Bulgarian defector living in Paris, had been attacked in a similar manner a month earlier. He experienced fever and pain and bleeding at the wound site, yet had no further complications. After learning of Markov's death, he sought medical evaluation; radiographs disclosed a small metallic pellet in subcutaneous fat. The pellet was surgically removed. Kostov then tested positive for anti-ricin antibodies, supporting the probable use of ricin in these attacks.[23]

In October 1979 a Russian emigrant newspaper published in Frankfurt, Germany, reported a sketchy story of a mysterious anthrax epidemic in the Russian city of Sverdlovsk (now Yekaterinburg). The military reportedly took control of hospitals in Sverdlovsk to care for thousands of patients with a highly fatal form of anthrax. Soviet officials attributed the epidemic to cutaneous and gastrointestinal anthrax contracted from contaminated meat. However, US intelligence agencies suspected that the outbreak resulted from inhalational anthrax following a release of *B anthracis* spores from Compound 17, a Soviet military microbiology facility.[69–71] The Central Intelligence Agency sought the opinion of Matthew Meselson, a Harvard biologist who had been a strong proponent of the Nixon ban of the US biological warfare program. He initially doubted the Soviet weapon release hypothesis. Other observers reviewing the same evidence reached different conclusions, however, and satellite imagery from the late spring of 1979 showed a flurry of activity at and around the Sverdlovsk installation consistent with a massive decontamination effort. The incident generated enough concern within the Reagan administration and the Department of Defense (DoD) to increase military biopreparedness.

Debate of the incident raged for the next 12 years. Meselson testified before the US Senate that the burden of evidence supported the claim that the outbreak resulted from the Soviets' failure to keep *B anthracis*-infected animals out of the civilian meat supply. In 1992, after the fall of the Soviet Union, Meselson was allowed to take a team of scientists to review autopsy material and other evidence from the Sverdlovsk incident. The team's attempts to review hospital records of cases from the outbreak were unsuccessful because the KGB had confiscated the records. However, the team performed the following:

- acquired an administrative list of 68 of the deceased;
- obtained information from grave markers in a cemetery designated for the anthrax casualties;
- obtained epidemiological data by interviewing nine survivors and relatives and friends of 43 deceased; and
- determined that the cases occurred among people who had either lived or worked in a narrow zone southeast of Compound 17 during the first week of April 1979.

Archived weather reports at the city's airport disclosed that the wind direction on April 2, 1979, correlated with the geographic distribution of cases. Meselson and his team concluded that the outbreak resulted from the escape of aerosolized spores from the facility on April 2, 1979, with downwind transmission.[69] Furthermore, Russian pathologists who had conducted autopsies on 42 fatalities, and had courageously preserved tissue specimens and autopsy records at great personal risk, shared their findings with Meselson's team and published their results confirming inhalational anthrax,[72] described the Soviet cover-up of the outbreak, and postulated a release of spores from Compound 17.[71]

In 1992 Russian leader Boris Yeltsin admitted in private conversations with President George H Bush that the KGB and military had misrepresented the anthrax deaths. Subsequently, in a press release, Yeltsin admitted to the offensive program and the origin of the Sverdlovsk biological weapons accident. Additionally, retired Soviet general Andrey Mironyuk disclosed that safety filters had not been activated on the fateful morning in early April 1979, resulting in the escape of aerosolized *B anthracis* and the ensuing epidemic.[73] Soviet defectors, including Ken Alibek, first deputy chief of Biopreparat from 1988 to 1992, confirmed that not only was the Sverdlovsk epidemic caused by an accidental release of spores from a biological weapons production plant, but also that the Soviet biological warfare program had been massive.[59] In September 1992 Russia entered an agreement with the United States and the United Kingdom that acknowledged a biological weapons program inherited from the Soviet Union, committed to its termination, and agreed to onsite inspections. The United States assisted the Russian Federation and other former Soviet republics through the Nunn-Lugar Biological Threat Reduction Program (later called the Cooperative Biological Engagement Program) to:

- dismantle biological weapons research, development, and production infrastructure;
- secure dangerous pathogens into central reference laboratories;
- upgrade laboratory safety and security;
- enhance capacities for diagnosis, surveillance, and public health response; and
- engage scientists with biological weapons expertise in projects directed to modeling, medical countermeasure development, and other peaceful purposes.[74,75]

This led to the dismantlement or conversion of three large production facilities and dozens of institutes that supported the biological weapons program, the destruction of 150 tons of *B anthracis* weapons agent on Vozrozhdeniya Island, and unprecedented transparency at potential dual-use facilities that had previously been closed to foreigners.[76] However, in 1999 President Vladimir Putin, proposed the development of weapons based on new genetic technology. Although this directive was promptly dropped from publicly available documents, he retracted the 1992 disclosures of President Yeltsin.[77] The Russian government currently denies that the former Soviet offensive program had ever existed, claiming that it had only conducted defensive research.[58,77] According a 2013 US Department of State report, it is still unclear if the Russian Federation has completed the destruction or diversion of the offensive program to peaceful purposes, or if it continues to conduct activities inconsistent with the BWC.[78]

THE SPECIAL CASE OF IRAQ

The most ominous biological warfare threat that US military forces have faced came during Operations Desert Shield and Desert Storm in 1990 and 1991. Intelligence reports suggested that Iraq had developed and operated a biological weapons program during the 1980s. Coalition troops trained in protective gear were issued ciprofloxacin in theater for use as postexposure prophylaxis against an Iraqi anthrax attack. Before the hostilities, approximately 150,000 US troops received the Food and Drug Administration–licensed anthrax vaccine, and 8,000 received a botulinum toxoid vaccine approved by the Food and Drug Administration as an investigational new drug. Postwar inspections by the multinational UN Special Commission (UNSCOM) on Iraq were repeatedly confounded by Iraqi misinformation and obfuscation. After General Hussein Kamal defected in 1995, the Iraqi government disclosed that it had operated a robust biological weapons program at six major sites since the 1980s, contrary to its obligations as a state party to the BWC. The Iraqi program conducted basic research on *B anthracis*, rotavirus, camelpox virus, aflatoxin, botulinum toxins, mycotoxins, and an anticrop agent (wheat cover rust); and it tested several delivery systems including aerial spray tanks and drone aircraft. Furthermore, the Iraqi government had weaponized 6,000 L of *B anthracis* spores and 12,000 L of botulinum toxin in aerial bombs, rockets, and missile warheads before the 1991 Persian Gulf War (Table 1-2 and Table 1-3). Although these weapons were deployed, they were not used.[79,80] The reasons behind Saddam Hussein's decision not to use these weapons are unclear; perhaps

TABLE 1-2

BIOLOGICAL AGENTS PRODUCED BY IRAQ*

Agent	Produced (L)	Weaponized (L)
Botulinum	19,000	10,000
Bacillus anthracis	8,500	6,500
Aflatoxin	2,200	1,580

*Disclosed by the Iraq government in 1995.
L: liter

TABLE 1-3

DELIVERY SYSTEMS FOR BIOLOGICAL AGENTS DEVELOPED BY IRAQ*

Aerial Bombs		Missile Warheads	
Botulinum	100	Botulinum	13
Bacillus anthracis	50	*Bacillus anthracis*	10
Aflatoxin	16	Aflatoxin	2

*Disclosed by the Iraq government in 1995.

he was concerned about provoking massive retaliation. Alternately, decisive factors may have included the possible ineffectiveness of untested delivery and dispersal systems, the probable ineffectiveness of liquid slurries resulting from poor aerosolization, and the potential hazards to Iraqi troops, who lacked the protective equipment and training available to coalition forces.[81] The Iraqis claimed to have destroyed their biological arsenal immediately after the war but were unable to provide confirmatory evidence. A covert military research and development program continued for another 4 years, with the intent of resuming agent production and weapons manufacture after the end of UN sanctions. Infrastructure was preserved, and research on producing dried agent was conducted under the guise of biopesticide production at the Al Hakam Single Cell Protein Plant until its destruction by UNSCOM inspectors in 1996. Despite their obvious successes, the UNSCOM inspectors never received full cooperation from the Saddam Hussein regime, and were ejected from Iraq in 1998.

The Iraqi regime continued to promote an air of uncertainty after 1998 as to whether it had an active ongoing biological weapons program. Amy Smithson, in her very detailed account of the Iraqi biological weapons program and the UNSCOM inspections, suggests three possible reasons why Saddam Hussein may have wanted to maintain the perception that his biological weapons program was still active[82]:

1. To deter attacks by regional rivals, especially Iran;
2. To promote his image internally as a strong and unassailable leader and thus preserve his own internal stranglehold over Iraq; and
3. To maintain his own outsized vision of his ultimate dream and legacy.

