2009

The Role of Science in Preparedness and Response

Kavita Marfatia Berger

Bluebook Citation

ARTICLE

THE ROLE OF SCIENCE IN PREPAREDNESS AND RESPONSE

KAVITA MARFATIA BERGER, PhD*

Unlike other weapons of mass destruction, biological weapons—whether developed by a state-sponsored program, terrorist organization, or lone actor—pose a very unique threat. The knowledge, tools, and techniques used to create biological weapons, as well as the biological agents themselves, are readily available in research laboratories throughout the world and in nature. Nearly all biological research is done for peaceful and legitimate purposes, and all biological agents, with the exception of smallpox, are public health threats somewhere in the world. Therefore, it is vitally important to emphasize from the outset that biological research and the knowledge, tools, and techniques gleaned from this research are essential to improving the human condition, environment, and agriculture. Any attempt to prevent the development of biological weapons and access to dangerous biological agents must take into account the benefits of biological research and be implemented with the full aid and consent of the global biological sciences community. Only then will we be able to achieve the balance between promoting beneficial biological research while successfully preventing the development of and effectively responding to biological weapon attacks. This paper will describe the legal and ethical framework for the role of science and scientists in preparedness and response—preventing unauthorized access to dangerous biological agents and misuse of knowledge, tools, and techniques to develop biological weapons—and the impact these have in responding to a biological attack. As the discussion below will demonstrate, science and scientific methods are critical components to all aspects of preparedness and response efforts against infectious disease threats, regardless of the outbreak’s source (i.e., natural, accidental, or intentional).

* The author has a BS in Molecular Genetics from The Ohio State University and a PhD in Genetics and Molecular Biology from Emory University. The author conducted her post-doctoral research in HIV and smallpox vaccine development at the Emory Vaccine Research Center.
Response to a bioterrorism incident involves many individuals from first responders and law enforcement personnel to public health professionals. In an overt incident, public health officials and law enforcement personnel work together to help mitigate the outbreak and identify the perpetrator. The more likely incident is a covert event where an agent is released, which can be done in a number of ways—not just via aerosol means. Though not first responders, health care professionals and public health officials are the first to collect patient samples, diagnose the disease, and treat the sick. If they deem the incident to be an intentional attack with a suspicious agent, route of exposure, or spread of the disease, the U.S. Centers for Disease Control and Prevention (CDC) would inform law enforcement, including the Federal Bureau of Investigation (FBI).

The function of science during a routine public health response, regardless of whether the exposure is intentional, accidental, or natural, is focused on performing diagnostic tests to accurately identify the causative agent of the outbreak and monitor the disease spread, and developing or manufacturing large amounts of vaccines or therapeutics to control the outbreak. Scientists funded by the U.S. Department of Health and Human Services (HHS) Regional Centers of Excellence (RCE) are required by contract to help in detection and surveillance should the CDC become overwhelmed in an emergency.1 Initial detection of the agent is not just restricted to hospital and public-health pathology laboratories but extends to domestic animal and wildlife disease surveillance since most dangerous pathogens, and many of our priority threat agents, are zoonotic, which means they can infect both animals and humans.2 In the United States’ recent history, several examples demonstrate the importance of accurately identifying the causative agent and mounting an appropriate and rapid public health response.

In 1999, seven Americans died and several more became ill in New York City from a virus misdiagnosed as St. Louis Encephalitis Virus, which is found in North America.3 Just two weeks earlier, veterinarians at the


2. See generally Anthony S. Fauci, Emerging Infectious Diseases: A Clear and Present Danger to Humanity, 292 JAMA 1887 (2004); Anthony S. Fauci, New and Reemerging Diseases: The Importance of Biomedical Research, 4 EMERGING INFECTIOUS DISEASES 374 (1998) (discussing contributions of basic scientific research).

Bronx Zoo observed zoo animals dying, and through post-mortem clinical tests, identified the causative agent as West Nile Virus. During the late 1990s, medical professionals and veterinary professionals did not readily work together, and information sharing about disease outbreaks between the human and animal health fields was essentially non-existent. Though some in the microbiology community had been advocating the One Health/One Medicine concept, it did not become well known until very recently. The One Health/One Medicine concept states that human, animal, and plant health are intimately tied to one another and improving the health of plants and/or animals can help improve the health of humans. It was not until several weeks after the initial outbreak of West Nile Virus in the United States that the veterinarians at the Bronx Zoo were able to share their data with the New York City Department of Health. This sharing of clinical data corrected the misdiagnosis of St. Louis Encephalitis Virus as the causative agent of the human outbreak; the pathologies between infected humans and animals were strikingly similar, and St. Louis Encephalitis Virus is not known to be zoonotic but West Nile Virus is. In recent years, public health and intelligence agencies have made progress in integrating animal and human disease surveillance data to better inform their activities. The West Nile Virus incident demonstrated that animals show disease symptoms before humans when infected with a zoonotic agent; animals can therefore serve as sentinel surveillance to a potential human outbreak. This can also be true for a bioterrorism incident, where the fitness of animals can help warn the human population of a potential outbreak or aerosol release of a dangerous zoonotic agent. For example, rats and other small rodents would become ill before humans if plague were released via aerosol in an urban environment. This is due to natural responses against the pathogen and size of the host—small rodent versus human. In 2007, the CDC established the National Center for Zoonotic, Vector-Borne, and Enteric Diseases, which staffs at least sixty veterinarians, to provide the CDC with expertise for epidemiological studies, bioterrorism preparedness, applied research, disease surveillance, and outbreak response. The U.S. Department of Homeland Security (DHS) Office of Health Affairs and the National Bio-surveillance Integration Center have also employed veterinarians as experts for bioterrorism preparedness and infectious disease surveillance.