Regardless of his strategic motives, the uncertainty about his biological weapons program ultimately contributed greatly to the Hussein government's fall and his own demise. The breakdown of the inspections, lack of firsthand information, misinformation provided by an informant (Rafid Ahmed Alwan al-Janabi, an Iraqi defector code named "Curveball" by the Central Intelligence Agency), and the 2001 anthrax mailings contributed to growing uncertainties, ambiguities, and apprehension, culminating in the 2002 US National Intelligence Estimate and assessments by the intelligence services of France, Germany, and the United Kingdom, that postulated a robust Iraqi biological weapons program.[83,84] International concern led to renewed inspections in 2002 under UN Security Council Resolution 1441. The Iraqi government failed to cooperate fully, and coalition forces invaded Iraq in 2003, believing at the time that Iraq's regime still posed a significant biological weapons threat. In 2005 the Iraq Survey Group (an international group composed of civilian and military members) concluded that the Iraqi military biological weapons program had been abandoned from 1995 through 1996 because the potential discovery of continued activity would risk severe political repercussions including the extension of UN sanctions. However, Saddam Hussein had perpetuated ambiguity regarding a possible program as a strategic deterrent against Iran.[85] The Iraqi Intelligence Service continued to investigate toxins as tools of assassination, concealed its program from UNSCOM inspectors after the 1991 Persian Gulf War, and reportedly conducted lethal human experimentation until 1994. Small-scale covert laboratories were maintained until 2003.[86]

OTHER NATIONAL PROGRAMS

South Africa is alleged to have operated a small-scale biological weapons program between 1981 and 1993, after becoming state-party to both the 1925 Geneva Convention (1960) and the BWC (1975). The South African biological weapons program, code-named Operation Coast, reportedly conducted research on *B anthracis*, *V cholerae*, ricin, botulinum toxin, and other agents, and intended to use genetic engineering to develop biological agents that would selectively target people of black African ancestry. Although Operation Coast acquired a collection of pathogens, it was not successful in developing large-scale delivery systems. *V cholerae* was reportedly used in 1989, but the attack failed because of the targeted water supply's chlorine content. After diplomatic interventions by the United States and Great Britain, the program was closed in 1993, coincident with the demise of the apartheid regime.[87–89]

V cholerae was allegedy used by Rhodesian forces with South African assistance during the civil war of the 1970s to contaminate rivers used as water

sources by rebel forces; these attacks are thought to have failed because of dilution. Rhodesian forces reportedly used *B anthracis* against livestock; the role of these attacks in an anthrax epizootic during 1979–1980 was investigated but could not be determined.[88]

Libya allegedly launched a clandestine biological weapons effort during the 1990s (while a state-party to the BWC), and sought assistance from Iraq, North Korea, and South Africa. However, in contrast to its chemical weapons program, the effort was limited to small-scale research, and according to one official never progressed beyond initial planning.[90] Colonel Muammar al-Qaddafi, an authoritarian dictator who ruled Libya for 42 years, formally renounced all weapons of mass destruction in 2003; inspectors from the United States and the United Kingdom found no evidence of an offensive biological weapons program.[90]

An unclassified 2013 US State Department report noted that North Korea may still consider the use of biological weapons as a military option, and that it is unclear if Iran is conducting activities prohibited by the BWC.[78]

The US Director of National Intelligence reported in an open US Senate hearing in 2013 that Syria (a signatory, but not a state-party to the BWC) maintains a biological weapons program capable of limited agent production; and although Syria is not known to have loaded biological agents in effective delivery systems, it possesses conventional and chemical weapons devices that could be adapted to launch biological attacks.[91,92] In the context of the ongoing Syrian civil war in 2014, there are concerns regarding potential deployment[93] and that further disintegration of the Assad regime could enable Al Qaeda and Hezbollah to seize Syrian unconventional weapons.[94]

Some 20 nations are thought to have engaged in offensive biological weapons efforts. The total number of nations and the extent of their efforts are difficult to establish because several have engaged in research and development, but not taken their efforts to testing, deployment, and use. Although the list of states appears to be down from the 20 or so that were thought to have biological weapons programs in the assessments in the 1980 and 1990s, several states including North Korea, Syria, and Iran are still thought to have biological weapons programs.[54(p68)]

BIOCRIMES

Biocrime is the malevolent use of biological agents when the perpetrator's motivation is personal, as opposed to a broader ideological, political, or religious objective. Although biocrimes constitute only a small fraction of criminal assaults and are usually unsuccessful,[95] a well-executed attempt may be deadly; the resulting disease may pose clinical and forensic challenges. Biocrimes have generally been more successful than bioterrorist attacks; 8 of 66 biocrimes reviewed by Tucker produced 29 deaths and 31 injuries.[96]

Perpetrators with scientific or medical expertise or those who have recruited trained accomplices typically attempt biocrimes. Criminals without a technical background have successfully extracted ricin from castor beans but have generally been unable to obtain or produce other agents. In a review of 14 episodes in which agent was used, biological agents were usually obtained from a legitimate source or stolen; the perpetrators produced agent in only two cases.[21,95] Preferred agents have been bacteria and toxins (eg, ricin). Food contamination has been preferred over direct injection or topical application as a means of attack.

One of the most striking examples of foodborne biocrime occurred in Japan between 1964 and 1966. Dr Mitsuru Suzuki allegedly contaminated food items, medications, barium contrast, and a tongue depressor with *Salmonella typhi* and agents of dysentery on numerous occasions resulting in more than 120 cases and four deaths.[23] A variation on the Suzuki crime occurred in 1996 when Diane Thompson, a hospital microbiologist, deliberately infected 12 coworkers with *Shigella dysenteriae*. She sent an email to her coworkers inviting them to eat pastries she had left in the laboratory break room. Eight of the 12 casualties and an uneaten muffin tested positive for *S dysenteriae* type 2, identical to the laboratory's stock strain by pulsed-field electrophoresis.[97] Police learned that her boyfriend had previously suffered similar symptoms and had been hospitalized at the same facility, and that Thompson had falsified his laboratory test results. Thompson was sentenced to 20 years in prison.[23]

Murders by direct injection included the use of diphtheria toxin in Russia in 1910. The director of a Norwegian nursing home was convicted in 1983 of murdering 22 patients by injecting a curare derivative. There have been at least four murder attempts by injecting victims with human immunodeficiency virus-infected blood.[23]

Numerous and highly varied biocrimes have been reported; only several representative examples are included in this chapter. The works of Carus,[23] Leitenberg,[21] and Tucker[96] provide comprehensive descriptions and analysis.

BIOLOGICAL TERRORISM

Bioterrorism is the use of biological agents by an individual or group not acting as official agents of a government to achieve a political or ideological objective. Bioterrorist incidents increased markedly after 1985, with two peaks in 1998 and 2001. The 1998 peak followed publicity of the anthrax threat posed by Larry Wayne Harris; the 2001 peak followed the September through October anthrax mailings. Successfully executed attacks have been few but high in impact; the 1984 Rajneeshee Salmonella attack resulted in 751 cases of infection; the 2001 anthrax mailings resulted in 22 cases of infection, five deaths, and approximately 10,000 individuals being offered postexposure prophylaxis. The vast majority of incidents (at least 98% during 2000–2002) have been hoaxes, which have nonetheless produced considerable social disruption.[98,99]

The first large-scale bioterrorism attack in the United States occurred in 1984. In the 1960s an Indian guru named Bhagwan Shree Rajneesh founded the Rajneeshee cult. Rajneesh succeeded in attracting followers from the upper middle class and collecting significant donations and proceeds from book and tape sales. Rajneesh acquired the Big Muddy Ranch near The Dalles, Oregon, and built a community for his followers named Rajneeshpuram, which became an incorporated community. Within a few years, the Rajneeshees came into conflict with the local population regarding development and land use. The Rajneeshees attempted to gain control of the Wasco County government by bringing in thousands of homeless people from cities around the country, counting on their votes in the upcoming elections. The Rajneeshees also plotted to sicken the local population to prevent them from voting.[21]

Two Wasco County commissioners visiting Rajneeshpuram on August 29, 1984, were given drinking water contaminated with *Salmonella typhimurium*; both became ill and one was hospitalized. In trial runs in the months leading up to the November 1984 elections, several attempts at environmental, public water, and supermarket food contamination were unsuccessful. In September, Rajneeshees began contaminating food at local restaurants by pouring slurries of *S typhimurium* into salad bars, salad dressing, and coffee creamers at 10 restaurants. This attack caused 751 cases of enteritis and at least 45 hospitalizations.[23,100]

In 1995 in Japan, the Aum Shinrikyo cult released sarin gas in the Tokyo subway system, resulting in 12 deaths and thousands seeking emergency care. The cult, founded by Shoko Asahara, had amassed approximately 10,000 members and $300 million in financial assets. Aum Shinrikyo mimicked the organization of the Japanese government with "ministries and departments." Seiichi Endo, who headed "health and welfare," had worked in genetic engineering at Kyoto University's viral research center. Hideo Murai, who headed "science and technology," had an advanced degree in astrophysics and had worked in research and development for Kobe Steel Corporation. Endo attempted to derive botulinum toxin from environmental isolates of *Clostridium botulinum* at the cult's Mount Fuji property. A production facility was built and horses were stabled for developing a horse serum antitoxin. It is uncertain whether Endo successfully produced potent botulinum toxin.[23]

In 1993 Aum Shinrikyo built a new research facility on the eighth floor of an office building owned by the cult in eastern Tokyo. The cult grew *B anthracis* and installed a large industrial sprayer for dissemination. The cult is also believed to have worked with *C burnetii* and poisonous mushrooms, and it sent a team to Zaire in the midst of an Ebola epidemic to acquire the Ebola virus. According to press accounts from 1990 to 1995, the cult attempted to use aerosolized biological agents against nine targets. Three attacks were attempted with *B anthracis* and six with botulinum toxin. In April 1990 the cult equipped three vehicles with sprayers containing botulinum toxin targeting Japan's parliamentary Diet Building in central Tokyo, the city of Yokahama, Yosuka US Navy Base, and Nairta International Airport. In June 1993 the cult targeted the wedding of Japan's crown prince by spraying botulinum toxin from a vehicle in downtown Tokyo. Later that month, the cult spread *B anthracis* using the roof-mounted sprayer on its eight-story building. In July 1993 the cult targeted the Diet in central Tokyo again by using a truck spraying *B anthracis*, and later that month it targeted the Imperial Palace in Tokyo. On March 15, 1995, the cult planted three briefcases designed to release botulinum toxin in the Tokyo subway. Explanations for the cult's failure include the possible use of a nontoxin-producing (or low yield) strain of *C botulinum*, use of a low-virulence veterinary vaccine strain of *B anthracis*, ineffective spraying equipment, and perhaps subversion on the part of some cult members who were reluctant to execute the planned operation.[19] Ultimately, Aum Shinrikyo gave up on its biological weapons and released sarin in the Tokyo subway on March 20, 1995.[23]

Meanwhile in the United States, two members of the Minnesota Patriots Council, an antigovernment extremist group, were arrested for producing ricin and planning to attack federal agents by contaminating doorknobs. Larry Wayne Harris, a clinical

microbiologist with ties to racist groups, was arrested in 1995 for using fraudulent information to obtain a culture of *Y pestis* from the American Type Culture Collection. He was arrested a second time in 1998 after making threatening remarks to US federal officials and violating his parole. Harris had constructed a covert laboratory in Nevada and was conducting experiments with the Sterne strain of *B anthracis*, a nonencapsulated but toxigenic live attenuated veterinary vaccine, and he threatened to attack Las Vegas with *B anthracis*.[68] His case led to the establishment of the Select Agent Program (42 CFR Part 73, Possession, Use, and Transfer of Select Agents and Toxins) that included the development of stringent regulations for the procurement and shipping of select microbes.

On October 4, 2001, just 3 weeks after the September 11th attacks on the World Trade Center and the Pentagon had made the nation acutely aware of its vulnerability to international terrorism, health officials in Florida reported a case of inhalational anthrax. During the first week of September, American Media, Inc, received a letter addressed to Jennifer Lopez containing a fan letter and a "powdery substance." The letter was passed among its employees, including Robert Stevens. Retrospectively, investigators would consider not this letter, but perhaps a subsequent letter, as the source of his infection.[101]

Stevens was admitted to a Palm Beach, Florida, hospital with high fever and disorientation on October 2, 2001. By October 5, he was dead from inhalational anthrax, the first such case in the United States in more than 20 years.

Soon afterward anthrax mailings were received at civilian news media operations in New York City and in the Hart Senate Office Building in Washington, DC.

At least five (four recovered) letters containing *B anthracis* spores had been mailed on September 18, 2001, and October 9, 2001. Twenty-two people contracted anthrax, with 11 inhalational cases resulting in five deaths. Thirty-five postal facilities and commercial mailrooms were contaminated. Screening and postexposure prophylaxis disrupted operations at the Hart US Senate Office Building. Decontamination of postal facilities cost more than $1.2 billion and resulted in the closure of heavily contaminated facilities in Washington, DC (October 2001–December 2003), and Trenton, New Jersey (October 2001–March 2005).[102] More than $27 million was spent on decontaminating Capitol Hill facilities.[102] Public alarm was compounded by numerous "white powder" hoaxes.

Farsighted emergency planning and training, in addition to the integration of federal and local medical, public health, and law enforcement agencies in New York City and other cities, enabled an unprecedented public health response. The Laboratory Response Network and military laboratories such as USAMRIID processed more than 125,000 clinical specimens and 1 million environmental samples. USAMRIID ran more than 260,000 assays on more than 30,000 samples in 9 months. Prophylaxis supplied from the national stockpile was offered to nearly 10,000 individuals at risk. No cases were found among prophylaxis recipients.[103,104] Treatment guidelines advocating multidrug antibiotic combinations and aggressive intensive care were disseminated,[105] and the case fatality rate for inhalational anthrax—historically exceeding 90%—reduced to 45%.[106,107]

The attacks provoked an unprecedented criminal investigation that coupled traditional law enforcement with the development and validation of novel emerging genetic sequencing techniques. The Federal Bureau of Investigation (FBI) special agents and US Postal Service Inspectors conducted the investigation for 7 years, and 29 government, academic, and commercial laboratories supported it. Investigators conducted more than 10,000 witness interviews on six continents and 80 searches, and they also collected more than 6,000 items of potential evidence and 5,730 environmental samples from 60 locations both within the United States and in foreign countries, with the cooperation of the respective host nation governments.[102]

US Attorney General John Aschroft named Dr Steven J Hatfill, a USAMRIID scientist between 1997 and 1999, a "person of interest" during a television interview in 2002. Dr Hatfill vehemently denied involvement, and sued the federal government, claiming that law enforcement officials had leaked information to the media in violation of the Privacy Act, and had ruined his reputation and career. The FBI exonerated him in 2008, and he received $5.82 million in restitution.[102,108,109]

Forensic analysis was confounded by the highly conserved *B anthracis* genome, which features more than 99.99% nucleotide sequence identity among the most genetically divergent strains. Investigators went beyond the contemporary standard of genetic typing by sequencing small DNA segments to advance the technique of whole genome sequencing. Comparison of the whole genomes of the index case isolate and a reference Ames strain disclosed that they were essentially identical, and it could not pinpoint the origin of the letter contents. However, a breakthrough followed the observation of four phenotypic colony morphology variants constituting less than 1% of colonies cultured from spore samples taken from three of the anthrax letters. Each colony morphology variant was associated with a distinct mutation restricted to four genetic loci. These mutations were absent in environmental

isolates taken during the investigation.[110] Specimens were obtained from every culture of *B anthracis* Ames strain (1,071 samples) from all 15 US and three foreign laboratories known to possess it. One or more of the mutants was detected in 71 of 947 samples that could be evaluated; all four mutants were present in eight samples. The probability of samples to contain all four mutants was calculated to be 0.4383×10^{-6} or 0.0004 samples in the 947 sample collection, if the samples were unrelated; these eight samples consisted of a specimen from RMR-1029, a flask containing a liquid spore preparation in the laboratory of anthrax researcher Dr Bruce E Ivins at USAMRIID, and seven specimens from another laboratory that were descendents of RMR-1029.[111,112]

The FBI concluded that Dr Ivins was the sole perpetrator based on the following:

- the genetic analysis results;
- inconsistencies during interviews;
- erratic conduct that included irregular laboratory hours before each mailing and an unauthorized and unreported decontamination of his office and laboratory during the investigation;
- deteriorating behavior as the investigation progressed; and
- exclusion of other individuals with access to RMR-1029 and its descendants.