The ability to properly respond to an unusual outbreak depends on recognizing the symptoms of a disease, being aware of the possible agents that might cause the symptoms, and conducting the appropriate diagnostic tests to identify and confirm the causative agent. Critical for all of these missions, regardless of job function (i.e., first responder, public health laboratorian, or health professional), is training. The first case from the 2001 anthrax attack was detected in Florida by a physician who had just returned from a bioterrorism training program at the CDC. He accurately diagnosed the infection to be caused by anthrax and requested confirmatory tests from the hospital, state public health laboratories, and the CDC. Once confirmed, exposed individuals were given ciprofloxin, and surveillance and decontamination efforts began. Considering they had not encountered an inhalational anthrax in twenty-five years, the CDC and Florida physician took the appropriate actions to rapidly confirm and mitigate the outbreak. Subsequent exposures in New York City, where health officials had not received recent bioterrorism training, followed a different path. News anchor Tom Brokaw has been outspoken about his failed attempts to identify the agent that caused his assistant’s illness. He states that he repeatedly consulted with experts at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) without receiving an accurate diagnosis. The causative agent of the New York City infections was not confirmed until the overt attack on the Senate Hart Building in October 2001. The result was the recognition that training health care professionals and public health officials on bioterrorism preparedness and response is critical to initially diagnosing the cause of the outbreak. Other very important lessons learned from the anthrax mailings were that public health officials and law enforcement must develop common protocols for handling samples and communicating with one another during an outbreak of unknown or unfamiliar origin, and that the Environmental Protection Agency (EPA) must develop plans for decontaminating affected infrastructure and conduct risk analyses to determine what constitutes the level of residual agent below which the public and surrounding environment is not at risk of infection.

More recently, an individual from Atlanta, Andrew Speaker, contracted tuberculosis and refused treatment through his local public health


10. See, e.g., COMM’N ON THE PREVENTION OF WMD PROLIFERATION AND TERRORISM, WORLD AT RISK 7 (2008).

department. As the CDC was confirming the strain of tuberculosis, it warned Mr. Speaker not to go on his upcoming honeymoon to Europe. Mr. Speaker moved the date of his travel up and left for his honeymoon before the CDC could contain him. The CDC’s tests diagnosed him as having extremely drug resistant tuberculosis (XDR-TB), which is very dangerous since no commonly prescribed antibiotic is effective against it. Just a few weeks before this incident, the revised International Health Regulations (IHR2005) entered into force. The IHR2005 is a binding international agreement aimed at controlling public health outbreaks of international concern. Mr. Speaker, with XDR-TB, fell into such a category. Although the U.S. CDC informed the European Centre for Disease Prevention and Control and a few European governments, officials were unable to stop him from traveling all over Europe before returning home via a land port between Canada and the United States. Despite being on the CDC alert list, the Customs and Border Patrol Officer let him into the country. The CDC took Mr. Speaker to Colorado for isolation, where tests later confirmed that he did not have XDR-TB but was infected with multi-drug resistant tuberculosis. Health officials treated him and sent him home. This case demonstrates the inability of the public health system to work quickly and accurately to identify the exact strain of the infectious agent, which is critical to assessing the appropriate response from the public health system and international community.

Development of medical countermeasures against unknown or known biological agents (except for those with vaccines or therapeutics in the Strategic National Stockpile) is an important role for scientists during response to a natural or intentional biological outbreak. Development of vaccines and therapeutics to control and mitigate the outbreak depends on current technologies and scientific advancement in vaccine and drug development as well as the transmission rates and infectivity of the infectious agent. Influenza, for example, is easily transmitted via aerosol routes between people. The threat of the pre-pandemic H5N1 influenza virus becoming a human pathogen has fueled the U.S. government to consider plans for rapid identification of the pandemic strain and development of vaccines against the pandemic strain. Current estimates indicate that development of a vaccine against the pandemic influenza strain would take three to six months. By this time, most of the country and world will have been infected with influenza. While development of a SARS (Severe Acute Respiratory Syndrome)
vaccine was rapid (nine months), development of vaccines against other priority threat agents may be more difficult. HHS is currently supporting (in principle, if not funding) broad-spectrum medical countermeasures and new technologies that allow for rapid development and manufacturing of effective vaccines.16