The purported motive was to ensure continued support for the anthrax vaccine research in which Dr Ivins was personally heavily invested and was under criticism from multiple sectors. The US Attorney's Office for the District of Columbia prepared an indictment charging him with Use of a Weapon of Mass Destruction, in violation of Title 18, United States Code, Section 2332a, and related charges. Dr Ivins, aware of the indictment, took an overdose of over-the-counter medications and died on July 29, 2008.[102]

Lingering doubts were expressed during a plenary session at the 2009 American Society for Microbiology Biodefense and Emerging Diseases Research Conference.[113] Evidence was considered circumstantial. No evidence of *B anthracis* contamination was found in Dr Ivin's home or vehicles. Unexplained aspects of the case included the contamination of the September 18 mailing with a *B subtilis* strain that could not be traced to USAMRIID and the use of dry spore preparations (the production of which is prohibited in the US biodefense program), for which there was no direct evidence within USAMRIID. A National Academy of Sciences review concluded that the genetic typing results were consistent with—but not definitive proof of—the derivation of the letter isolates from RMR-1029. Although generally supportive of the FBI's efforts, the reviewers criticized the FBI's statistical methods and stated that an alternative source could not be excluded because of possible sharing and mixing of samples among laboratories, and because the possibility of identical mutations arising through parallel evolution independently in unrelated cultures had not—in their opinion—been adequately explored.[112] Abnormally high concentrations of silicon[114] and tin existed in the spores that were absent in spores from RMR-1029; this raised controversies regarding potential production at the Dugway Proving Ground or at a civilian contractor laboratory, where work with silicon and surrogate spores had previously been done.[115] Finally, Department of Justice lawyers used the argument that Dr Ivin's lab had no equipment to produce dry spore preparations to defend the government against a wrongful death lawsuit filed by Robert Stevens' widow.[116]

However, the investigation spurred the advancement of whole genome sequencing, accelerating the time required to sequence a bacterial genome from 4 months to several days,[117] and advanced the emerging science of microbial forensics. The investigation raised issues regarding laboratory programs for physical security, personal reliability, and mental health screening that—while not directly incriminating Dr Ivins—underscored the importance of re-evaluating laboratory security measures and the value of robust employee occupational health programs to screen and monitor the mental health of researchers working with highly virulent pathogens. These issues were addressed by strengthening the federal regulations that direct CDC oversight of research on dangerous pathogens (see discussion of the Federal Experts on Security Advisory Panel in Toward Pan-hazard Preparedness).[118,119]

The threat of bioterrorism did not end with the US anthrax experience. Al Qaeda initiated a biological weapons program in Afghanistan before the overthrow of the Taliban regime. Investigations after the US military intervention of 2001 uncovered two Al Qaeda laboratories for biological weapons development, supplied with commercially acquired microbiology equipment and staffed by trained personnel. Fortunately, a deployable weapon had not been constructed.[120] US forces operating in northern Iraq in 2003 seized a camp linked to Al Qaeda reportedly containing instructions and equipment for ricin extraction.[121]

During the period that followed the US anthrax attacks, ricin became the bioweapon of choice for a number of misanthropes intent on nefarious use of biological agents, perhaps because of its relative ease of access. The castor beans (ricin source) are available worldwide because the oil is extracted for lubricant in

many countries. The toxin extraction techniques have been published in many forums to include many anarchist and terrorist websites. Examples are provided of confirmed cases, but many more incidents have occurred worldwide, and most have proven to be hoaxes.

In January 2003 British authorities uncovered the Wood Green ricin plot. A police raid on a London apartment yielded a copy of a protocol for ricin production, toxin source materials (castor beans), and a suitable solvent (acetone) for its extraction. Although tests for ricin were negative,[122] one of the tenants, an Al Qaeda-trained operative, was convicted of plotting a ricin attack. He had planned to contaminate handrails in the railway system connecting London and Heathrow Airport.[123] In March 2003 two flasks containing ricin were discovered in a railway station in Paris.[124]

In 2003 US Postal Service employees discovered two letters directed to the US Department of Transportation containing vials of ricin. The first letter was found on October 15, 2003, at the mail sorting center in Greenville, South Carolina.[125] The second was discovered at the White House mail processing facility in Washington, DC. Both letters were from an antagonist who identified himself as "Fallen Angel" and was angry about the Department of Transportation's new limitations being placed on truck drivers' daily work hours.[126] In February 2004 ricin was found in the sorting machine of Senate Majority Leader Bill Frist's office in the Congressional Office Building. No evidence was ever found linking the Fallen Angel and Frist cases and perpetrators are still at large. On June 23, 2004, Michael Crooker, a resident of the Boston suburb of Agawam, Massachusetts, had his house searched by law enforcement officials after attempting to mail a firearm. Agents discovered a weapons lab that contained castor and abrus seeds (sources of ricin and abrin toxins, repectively) as well as the materials needed for toxin extraction. Crooker sent a letter to the prosecuting attorney threatening to cripple the US Postal System by sending toxin-laden letters through the mail. He also notified local news journalists that he would provide toxins to felons he had met in prison who had previously engaged in terrorist activities. He pled guilty to possession of ricin and threatening a government official and was sentenced in June 2011.[127] In February 2008 Roger Bergendorff, an anarchist living in an extended stay hotel in Las Vegas, Nevada, developed a mysterious illness that puzzled his healthcare providers. He was hospitalized and while investigating the cause of his illness, officials discovered evidence of a ricin extraction operation in his room. He and his cousin were both eventually convicted of charges related to ricin production. The specifics of intended use—if known—have not been disclosed.[128] In March 2011 four men who were members of a militia organization began having clandestine meetings in which they allegedly planned numerous criminal activities to include acquisition of illegal weapons, manufacture of toxic agents, theft, and assassination. During these meetings they allegedly discussed use of weapons to include biologic agents to attack government facilities and government employees to include law enforcement officials. One of their plans included producing 10 pounds of ricin and dispersing it from a moving vehicle in the Atlanta area. An FBI informant alerted authorities and the operation was disrupted without incident in November 2011.[129]

Attacks against government officials resumed after a nearly 10-year hiatus with the discovery of an envelope testing positive for ricin intercepted at the US Capitol's mail facility in April 2013. The letter was addressed to Senator Roger Wicker, and a day later an envelope addressed to President Obama was discovered that also contained ricin. A third letter containing ricin was mailed to the Lee County Mississippi Court Judge Sadie Holland. Within a few weeks the FBI arrested Everett Dutschke for producing a toxin weapon and using the mail to threaten President Barack Obama, Senator Wicker, and Judge Holland. These mailings appear to be acts of reprisal in the settlement of personal grudge(s).[130] Less than 2 months later, in May 2013 three letters intended for New York Mayor Michael Bloomberg were intercepted containing a suspicious oily substance that turned out to contain ricin. Similar letters were also mailed to President Obama, according to a Secret Service press release. Gun control opponents purportedly sent the letters, and Shannon Richardson notified the FBI that her estranged husband was responsible for the mailings. When the allegations failed to withstand police scrutiny she was arrested, and received an 18-year prison sentence, having falsely implicated her husband.[131] Despite numerous ricin mailings by many diverse individuals, the mail delivery of ricin toxin has been ineffective as an instrument of harm or assassination—these mailings appear to have little impact beyond their psychological "scare" effect. Although ricin is a toxin of very high lethal potency, its effectiveness is limited by the delivery method. No illness or significant environmental contamination has resulted from any of the ricin mailings.

Many of the bioterrorist incidents have been small scale, not well perpetrated, and not particularly successful in terms of mortality and morbidity. Still, it is clear that several terrorist groups aspire to use biological weapons. For example, Al Qaeda radical cleric Anwar al-Awlaki in an article stated that "the killing of women and children and the use of chemical and biological weapons in addition to bombings and gun attacks" is acceptable and even encouraged.[54]

In Inspire, an online Al Qaeda magazine, the authors called for "chemists and microbiologists" to develop weapons and attack the West. These programs continue to be aspirational, rather than well-established developmental efforts. However, with the proliferation and industrialization of biotechnology described previously, the threat of bioterrorism continues to increase.[54(p60)]

SOLUTIONS: TOWARD PAN-HAZARD PREPAREDNESS

Disarmament: The Biological Weapons Convention

In July 1969 Great Britain issued a statement to the UN Conference of the Committee on Disarmament calling for the prohibition of the development, production, and stockpiling of bacteriological and toxin weapons. In September 1969 (the same year) the Soviet Union unexpectedly recommended a disarmament convention to the UN General Assembly. In November 1969 WHO issued a report on biological weapons, after an earlier report by the 18-nation Committee on Disarmament, describing the unpredictable nature, lack of control, and other attendant risks of biological weapons use. The United Nations then developed the 1972 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (1972 BWC), which prohibited any malicious research, production, or possession of biological agents. Among the 103 initial cosignatory nations, agreement was reached to "never develop, produce, stockpile, or otherwise acquire or retain microbiological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; and weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict."[132] The United States ratified both the 1925 Geneva Convention and the BWC in 1975. Signatory states suspecting others of treaty violations may file a complaint with the UN Security Council, which, in turn, may order an investigation. However, mandatory measures for verification and enforcement are lacking; numerous attempts to formulate such measures have been unsuccessful because of political, security, and proprietary issues.[21]

Since the BWC entered into force in 1975, seven review conferences have taken place; these "RevCons" (as they are called) constitute the only decision-making forums for the BWC and are held every 5 years in Geneva. RevCons are 3-week international meetings that allow member nations to reinforce the norm against the prohibition of biological weapons, discuss international collaboration on biotechnological issues, assess the continued relevance of the BWC given changes in biotechnology, and make proposals for revitalizing the BWC. Unfortunately, RevCons have not produced many tangible results and have demonstrated an inability to deal with difficult issues. The most noteworthy accomplishment was development of confidence-building measures for annual reporting by member state parties. Only 70 or so of the 170 member nations actually submit annual reports on their activities. On questions such as the relationship of the Sverdlovsk anthrax epidemic to the Soviet biological weapons program, the Iraqi weapons program, and the smallpox retention versus destruction issue, the BWC has remained unengaged.