The manufacturer of vaccines against the pre-pandemic H5N1 influenza is Sanofi-Pasteur. Sanofi-Pasteur, like most large pharmaceutical and biotechnology companies, is multinational, and many of the facilities are in developed nations. During a pandemic, many nations, including the United States, could try to claim the vaccines manufactured in their country for their own citizens. Indonesia, which is the only country to have had limited person-to-person transmission of the pre-pandemic H5N1 influenza virus, has blocked sharing of viral isolates and information with developed nations because of intellectual property and technology transfer concerns.17 The Indonesian government is mostly concerned that vaccines and therapeutics developed from the strains initially isolated in Indonesia will not be shared with them. Until recently, pharmaceutical companies did not donate doses of vaccine for use in developing countries like Indonesia. In early 2009, however, the Bill and Melinda Gates Foundation successfully negotiated with the pharmaceutical industry to donate 110,000 doses of H5N1 influenza vaccine to the World Health Organization (WHO) for use in developing nations.18 The 2009 H1N1 pandemic prompted two multi-national companies—Glaxo Smith Kline and Sanofi-Pasteur—to donate H1N1 vaccine to the WHO for developing nations.19 Beyond these real intellectual property concerns and concerns about access to medical interventions, Indonesia has recently moved beyond intellectual property concerns to security concerns. Indonesia has claimed that the United States’ security policies prevent sharing of information about the H5N1 strains that were originally isolated in Indonesia and unfoundedly claimed that the United States is using their influenza strains to make biological weapons.20 There is a growing concern that other developing nations may follow Indonesia’s lead. It is

vitally important to promote international collaboration and coordination among academic, government, and industry scientists and public health officialis to ensure that the proper vaccines are being made and delivered to all who need them, and not just those who can afford them.

II. THE SELECT AGENT PROGRAM AND INFECTIOUS DISEASES

The development and use of vaccines against infectious diseases commonly afflicting children—childhood diseases—and the successful global eradication of smallpox in 1977 made many in the scientific community consider the fight against infectious diseases an easily attainable endeavor. Then, Human Immunodeficiency Virus (HIV), unidentified at the time, became more prevalent. Although HIV initially entered the human population during the 1950s, its effects in western countries were not seen to great degrees until the 1980s. During the subsequent decades, scientists identified more infectious agents and recognized that infectious diseases were everywhere and would continually plague the human race.

We now know that many infectious diseases exist—most are newly-emerging or re-emerging within the population. More than 75 percent of infectious diseases are zoonotic, which means they can infect both animals and humans. Many of the newly emerging pathogens are zoonotic and have existed in animal hosts for decades or centuries before they emerge in the human population. For example, the natural hosts for HIV are new world monkeys; for Ebola virus, great apes; for plague, rodents; and, for influenza, birds and pigs. In fact, an overwhelming majority of the United States’ priority national security threat agents are naturally-occurring zoonotic agents. Smallpox (human only) and foot-and-mouth disease (hoofed animals only) are among the few that are not zoonotic.

In 1992, after the fall of the Soviet Union, Russian Prime Minister Boris Yeltsen admitted that the former Soviet Union had an enormous bio-

24. Fauci, Emerging Infectious Diseases: A Clear and Present Danger to Humanity, supra note 2, at 1887; see also Fauci, New and Reemerging Diseases: The Importance of Biomedical Research, supra note 2, at 374 (discussing diseases that have emerged since 1918)
logical weapons program.\(^{27}\) The concern over bioterrorism first began during the mid-1990s when the Japanese group, Aum Shinriko, who successfully released sarin gas in a Tokyo subway station, attempted to weaponize and disseminate anthrax.\(^{28}\) Much to the group’s dismay, the strain of anthrax it was using was the stern strain—an animal vaccine strain—but the group was supposedly successful at aerosolizing the bacteria and managed to release the aerosolized vaccine on top of a Tokyo building. In addition to anthrax, Aum Shinriko reportedly tried to acquire Ebola virus from a village in Africa during an outbreak but failed. Although the group invested millions of dollars to acquire dangerous pathogens or create biological weapons, it was unsuccessful.\(^{29}\)

Shortly after the revelations of Aum Shinriko, an American microbiologist and member of the Aryan Nations, Larry Wayne Harris, acquired the plague bacteria from the American Type Culture Collection under false pretenses.\(^{30}\) He was convicted of mail fraud, since unauthorized possession of dangerous pathogens was not illegal.\(^{31}\) This incident spurred fears that anyone could get dangerous pathogens; the pathogens of greatest concern were those known to be weaponized by the Soviet Union. The result was the creation of the Select Agent Program under the Antiterrorism and Effective Death Penalty Act of 1996.\(^{32}\) This statute restricts the transfer of a select set of dangerous biological agents. Following the 2001 anthrax mailings, Congress passed the USA PATRIOT Act and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which expanded the Select Agent Programs to include background checks by the Department of Justice for anyone seeking to work with select agents and registration of individuals and facilities seeking to work with biological agents on the select agent list.\(^{33}\) The list now includes human, zoonotic (referred to as “overlap” agents), animal, and plant pathogens and toxins; the program is jointly run by the CDC Prevention and the USDA Animal and Plant Health Inspection Service (APHIS).

The select agent regulations have disrupted research collaboration among American and foreign scientists.\(^{34}\) The National Institute of Allergy and Infectious Diseases (NIAID) policies state that laboratories of foreign


\(^{32}\) 42 C.F.R. § 73 (2009).

\(^{33}\) *Id.*; 7 C.F.R. § 331 (2009); 9 C.F.R. § 121 (2009).

collaborators of NIAID-funded investigators have to be at the same safety and security standards as U.S. laboratories. In many nations where select agents pose serious public health threats, there are not enough resources to build and maintain laboratory facilities at American standards. Disruption of international collaborations greatly hampers the United States’ ability to help identify and respond to public health threats of international concern. During the SARS outbreak in 2003, a group of preeminent scientists from throughout the world requested that SARS be left off of the select agent list in order to ensure that the best scientists can collaborate to identify, characterize, and develop medical interventions against the disease-causing agent. There is anecdotal evidence suggesting that scientists outside the United States were initially hesitant to work with American scientists on SARS because of the security challenges associated with the Select Agent Program. Importantly, the lack of restrictions on SARS facilitated international collaboration among leading public health experts and scientists in coronavirus biology, resulting in the rapid identification of the novel infectious agent and development of an effective vaccine against SARS in nine months. While not all pathogens are like SARS—influenza, for example, mutates rapidly so developing an effective vaccine from an original pandemic strain may be difficult—the exceptional scientific response to the SARS outbreak demonstrated the powerful role science plays in public health response.

The SARS experience highlights the need for evaluating the costs of the Select Agent Program to human, animal, and/or plant health; science; and other national goals as compared to the program’s actual benefits to national security. There are currently seventy-two agents on the select agent list. Some agents, like smallpox, hemorrhagic fevers, anthrax, and foot-and-mouth disease, are primarily on the list because they were previously weaponized in state-sponsored programs or used in biological warfare. All select agents, with the exception of smallpox and the 1918 influenza


36. In addition to this function, international collaborations build relationships and trust among scientists from many countries, which contribute to diplomatic efforts and transparency.


41. JAMES MARTIN CENTER FOR NONPROLIFERATION STUDIES, CHEMICAL AND BIOLOGICAL WEAPONS: POSSESSION AND PROGRAMS PAST AND PRESENT, http://cns.miis.edu/cbw/possess.htm (last visited Aug. 26, 2009); See also SELECT AGENTS AND TOXINS LIST, supra note 40.
virus, are current global human, animal, or plant health problems. DHS has developed a risk assessment tool that identified twelve material biological threats to national security. All of these biological threats are on the select agent list. With added concerns about creating pathogens from scratch, modifying harmless pathogens to be more dangerous, and recreating extinct pathogens, the security community has advocated modifying the select agent list to cover those agents. The National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee at the U.S. National Institutes of Health (NIH) tasked to provide the U.S. government recommendations on the criteria, oversight, and education of dual-use life sciences research and synthetic biology, has recommended that the federal government convene a group of experts to review the select agent classification scheme to "reconcile the current controls for Select Agents with the anticipated scientific advances enabled by synthetic genomics," and consider an alternative framework that uses predictive properties of genomic sequences for classifying select agents in lieu of a finite list. The NIH has tasked the U.S. National Academy of Sciences to review the feasibility of the alternative framework of the select agent list based on predictive properties of biological agents. On February 26, Senators Kennedy and Burr and Representatives Harmon and Rogers introduced companion bills for the reauthorization and modification of the select agent program—the Select Agent Program and Biosafety Improvement Act (H.R. 1225 and S. 485). This bill, among other mandated actions, includes language to review the select agent list for its inclusion of unknown or novel biological agents as well as a review of the program’s effects on scientific advancement and international scientific collaboration. More recently, on November 4, 2009, the Senate Homeland Security and Governmental Affairs Committee passed the WMD Prevention and Preparedness Act (S.1649). This bill established a tiered system of biological agents with commensurate security measures; gave the Department of Homeland Security authority to establish security standards and oversee the security components of laboratories; gave the Department of State the authority to facilitate consolidation of "Tier I" agents found in international laboratories to a single laboratory in each nation; and explicitly described the security topics on which the De-

45. Select Agent Program and Biosafety Improvement Act, H.R. 1225, 111th Cong. § 102 (2009).
partment of State should engage the international community. International scientific collaboration was critical in the identification of SARS, and both international collaboration and scientific advancement were crucial for rapid development of an effective medical intervention against SARS.