Several RevCons have dealt directly with the potential for developing a verification protocol. The 1991, 1996, and 2001 RevCons saw the establishment of the Ad Hoc Group, the progress made in the Review Conference Final Declaration, and the disaster of the United States walking out of the RevCon,[54(p117)] respectively. After the 2001 RevCon the BWC saw a tumultuous period where its future was questioned. The "success" of the 2006 RevCon served to reenergize the BWC. The key outcomes were the agreement concerning the importance of the BWC forum and the development of an intersessional process that would include annual member state nations and experts meetings to discuss topical issues. However, neither of these two new annual meetings allows for decision-making.

The lead-up to the 2011 RevCon was anticipated by participating nation-states.[54(p119)] The United States had released a national strategy for countering biological threats at the 2009 meeting of state parties. Several pre-BWC conferences were held in which it appeared the international community was moving toward tangible outcomes in the 2011 RevCon. The president of the 2011 meeting, Paul van den Ijssel from The Netherlands, had declared the mantra would be "ambitious realism."[54(p122)] Unfortunately, it failed to live up to expectations. One review of the RevCon states, "The December 2011 review conference of the Biological Weapons Convention (BWC) demonstrated the danger of the bioweapons ban drifting into irrelevance. Standstill was the motto of the meeting. Only incremental improvements on some procedural issues were achieved."[54(p120)] Even modest enhancements, such as expanding the implementation support unit's three-person organization, were not approved.

In examining the BWC's future, several tensions arise because it is a state-to-state treaty, yet many of the current biological threats deal with nonstate issues

such as bioterrorism, biocrimes, and misuse of the life sciences. Although member nations allow for discussing these issues within the BWC, few have demonstrated the desire to make these more topical issues the focus of future BWC negotiations, although states-parties are obligated under article IV to prohibit and prevent proscribed activities within their borders. Several other articles of the BWC also create tensions. For example, article I establishes the norm against biological weapons, yet provides no ability to enforce the convention. Articles III and X call for not transferring, assisting, inducing, acquiring, and retaining biological weapons, whereas article X encourages the peaceful exchanges of biological science and technology. Although the words do not conflict, the interpretation between developed and developing nations varies greatly.

Another area of contention concerns the perennial issue of verification. The US position remains as it has since 2001 that verification of the BWC is not possible. Instead, the United States supports adherence to a policy of compliance that begins with national implementation including ensuring all nations have appropriate national laws, regulations, and policies that support the BWC, as stipulated in article IV. The US position on verification also rests on the assertion that articles V and VI that call for bilateral and multilateral consultation and the potential for bringing concerns to the UN Security Council, respectively, provide sufficient opportunities for voicing concerns about compliance. Two other issues that feature prominently in the BWC debate are continued concerns about its relevance given the pace of biotechnological enhancements and the lack of universal adherence to it. On the first issue, members continue to profess that the BWC remains relevant despite exponential changes in biotechnology. With respect to universal adherence, the BWC continues to be undersubscribed as compared to other treaties dealing with weapons of mass destruction issues, in particular the Nuclear Non-Proliferation Treaty and the Chemical Weapons Convention. The BWC has 170 member nations, whereas the Nuclear Non-Proliferation Treaty and the Chemical Weapons Convention have 189 and 188 member nations, respectively.

Finally, only one allegation has been formally registered under the BWC: in June 1997 Cuba accused the United States of a biological attack with a crop pest insect, *Thrips palmi*. The allegations were unsubstantiated in a BWC consultation that concluded in December 1997.[21] Other attempts at biological arms control have been conducted outside of the context of the BWC; for example, inspections and sanctions against Iraq from 1991 to 1998 and 2002 to 2003 were accomplished under separate UN Security Council Resolutions, 681 and 1441, respectively.

Smallpox Preparedness

CDC launched a comprehensive smallpox preparedness program in 2002 because of the potential use of variola as a biological weapons agent. WHO, the United Kingdom, Germany, and other WHO member states initiated similar programs including vaccine stockpiles. The US program integrated community, regional, state, and federal healthcare and public health organizations and featured logistical preparation; training and education; risk communication; surveillance; and local preparations for mass vaccination, isolation, quarantine, active surveillance, and humane treatment of patients in designated facilities. A strategy was adopted based on preexposure vaccination of carefully screened and trained members of first-response teams, epidemiological response teams, clinical teams at designated facilities, and military personnel set to deploy into the theaters of war.[133] More than 400,000 selected military personnel and 38,000 civilian emergency responders and healthcare workers in designated smallpox response teams were vaccinated. Contracts for the production of a new cell culture-derived vaccine were awarded in 2000; the Strategic National Stockpile has sufficient cell culture-derived vaccine for the entire US population, a replication-deficient vaccinia (Modified Vaccinia Ankara) for use in immunocompromised individuals, and vaccinia immune globulin to treat vaccine complications. In addition, the US government supported the development of new smallpox antiviral therapeutic candidates and funded animal model development to enable efficacy testing of medical countermeasure candidates.

The disposition of the remaining WHO-authorized variola virus stocks, held in two secure WHO Collaborating Centers at CDC in the United States and at VECTOR in Koltsovo, Novosibirsk, Russia, was debated at the WHO 64th World Health Assembly in 2011. Two camps emerged, the destructionists and retentionists, and each made arguments to support their positions. In the end, the World Health Assembly remained committed to its previous position calling for the destruction of the viral stocks as a long-term goal, but agreed to their retention until the completion of research leading to two antiviral drugs with different mechanisms of action, a safer and effective vaccine, a rapid and accurate diagnostic kit, and the refinement of nonhuman primate animal models. The issue was also revisited at the 67th World Health Assembly in 2014. The risks posed by recombinant technology were also addressed; a private company in the United States that had inserted 63 nucleotides from the variola genome into an attenuated but transmissible orthopox virus to develop a positive control for a diagnostic test

would be asked to destroy its reagent and to report its destruction to WHO.[134] This underscored the need to re-evaluate and publicize WHO guidance regarding the use of variola genetic sequences in recombinant technology.

Dual Use Research of Concern

In addition to the threats posed by the deliberate release of biological agents, there has been increasing recognition of the potential risks posed by legitimate scientific research for benevolent medical purposes that includes the characterization of, and development of medical countermeasures against, highly pathogenic microbes. Risks include laboratory accidents resulting in pathogen release, laboratory acquired infections (some of which may be communicable to the community), unanticipated results of experiments resulting in increased microbial virulence or transmissibility, and the deliberate misuse of knowledge generated by legitimate scientific research for biological weapons proliferation. Dual use research of concern (DURC) has been identified as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security. Examples include, but are not limited to, the following:

- The genetic modification of mousepox virus to express both an ovarian protein and the immunomodulator interleukin-4 to induce sterility in mice for pest control, reported in 2001. Immunomodulator interleukin-4 was intended to enhance immune responses to the ovarian protein. However, the vaccine candidate was lethal in small-animal testing; immunomodulator interleukin-4 had the unanticipated effect of immune suppression, resulting in a highly virulent mousepox virus.[135]
- The in vitro synthesis of wild-strain poliovirus type 1 by using synthetic DNA encoding the poliovirus genome (with minor mutations as genetic markers) in a cell-free extract by researchers at the State University of New York at Stony Brook in 2002. The researchers noted that the knowledge that polioviruses can be synthesized using chemical methods and reintroduced through bioterrorism may inform the closing strategies of WHO's polio eradication campaign.[136,137] It was later explained that they had hoped to deliver a "wake-up call" regarding the possible misuse of viral synthesis for bioterrorism; that WHO's polio eradication campaign may be futile because of either possible bioterrorism using synthetic virus, laboratory accidents, or live attenuated oral polio vaccine and circulating oral polio vaccine-derived virus-related disease; and that control may be a more attainable outcome.[138] Aside from risking an accidental reintroduction to the local community (after the elimination of circulating wild-strain polioviruses from the western hemisphere), the study raised questions regarding its scientific value,[139] whether demonstrating technical capabilities to deliver warnings constitutes a legitimate scientific purpose, and whether the synthesis of a wild-strain poliovirus, which is otherwise available to researchers, served any benevolent medical purpose.
- The reconstruction of the 1918 H1N1 influenza A pandemic virus,[140] reported in 2005. This enabled characterization of a virulent pathogen that—in contrast to poliovirus—was otherwise not available for study. This enabled insights into pathogenesis, and potentially the identification of virulence factors and drug targets that could be relevant to counter future pandemic strains.[141] Using appropriate biosafety and biosecurity measures minimized risks to the public.
- The generation of a mutant of the highly pathogenic avian influenza A virus H5N1 (HPAI H5N1) with enhanced transmissibility between mammalian hosts (ferrets) that was as contagious as seasonal influenza viruses and retained the virulence of the wild strain[142,143] (55%–60% mortality in humans) by researchers at Erasmus University (although it was later reported that the mutant was attenuated and not as communicable as originally claimed), reported during the autumn of 2011. Concurrently, researchers at the University of Wisconsin developed a recombinant 2009 pandemic H1N1 virus expressing H5 hemagglutinin receptor binding proteins that was transmissible between ferrets. These announcements stunned many in the scientific community and the general public as risking a pandemic catastrophe following a laboratory accident or intentional release. Policy makers became concerned that the publication of these studies would support biological weapons proliferation by providing information that could be used to produce highly communicable and lethal influenza viruses.