On January 6, 2009, President Bush issued an executive order (Executive Order 13486) to review all U.S. laws and regulations governing select agents, the criteria for determining which individuals can have access to select agents (called “personnel reliability”), and the oversight of high-containment laboratories. The charge is to identify gaps or challenges, and to provide recommendations to address them and improve laboratory biosafety and security. This review includes an assessment of transportation of select agents, physical security of facilities housing select agents, and the responsibilities of scientists working with select agents. The White House tasked the NSABB to review personnel reliability programs and issue recommendations on how to develop and conduct a personnel reliability program for personnel working with or around select agents. The NSABB recommended against a formal, national personnel reliability program for select agent researchers, while supporting enhancement of existing measures and a culture of responsibility and accountability within institutions conducting select agent research. The White House also tasked the National Academies to review personnel reliability; the recommendations were released on September 30, 2009. The interagency review is now complete, and the recommendations are currently under review within U.S. government and have not been publicly released.

III. THREAT ASSESSMENT AND ACTIONS

Assessing the potential threat of biological agents is very complex. Biological agents exist naturally and in most cases are global health threats to humans, animals, or plants. The Select Agent Program lists pathogens that are considered by the U.S. Departments of Health and Human Services (HHS) and Agriculture (USDA) to be threats to national security regardless of their impact on global health. The challenge faced by the intelligence and security communities to assess the risk of biological agents as national security threats not only depends on the capabilities possessed by suspects but

49. NAT’L SCI. ADVISORY BOARD FOR BIOSECURITY, ENHANCING PERSONNEL RELIABILITY AMONG INDIVIDUALS WITH ACCESS TO SELECT AGENTS 11 (2009).
also the state of the science to create and weaponize a biological agent, the infectious and pathogenic properties of dangerous agents, and the accessibility of those agents. The fear that synthetic biology techniques could be used by nefarious actors to create a dangerous or novel pathogen has fueled much of the concern over advancing biotechnology and the dual-use dilemma.\footnote{Erika Check, \textit{Synthetic Biologists Face Up to Security Issues}, 436 \textit{Nature} 894, 894 (2005).} The dual-use dilemma in the life sciences is defined as legitimate and beneficial research that could be misapplied for malicious purposes;\footnote{\textsc{National Research Council}, \textit{Biotechnology Research in an Age of Terrorism} 18–19 (2004).} this definition is distinctly different from the traditional use of the term “dual use,” which describes technologies that have civilian and military uses.\footnote{Ronald M. Atlas & Malcolm Dando, \textit{The Dual-Use Dilemma for the Life Sciences: Perspectives, Conundrums, and Global Solutions}, 4 \textit{Biosecurity & Bioterrorism} 276, 276 (2006).} The recent report, \textit{World at Risk}, by the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism (WMD Commission) states that the bioterrorism risk is equal to or greater than the nuclear terrorism risk because dangerous biological agents are easily accessible and the threshold for obtaining the needed biotechnologies to create a dangerous biological agent are sufficiently low that anyone with minimal scientific background can create a biological weapon.\footnote{\textsc{Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism & Bob Graham}, \textit{World at Risk: The Report on the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism} 11 (2008).}

Although the priority with which the Obama Administration regards biodefense is currently unknown, the security community is convinced that biological terrorism is a real threat. The common belief is that an integrated prevention and response capability in biosecurity will significantly help reduce the likelihood that a bioterrorism incident will occur. Prevention strategies were partially mentioned before with minimizing the likelihood of misuse of legitimate research—an issue taken up at the 2008 Intersessional Meeting of the Biological Weapons Convention\footnote{Conference of the State Parties to the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, Geneva, Switz., Dec. 12 2008, \textit{Report of the Meeting of State Parties}, ¶ 17.}—cooperative threat reduction programs, and bioengagement programs. Biological cooperative threat reduction programs have invested in redirecting former Soviet weapons scientists and facilities to peaceful research endeavors.\footnote{See \textit{Opportunities for Reducing Nuclear and Biological Threats at the Source: Hearing Before the H. Homeland Sec. Comm.}, 109th Cong. 1 (2006) (statement of Francis Record, Acting Assistant Secretary of State for International Security and Nonproliferation); \textsc{National Research Council}, \textit{Countering Biological Threats: Challenges for the Department of Defense’s Nonproliferation Program Beyond the Former Soviet Union} (2009).} The BioIndustry Initiative has redirected research and development at weapons facilities in the former Soviet Union to create needed vaccines and therapeutics to

\footnotesize{\begin{quote}
\textsuperscript{52} \textsc{National Research Council}, \textit{Biotechnology Research in an Age of Terrorism} 18–19 (2004).
\end{quote}}
combat infectious disease outbreaks. The Department of State’s Biosecurity Engagement Program has sought to build relationships between American scientists and foreign scientists on scientific and health related issues important to the foreign scientists, such as disease surveillance and biosafety laboratory capacity and training. This model of bioengagement, which started in the U.S. Department of State’s Bureau of International Security and Nonproliferation, is now being adopted by the Department of Defense (DoD) as a next generation CTR program. The DoD program has begun to engage nations on disease surveillance and other global health activities.