Within 4 months of the publication of poliovirus synthesis, the Center for Strategic and International Studies and the National Academy of Sciences held a workshop on scientific openness and national security that involved a wide stakeholder community from government, academia, and scientific editorial communities that generated voluntary guidelines for ensuring the publication of new knowledge while safeguarding information that may pose security risks. Issues raised by DURC led to the foundation of the National Science Advisory Board for Biodefense (NSABB) in 2004. NSABB is a federal advisory committee within the Office of Science Policy in the National Institutes of Health (NIH) that provides advice, guidance, and leadership regarding biosecurity oversight of dual use research, defined as biological research with legitimate scientific purpose that may be misused to pose a biological threat to public health and/or national security. NSABB is chartered to recommend strategies and guidance for enhancing personnel reliability among individuals with access to biological select agents and toxins; provide recommendations on the development of programs for outreach, education, and training in dual use research issues for scientists, laboratory workers, students, and trainees in relevant disciplines; advise on policies governing publication, public communication, and dissemination of dual use research methodologies and results; recommend strategies for fostering international engagement on dual use biological research issues; advise on the development, utilization, and promotion of codes of conduct to interdisciplinary life scientists and relevant professional groups; advise on policies regarding the conduct, communication, and oversight of dual use research and results, as requested; advise on the Federal Select Agent Program, as requested; and address any other issues as directed by the Secretary of Health and Human Services. NSABB concerns include knowledge, products, or technologies that may:

- enhance the harmful consequences of a biological agent or toxin;
- disrupt the immunity or the effectiveness of an immunization without clinical and/or agricultural justification;
- confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions or facilitate their ability to evade detection methodologies;
- increase the stability, transmissibility, or the ability to disseminate a biological agent or toxin;
- alter the host range or tropism of a biological agent or toxin;
- enhance the susceptibility of a host population; and
- generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent.

Examples of initiatives coordinated through NSABB include Department of Health and Human Services (DHHS) guidelines for synthetic biology[144] and guidance for providers of double-stranded DNA to screen procurement orders.[145]

In December 2011 NSABB reviewed manuscripts of the Erasmus University and University of Wisconsin studies on enhanced transmission of HPAI H5N1 that were being prepared for publication and made the unprecedented, nonbinding recommendation to redact methods and experimental details.[146] In addition, the influenza research community voluntarily invoked a moratorium on gain-of-function research using HPAI H5N1.

NSABB members asserted that their recommendation was an exceptional and adaptive response to a special case—a situation generated by the life sciences, biodefense, and general public communities being caught off-guard—and having limited awareness of the research until the manuscripts were being prepared (even though NIH had funded both projects), they reasoned that:

- in the future, the value of conducting and supporting specific dual use research projects should be carefully considered a priori by a wide stakeholder community including experts in life sciences, biosecurity, and members of the general public; and
- decisions to publish results should follow the principle of "do no harm," with the best interest of public health in mind.[147]

However, supporters of the research and its publication argued that:

- medical science must address the most virulent pathogens to be valuable;
- new knowledge of determinants of transmissibility may be useful to predict the likelihood of an epi- or enzootic virus being capable of a "species jump" to humans and consequent person-to-person transmission;
- the mutants afforded an opportunity to test vaccine and therapeutic candidates against potential future emerging viruses;

- methods used in the studies are already well-known in the scientific community;
- persons with malicious intent could use simpler means to inflict disease and injury; and
- redacting the manuscripts constituted censorship, thus violating long-standing principles of academic freedom.[148–151]

As the debate raged,[152–156] WHO concluded that such research and its publication is in public health's best interest and should be continued in the context of rigorous biosafety, biosecurity, and risk communication.[157] NSABB reconvened in late March 2012 and recommended the full publication of the University of Wisconsin manuscript and publication of the Erasmus University manuscript after appropriate scientific review and revision, with the caveat that the US government should develop a mechanism to control access to sensitive scientific information.[158] The two manuscripts were published later in 2012.[159,160]

The controversy resulted in an updated US Government Policy for Oversight of Life Sciences DURC, which was released in March 2012.[161] This policy directed federal departments and agencies that conduct or fund life sciences research to do the following:

- review all current or proposed research projects to identify those that could potentially provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security;
- conduct risk assessments and develop risk mitigation plans addressing experimental design and methods, biosecurity, biosafety, and availability of medical countermeasures;
- review annual progress reports to determine whether DURC results have been generated;
- request voluntary redaction of research publications or communications or classification of research findings; and
- coordinate information regarding DURC projects with the Assistant to the President for Homeland Security and Counterterrorism.

In addition, the Office of Science and Technology Programs is formulating a complementary policy that delineates oversight responsibilities for research institutions receiving federal funds to perform DURC.[162]

In December 2012 NIH hosted a meeting of the influenza research community to discuss guidelines for funding HPAI H5N1 influenza virus gain-of-function research, followed by an opportunity for public comment. The resulting guideline was issued on February 21, 2013,[163,164] and it identified criteria for funding research proposals that may enhance the transmissibility of HPAI H5N1 among mammals:

- the virus anticipated to be generated could be produced through a natural evolutionary process;
- the research addresses a scientific question with high significance for public health;
- there are no feasible alternative methods to address the same scientific question in a manner that poses less risk than the proposed approach;
- biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;
- biosecurity risks can be sufficiently mitigated and managed;
- the research information is anticipated to be broadly shared to realize its potential benefits to global health; and
- the research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research.

The framework also outlined a review process that includes department-level scrutiny of proposals considered for funding by DHHS agencies.

Five days after the release of the DHHS framework, the ethical, societal, scientific, safety, and security issues raised by DURC were discussed at the international level at WHO. There was consensus that DURC issues are relevant to all nations and multiple stakeholders; management of DURC should take place during all phases of research; ethical considerations are fundamental; and because management of DURC will require a diversity of approaches in different member states, an internationally binding agreement would be difficult, impractical, and not necessarily effective. However, the participants remained open to future international guidelines and suggested that existing international agreements (eg, the BWC, WHO's International Health Regulations [IHR]) could provide a basis for overarching principles. WHO will continue to engage member states and other stakeholders to explore effective approaches.[165]

In the meantime, the influenza research community had already ended its moratorium for scientists using biosafety and biosecurity measures in compliance with its respective national regulations.[166] The subsequent publication of a study completed before

the moratorium using reverse genetics to generate 127 hybrids of HPAI H5N1 and 2009 pandemic H1N1 viruses, of which five were communicable among guinea pigs,[167] again raised questions regarding the medical utility and public health risks of hazardous experiments.[168] In August 2013 proponents of gain-of-function research publicly announced their intention to conduct studies using influenza A H7N9 virus.[169] Concurrently, DHHS gave assurances that research proposals for H7N9 gain-of-function research would undergo rigorous scrutiny by experts in multiple disciplines including biosafety and ethics and final review at the department level,[170] consistent with the February DHHS framework. The a priori publication of H7N9 research goals was seen as a proactive step to enhance transparency and prospective discussion and to prevent a recurrence of the 2011–2012 H5N1 disputes. However, gain-of-function research remains a contentious issue[171] because no certainty exists that laboratory-generated mutants will emerge in nature. The issues generated by potential dual use research will continue to fuel discourse regarding relationships among stakeholders, and optimal policy and technical solutions.[172–179]