With regard to preparedness and response, much of the funding and focus has been on developing vaccines, therapeutics and diagnostic capabilities to be able to effectively identify and mitigate any outbreak regardless of origin—intentional, accidental, or natural. Homeland Security Presidential Directive 10 (HSPD-10): Biodefense for the 21st Century tasks the DHS to biennially assess biological threats to the United States to help guide biodefense research and medical countermeasure development against those priority biological threats. The first Bioterrorism Risk Assessment (BTRA) was completed in 2006 and a revised assessment was produced in 2008. The first BTRA used computer-based tools to assess the risk of twenty-seven natural pathogens and one engineered pathogen. The pathogens were ranked according to “subjective event probabilities” (e.g. indoor or outdoor aerosol) and the resulting consequences. Thirteen priority threats were identified from the 2006 risk assessment. These priority threats undergo material threat determinations (MTD) “with inputs from the intelligence, law enforcement, scientific and public health communities,” and population threat assessments (PTA), which estimates the exposed population to gauge the affected population and infrastructure in a

60. NATIONAL RESEARCH COUNCIL, supra note 55, at 25.
64. Id.
The results of the MTDs and PTAs are shared with the HHS Office of the Assistant Secretary of Preparedness and Response (ASPR), who conducts consequence modeling of the material threats and evaluates whether vaccines, therapeutics, or effective diagnostics exist for priority threats. These determinations will guide basic research and development of medical countermeasures that do not exist for priority threats as well as funding for procuring existing safe and efficacious medical countermeasures for use in an emergency.

IV. MEDICAL COUNTERMEASURE DEVELOPMENT

The 2001 anthrax event, SARS outbreak, and West Nile outbreak demonstrated the need for increased research on biological agents involved in an intentional or natural outbreak, and development of effective medical interventions for those agents. One critical component to bioterrorism preparedness is development and procurement of vaccines, therapeutics, and diagnostic tests (collectively termed “medical countermeasures”). Research and development (R&D) of vaccines and therapeutics is complex. The average total cost of developing a medical intervention from concept to Food and Drug Administration (FDA) approval is approximately $800 million to $1 billion per product and takes ten to fifteen years to get through clinical trials, advanced development, and FDA approval. In order to get one successful product through the R&D pipeline, hundreds to thousands of vaccine or drug candidates are tested in cell culture, small animal models, and large animal models using various routes of delivery to get optimal safety and efficacy results. Much of this basic research is covered by profits (in the case of private industry) or funding from the federal government or foundations. Generally, a few promising vaccine or drug candidates emerge from the basic research and enter pre-clinical and clinical trials where safety and efficacy of the products in humans is determined. While early stages of pre-clinical development can be done using NIH funds and in an academic setting, the majority of research in this phase of R&D is done in collaboration with pharmaceutical companies. Pharmaceutical companies have the means to manufacture vaccines and drugs for human consumption on a large scale and under good laboratory and manufacturing practices, to perform large-scale clinical trials, and to absorb the costs associated with registering the product with the FDA (i.e. registering the drug as pre-investigational new drug and investigational new drug) and with subsequent FDA approval. Clinical trials assessing safety are typically done by observing the effects of the candidate product in healthy human populations as compared to a placebo and an existing product for the same indication (if

66. Id.

one is available) in a controlled setting. Trials assessing efficacy are generally done in a population enriched for the target disease (e.g., testing an HIV vaccine candidate in a population highly susceptible to HIV infection, like injection-drug users) and alongside groups receiving placebo or existing product (if available) using a controlled protocol. All research requires approval by the Institutional Biosafety Committee, all animal research requires approval by the Institutional Animal Care and Use Committee, and all clinical trials require institutional review body approval and consent by trial participants. All of these levels of research are overseen by internal mechanisms, the FDA, NIH, USDA, and potentially the CDC. As mentioned in the section on High-Containment Laboratories, other federal and state agencies conduct oversight of biological research.