Toward Pan-Hazard Preparedness

During the late 1990s the US government launched an ambitious program to enhance biological preparedness at local, state, and federal levels, including measures such as the Presidential Decision Directive-39 (1995), Presidential Decision Directive-62 (1998), and Presidential Decision Directive-63 (1998). The Federal Response Plan (now called the National Response Plan) coordinates federal agencies responding to disasters. The Select Agent List was created to regulate the purchase, shipment, and research of designated microbial agents; lead proponents for the Select Agent list were DHHS and USDA. DHHS was given oversight of health and medical services, and its Office of Emergency Preparedness organized local medical response teams in 125 jurisdictions. Preparations in New York City and other locations included plans and exercises for local incident command; coordinated clinical response; surveillance; and massive distribution of postexposure prophylaxis at multiple distribution centers designed for efficient screening, triage, distribution, and documentation. Federal response teams were organized, staffed, and deployed to large official and public gatherings. CDC established a center for bioterrorism response to enhance state public health laboratories, improve surveillance systems, and improve rapid communication and coordination. The Strategic National Stockpile of key pharmaceutical agents and vaccines was prepared. The Laboratory Response Network, also managed by CDC, provided coordination of testing, sample shipment, and communication between designated local, regional, and reference laboratories. DoD assets integrated into the National Response Plan included USAMRIID for emergency medical consultation and reference laboratory support; the Naval Medical Research Center for laboratory support; the US Marine Corps Chemical and Biological Incident Response Force for reconnaissance, initial triage, and the decontamination of casualties; and the Army Technical Escort Unit for sampling, transport, and disposal of dissemination devices. The Army Medical Department also fielded six regionally based chemical/biological special medical augmentation response teams to deploy within 12 hours to assist local civilian authorities. The National Guard Bureau, under legislative direction from Congress, fielded regional biological response teams initially called rapid agent identification teams, and later renamed civil support teams. Many of these new response mechanisms and agencies were tested in the autumn of 2001.

After the anthrax mailings of 2001, bioterrorism response was strengthened with additional infrastructure and linkages among the emergency response, public health, clinical, and laboratory sectors.[103,104] The Office of Public Health Emergency Preparedness at DHHS was formed to coordinate civilian medical countermeasure development by the National Institute of Allergy and Infectious Diseases, CDC, and DoD, under the leadership of eminent scientists and physicians such as DA Henderson and Philip K Russell.

In April 2004 President George W Bush signed Homeland Security Presidential Decision Directive-10, Biodefense for the 21st Century, which outlined a national strategy for combating biological terrorism and mandated an interagency approach using strengths of various executive branch departments, including the Department of Homeland Security, DHHS, and DoD. Subsequently, the Homeland Security Council and the National Security Council formed an interagency steering committee called the Weapons of Mass Destruction Medical Countermeasures Subcommittee, whose principals were at the assistant secretary level; the group coordinates the various departmental efforts to prevent and respond to weapons of mass destruction attacks. The Department of Homeland Security took the lead on biological threat assessments, and DHHS took the lead on medical countermeasures.

On July 21, 2004, Project Bioshield was initiated as a $6 billion, 10-year program for acquiring new medical countermeasures for the Strategic National Stockpile. This legislation provided a significant funding boost to

the Office of Public Health Emergency Preparedness. Medical countermeasures added to the Strategic National Stockpile include significantly increased doses of botulinum antitoxins; antibiotics to treat anthrax, tularemia, and plague; anthrax adjunctive therapies; and ventilators for respiratory support.

The potential for the malevolent use of genetic engineering to develop novel biological threats with enhance virulence[180] resulted in a shift of technical emphasis from pathogen-specific projects to a global response capability—a threat-agnostic response capacity—to enable responses to outbreaks of any known or genetically engineered biological agents, or novel emerging pathogens. This capability includes flexible technology platforms to enable rapid pathogen identification and characterization, drug target identification, and medical countermeasure development and mass production. An emphasis has been placed on the development of anti-infective therapeutics that has a broad spectrum of activity to enhance their potential utility against a wide range of emerging pathogens. In addition to exploiting highly conserved pathogen targets, proposed approaches have included host-directed anti-infective therapeutics to upregulate innate immunity, antagonize host receptors and processes that are hijacked by pathogens to complete their life cycles, and attenuate sepsis and other pathogenesis pathways.

The National Strategy for Countering Biological Threats[3] proposed an integrated approach to all biological threats, whether from intentional releases (biological warfare or terrorism) or accidental releases (laboratory accidents or unintended consequences of legitimate scientific research) or naturally occurring emerging diseases. The strategy is based on the concept that all of these challenges require a common set of responses (pathogen identification and characterization; patient diagnosis; development, mass production, and distribution of medical countermeasures; medical and public health interventions; risk communication; promotion of ethical standards; professional and legal codes of conduct; and law enforcement). It proposes a pan-sector "all of society" approach that integrates the public at large and the scientific, medical, veterinary, public health, law enforcement, and diplomatic communities. Initiatives have included reorganization of civilian biodefense under the Department of Homeland Security; strengthening of programs under DoD and DHHS (NIH, the Biomedical Advanced Research and Development Authority, CDC) that have multipurpose utility for biological attacks, naturally occurring outbreaks, and other mass casualty disasters; the construction of the Fort Detrick biodefense campus, which includes laboratories for the Department of Homeland Security and NIH as well as a new USAMRIID facility; export controls to regulate exportation of potential dual use technologies; the medical countermeasures initiative to enhance mass production of medical countermeasures; investments to enhance biosurveillance; and federal guidelines for synthetic biology and the use of double-stranded DNA.

The Federal Experts Security Advisory Panel's interagency working group was initiated in 2010 to update 42 CFR Part 73, Possession, Use, and Transfer of Select Agents and Toxins, to prevent intentional or accidental releases of highly virulent pathogens without placing counterproductive regulatory burdens on laboratories that conduct research on CDC select agents. Topics that were considered included revising the list of select agents, physical security measures, laboratory safety, occupational health, and personal reliability. A simplification of the select agent list was proposed, removing or recategorizing agents that are either easy to obtain from their natural reservoirs, or that constitute low risk due to low virulence, low transmissibility, or the availability of medical countermeasures. The Federal Experts Security Advisory Panel developed a comprehensive set of recommendations regarding biosecurity—the presence of physical security measures such as laboratory access controls, closed circuit visual monitoring, etc, and personal reliability—as well as background checks of laboratory workers' law enforcement history, substance abuse, and mental health, with continuing monitoring and periodic reassessments of suitability for continued employment. Robust occupational health programs, with mandatory reporting of illnesses requiring medical intervention, were emphasized to prevent behaviors that could result in accidental or deliberate releases of select agents and to promptly recognize and treat laboratory-acquired infections and prevent their transmission to the general community. The Final Rule (October 5, 2012) included a revised select agent list; physical security standards for laboratories possessing Tier I Select Agents and Toxins; a requirement to conduct pre-access assessments and ongoing monitoring of personnel with access to Tier I agents and toxins; and clarifications of regulatory language concerning security, training, biosafety, and incident response.[118,119]

The optimization of biosafety and biosecurity is an iterative process. USDA's Office of the Inspector General noted that while there had been enhanced compliance with security regulations and inspection processes within the USDA Select Agent program between 2005 and 2012, there had been transfers of *B anthracis* and *Y pestis* samples to unregistered facilities, and access to select agents by a person with an expired security clearance. USDA concurred with recommendations

to clarify restricted access requirements and establish policies and procedures for handling requests for transferring select agents under special circumstances to unregistered facilities.[181] On March 24, 2013, a vial of Guanarito virus (a Tier I Select Agent) was reported missing from the University of Texas Medical Branch at Galveston.[182] On the following day, the Government Accountability Office issued a report concluding that US government interdepartment and interagency biodefense programs using high containment laboratories should improve their coordination. It also recommended that the Office of Science and Technology within the Executive Office of the President conduct periodic assessments of the requirements for, and the number, locations, and missions of high-containment laboratories, and evaluate the need to establish national standards for their design, construction, commissioning, operation, and maintenance.[183]

International efforts include the following:

- outreach by DoD and CDC to enhance surveillance with international partners;
- DoD's Cooperative Biological Engagement Program that builds partnerships to convert former biological weapons programs to peaceful purposes and enhance public health capacity;
- collaborations to strengthen biological defense capacities of partner nations (eg, through the North Atlantic Treaty Organization and the Australia–Canada–United Kingdom–US–New Zealand partnership);
- US government support of BWC confidence-building measures and international public health efforts that may also lead to the early identification and containment of biological attacks (eg, WHO's IHR); and
- WHO efforts to enhance implementation of the IHR and strengthen ties with the World Organization for Animal Health and Interpol.

SUMMARY

The use of microbes and toxins to intentionally cause harm has been attempted repeatedly throughout recorded history. However, military use before the development of modern microbiology was limited, possibly because of the availability of other weapons with more rapid and predictable results.

Following the inception of modern microbiology, several nations began offensive biological warfare programs. Information regarding the history of state-sponsored biological weapons programs is obscured by secrecy, propaganda, and a lack of rigorous microbiologic or epidemiologic data to confirm allegations of use. Disclosures of former national programs underscore the ambitious intent and potential realization of covert state-sponsored programs. However, military deployment has been limited, and never decisive in armed conflict. With the exceptions of alleged German sabotage during World War I, Japanese field trials during World War II, limited deployments by South African and Rhodesian forces, and small-scale covert operations, there are no well-documented biological attacks by nation-states. Deterrents may include poor tactical utility related to multiple variables during production, storage, and delivery; variable incubations and host susceptibilities; availability of medical countermeasures; nuclear deterrence; diplomatic efforts; and political vulnerabilities. The public health disaster at Sverdlovsk, the loss of international goodwill toward the United States following disclosures during the Cold War, and political consequences following the 1996 disclosures by Iraq underscore that the attendant liabilities of state-sponsored biological weapons programs have outweighed potential strategic advantages.

Non-state groups, lone actors, and even members of the medical community have committed bioterrorism and biocrimes. The likelihood of amateurs using homemade equipment to successfully develop and deploy a biological weapon of mass destruction is remote. Terrorists still rely on simple yet effective explosives as their weapon of choice. However, the Aum Shinrikyo program and Al Qaeda aspirations demonstrate intentions to harness modern microbiology for malicious purposes. Although most bioterrorism incidents and biocrimes have had limited results, the 1984 Rajneeshee episode and the 2001 anthrax mailings illustrate that even relatively small-scale attacks can have enormous public health, economic, and social consequences.

Biological weapons have been renounced by 170 states-parties to the BWC for numerous political and strategic considerations. Counterproliferation efforts, including verification of compliance of signatory states, remain challenging. According to an unclassified 2013 US Department of State report, uncertainties exist about activities in Russia, Iran, North Korea, and Syria.[78] These ambiguities, in addition to the miscalculations of the 2002 National Intelligence Estimate, underscore the difficulty of assessing biological weapons programs even through the rigorous efforts of highly dedicated and skilled professionals. These concerns highlight the importance

of strengthening international goodwill and transparency through the BWC and international engagement programs.

The threats of biological weapons have led to new technical strategies:

- a movement from addressing a static list of a limited number of specific pathogens toward a threat-agnostic capability-based approach using flexible enabling technology platforms that can be rapidly adapted to counter novel, unanticipated pathogens;
- broad spectrum therapeutics; and
- versatile response capacities that can be used to counter biological weapons attacks, naturally occurring epidemics, or other mass casualty disasters.

The past decade has also seen efforts to integrate multidisciplinary societal sectors ranging from research to operational response-surveillance; medical care delivery; risk communication; the development, mass production, and stockpiling of medical countermeasures; and planning and exercises at local, regional, national, and international levels. The enhancement of diagnostic platforms, disease surveillance and reporting networks, medical countermeasures, and health delivery systems that can be rapidly adapted as common solution sets to either biological attacks or natural epidemics is essential to cost-effective, economically sustainable disease mitigation in an era of limited resources.

Scientific research on highly virulent pathogens is essential to biodefense and public health—broadly inclusive—to counter biological weapons and novel emerging diseases. Such research inevitably carries risks, including accidental releases, transmission of laboratory-acquired infections to the community, unanticipated consequences of well-intended experiments, and the generation of knowledge that could be misused to execute biological attacks. Even with effective risk management, risk never reaches zero, but can be decreased to an "irreducible minimum" through rigorous biosafety and biosecurity. Steps in the right direction include the formulation and enforcement of standards and regulations for biosafety, biosecurity, and handling of select agents. Risks and benefits should be carefully considered a priori, with engagement of a broad stakeholder community. Risk management must preserve opportunities for scientific creativity and academic freedom and also must be open to unanticipated experimental results that may serendipitously lead to valuable new discoveries, such as the reactogenicity of tuberculin purified protein derivative, that led to the repurposing of a failed therapeutic to a valuable diagnostic reagent, and the fungal contamination of a bacterial culture that led to the discovery of penicillin.

Although technical solutions are essential, they are not sufficient. An understanding of the history of the development and use of biological weapons, as well as analyses of risk perception and misperception, and appropriate or misguided responses to perceived risks requires examination from both technical and sociological points of reference, particularly the sociologies of scientific and policy decision-making. Important issues include the psycho-social milieus that generate biological weapon development and use, and that lead either to effective responses to credible threats or to misinterpretation and over-reaction to legitimate biotechnology.[184]

The late Joshua Lederberg, the 1958 Nobel laureate for medicine or physiology, a pioneer of bacterial genetics and recombinant technology, and an expert opinion leader in the fields of emerging infectious diseases and biological defense,[185] remarked:

> There is no technical solution to the problem of biological weapons. It needs an ethical, human and moral solution if it's going to happen at all. Don't ask me what the odds are for an ethical solution, but there is no other solution.[186]

Value-related paradigms of ethical medical research directed toward the good of humanity, which underlie the preamble of the BWC's appeal "to the conscience of mankind,"[187] and the National Strategy for Countering Biological Threats' emphasis that life sciences research should be used "solely for peaceful and beneficial purposes,"[188] proscribe biological weapons, and may also inform approaches to dilemmas posed by DURC. Proposals to obtain new data, information, and knowledge should be evaluated in the context of wisdom and in its relevance to the advancement of the common good, and be open to the possibilities that human actions may have intrinsic meaning and moral value. History demonstrates that when ethics and science are decoupled, potential outcomes include biological weapons. Ethical considerations are as relevant to basic and applied microbiology as the principle of beneficence is to medical research involving human subjects. Academic freedom must be maximized and ethical constructs must be flexible, yet circumstances exist in which it is appropriate to take principled stands.

Moral principles lead to codes of professional conduct based on a commitment that basic and applied sciences must be value-related—purposely directed toward the benefit of society as their long-term goal

with a caveat to "do no harm."[179] Professional ethics must go deeper than financial disclosures and honest reporting of data to address the value and risks of proposed experiments. Because an experiment can be done—as an achievement outside of a value- and goal-related context—does not mean that it should be done. It is essential to build a culture of responsibility at every level of individual investigators, laboratory institutional review boards, funding organizations, and national authorities considering the permissibility of specific research proposals in the context of purpose, methods, potential unintended consequences, and value to society. Moral principles underlying the BWC and the National Strategy for Countering Biological Threats have found expression in the ethical codes of the American Society for Microbiology and other professional organizations, US government guidelines for synthetic biology and DURC, the Cooperative Biological Engagement Program, support for implementation of the IHR, and NSABB's call for the development and dissemination of ethical codes of conduct.[189]

The use of synthetic biology to produce wild-strain poliovirus illustrates the relevance of ethics to biological weapons proliferation and DURC, and the role of coordinated multidisciplinary approaches for risk mitigation. An intended outcome was to sound an alarm that viruses can be synthetically produced to develop biological weapons; a conclusion was that WHO's goal of polio eradication may be unrealistic and should be reconsidered in view of issues that include the potential reintroduction of synthetic poliovirus as an act of bioterrorism.[136,138] Alternatively, the chemical synthesis of the oral polio vaccine would have demonstrated an innovative cell-free platform for the production of attenuated live viruses for vaccines. This would have been an unambiguously benevolent action and would have supported the investigators' intention to test the hypothesis that live viruses can be synthetically produced. The inductive proposition that synthetic viruses may pose biological weapons proliferation risks would have been obvious. The investigators later directed their platform toward novel approaches to vaccine development[138,190–193]; in the context of altruistic medical research, this could have been their stated objective and technical approach from the outset.

During the timeframe when the synthesis of wild-strain poliovirus was being conducted and reported, WHO was already proposing material and nonmaterial solutions for the contingency of a posteradication outbreak resulting from either bioterrorism or an accidental reintroduction.[194–198] A 2013 WHO strategic plan for the final phase of polio eradication combines multidisciplinary pan-sector approaches including the global incorporation of inactivated polio vaccine into routine immunization programs, coordinated withdrawal of oral polio vaccine, biocontainment of all wild and vaccine strains, enhanced surveillance, a vaccine stockpile for emergency use, communication, and response.[199] The potential abuse of synthetic biology for biological weapons proliferation has not derailed the polio eradication campaign,[199–202] just as the risk of biological warfare using variola did not obviate the goal of smallpox eradication.

Medical capabilities and biomedical research are being linked to diplomacy, commerce, education, ethics, law enforcement, and other activities to enable a common set of multidisciplinary pan-societal sector responses to both biological weapons and the inevitable and dynamic challenges of naturally occurring emerging infectious diseases.[3] Integration of biological defense and public health programs and their mutual development must be continuous to optimize outcomes and maximize efficient utilization of limited resources and because the challenges posed by both biological weapons agents and naturally emerging pathogens are open ended.

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