The process just described is typical for most vaccines, therapeutics, and diagnostic tests. Medical countermeasures against select agents and biodefense priority threat agents, however, are more complex and involve more risk. Despite many of the priority threat agents being global health threats, they do not generally affect the United States or developed nations. This adds to the financial and scientific challenges associated with research and development of vaccines, drugs, or diagnostic tests against biodefense agents. The financial risk is greater with medical countermeasures against priority threat agents because there is no natural market for the vaccines, therapeutics, and diagnostic tests beyond the U.S. federal government.68 Although attempts have been made to engage the international community to sign contracts to procure the medical countermeasures for their own countries, very few nations have invested in stockpiling medical countermeasures.69 The financial risk exacerbates the scientific challenges of developing medical countermeasures against biodefense agents. The issue of safety and security of select agent research is a critical challenge, especially in today’s political climate. With increased funding for research and countermeasure development against select agents comes an increased safety need, which includes building high-containment laboratories to protect laboratory workers and the environment from accidental exposure to the agents researched in those labs.70 Another major issue is that of testing the efficacy of promising candidate vaccines, drugs, and diagnostic tests to prevent or control infection with a priority threat agent. These studies typically involve multiple testing sites enrolling several hundred to thousands of human subjects suffering from the target indication in a placebo-controlled clinical trial. Natural outbreaks of many of the priority threat agents are so small and potentially unpredictable that planning for a well-con-

70. See Section V on High-Containment Laboratories for a more detailed discussion.
trolled study using natural infection is extremely difficult. Since testing the efficacy of a candidate product by challenging human subjects with the threat agent is wholly unethical, the use of animal models is critical for advanced development of these vaccines and therapeutics.71

Developing animal models that mimic human infection is scientifically difficult and costly. The regulatory framework and standards for developing these models and subsequent testing of the candidate countermeasures is relatively unfamiliar and evolving as our medical countermeasure needs evolve. The DoD has tasked the National Academy of Sciences to review animal models for testing medical countermeasures against biological threat agents. Developing diagnostic tests poses distinct challenges to vaccines and drugs as their efficacy evaluations depend on having appropriate samples to identify appropriate test materials and minimize non-specific reactions to those materials while enhancing specific reactions against the biological agent. It is not clear that there have been advances in understanding or developing the appropriate samples to evaluate diagnostic tests against priority threat agents.

In September 2003, NIAID awarded eight universities to head RCEs to support investigator-driven biodefense research with an emphasis on development of vaccines, therapeutics, and diagnostics;72 as of 2009, NIAID supports ten RCEs. These RCEs in combination with individual investigators directly funded by NIAID and small biotechnology firms conduct the basic research needed to understand the infectivity and pathogenicity of infectious agents and develop medical countermeasures against them. Project BioShield, enacted in 2004, established a special reserve fund for procurement of medical countermeasures against U.S. priority threat agents.73 In order to be procured, these vaccines, therapeutics, and diagnostics would have to be within eight years of FDA approval.74 Project BioShield also established the emergency use authorization so a procured vaccine or therapeutic whose FDA approval is pending can be used during an emergency.75 Procured medical countermeasures are stored in the Strategic National Stockpile. Lawmakers intended for the BioShield program to provide an end market for safe and effective medical countermeasures against biological agents rarely found in the United States. Large pharmaceutical and biotechnology companies were not interested in participating in the BioShield program because the biodefense industry was not profitable enough and the cost of

74. Matheny et al., supra note 66, at 232.
redirecting existing manufacturing facilities or building new facilities to accommodate the biodefense countermeasure was not cost effective for large pharmaceutical or biotechnology companies. This left small companies with little available capital to absorb the cost of R&D of candidate countermeasures and whose sole or main product was the BioShield-contracted product. To help companies transition between the basic research phase and procurement phase of medical countermeasure development, the Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA)\textsuperscript{76} established the Biomedical Advanced Research and Development Authority (BARDA)\textsuperscript{77} to fund advanced development (including efficacy testing in animal models) of promising candidate products before BioShield funds are provided for procurement. Though BARDA has been able to fund some advanced development, the program has not been appropriated more than one-tenth the authorized amount (authorized at $1.07 billion) per year in fiscal years (FY) 2007 and 2008, limiting the program’s effectiveness.\textsuperscript{78} In FY2009, BARDA received $275 million from the Strategic National Stockpile.\textsuperscript{79} The PAHPA also added milestone payments to companies developing medical countermeasures against priority threat agents to help smaller companies recoup some of their R&D costs before the final procurement and payment. The PAHPA also created the National Biodefense Science Board (NBSB)\textsuperscript{80} to evaluate scientific incentives to help bolster development of medical countermeasures against priority threat agents.\textsuperscript{81} Examples of scientific incentives include platform technologies (a single technology that can be used to rapidly generate several distinct products) and warm-base manufacturing (continued support for a low level of product manufacturing after the initial contracted product has been delivered to the Strategic National Stockpile). In reality, the NBSB has considered public health responses and financial incentives for countermeasure development but has not evaluated the scientific incentives. In 2007, President Bush issued HSPD-18: \textit{Medical Countermeasures against Weapons of Mass Destruction}\textsuperscript{82} and HSPD 21: Public


\textsuperscript{79} Bradley T. Smith et al., \textit{Developing Medical Countermeasures for Biodefense}, 7 \textit{Biowere & Biosecurity & Bioterrorism: Biodefense Strategy, Practice, and Science} 42, 42 (2009).


\textsuperscript{81} 42 U.S.C. §§ 247d-7f–Sec 319M; 42 U.S.C. § 217a–Sec 222.

Health and Medical Preparedness, both of which support the development of the medical countermeasure enterprise.

Project BioShield has procured vaccines against anthrax and smallpox, and botulinum toxin antitoxin. In addition, there is an active contract for antivirals against smallpox. BioShield has also procured the CHEMPak, which contains anti-nerve agents, and potassium iodide. There has been significant criticism of the BioShield program, primarily due to the large amount of funds appropriated and small list of procured countermeasures. The BioShield office within the ASPR released the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) strategic plan in 2006 laying out short-, mid-, and long-term goals for medical countermeasure procurement. Although the short-term goals still conform to the “one bug/one drug” concept, the mid-term and longer-term goals include seeking broad-spectrum products, which are products that are effective against several biological agents. Following enactment of PAHPA, the BioShield office (renamed to PHEMCE office) became the BARDA office and released the BARDA strategic plan, which aimed to facilitate the goals of the HHS Pandemic Influenza Plan and the PHEMCE Strategic Plan by improving advanced development for promising medical countermeasure candidates. As mentioned above, although BARDA has been able to provide some funds, their lack of appropriations have made implementing their strategic plan difficult.

V. HIGH-CONTAINMENT LABORATORIES

The extensive increase in funding for biodefense research to study biological agents and create vaccines, therapeutics, and detection devices against those agents have resulted in more researchers working on select agents and in high-containment laboratories. High-containment laboratories, which include biosafety level 3 and 4 (BSL3 or BSL4) laboratories in

86. The “one bug/one drug” concept means one medical intervention is developed for one biological agent and sometimes only one variant of a biological agent.
87. An example of a broad-spectrum medical intervention is the antibiotic ciprofloxacin; a combination vaccine that has components of several biological agents it can elicit a protective immune response against those agents and is effective against different species of bacteria.
the United States, are designed based on guidelines developed by the CDC and NIH, the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual.89 The BMBL is a biosafety document that provides guidelines for what agents and experiments should be followed in higher containment laboratories and what types of safety training personnel working in those laboratories should receive. While the BMBL are guidelines, they have been used as contractual requirements in grants and contracts for work with agents requiring higher containment laboratories. High-containment laboratories are used to protect laboratory workers and the outside environment from accidental exposure to the pathogens studied in those laboratories; they are not a security facility as many from the traditional arms-control community consider them to be. The highest containment laboratory is BSL4, which houses the most dangerous pathogens, like Ebola virus, and where personnel wear full body suits and use an external oxygen source.90 The level below is BSL3, in which many harmful pathogens that could be aerosolized or are used in large quantities, like HIV, tuberculosis, and anthrax, are researched and require personnel to don gowns, masks, thicker and/or more gloves, foot covers, and goggles. Many of the safety features in the BMBL can serve biosecurity purposes by imposing physical protective barriers between the laboratories and the outside community, including anterooms for wearing or removing personal equipment and restricted access. Most high containment laboratories do not have armed guards but those that do are mainly protecting the facility against violent animal-rights activists.

In recent years, the number of high-containment laboratories has significantly increased.91 Following the anthrax mailings in 2001, NIAID built two national BSL4 laboratories—Galveston National Laboratory and National Emerging Infectious Diseases Laboratory—and several regional BSL3 laboratories to complement the increased biodefense funding on vaccine, therapeutics, and detection and diagnostic devices against select agents by NIAID, including the Research Centers of Excellence.92 All BSL4 laboratories are registered with the CDC and/or APHIS because they work on select agents.

---


are registered with the CDC and/or APHIS but those that do not work on select agents are not. The proliferation of high-containment laboratories, the unfounded fear that these labs provide unsupervised capability to malicious actors, and/or the WMD Commission’s report recommending that oversight should be reviewed\textsuperscript{93} have resulted in congressional hearings\textsuperscript{94} and bills\textsuperscript{95} as well as an executive order (EO 13,486)\textsuperscript{96} associated with improving oversight of high-containment laboratories.

High-containment laboratories are also essential to protecting personnel working with select agents and harmful pathogens not on the select agent list, like tuberculosis. There are very few BSL3 or BSL4 laboratories that have no oversight system in place, whether federal, state, local, or internal. Private industry largely does not have many high containment labs; there are no BSL4 labs in private industry in the United States, and the majority of laboratories in industry (BSL2 or BSL3) are regulated by the FDA for compliance with good laboratory practice and good manufacturing practice because they produce products that will eventually enter human consumption. Internal audits of research and laboratory capacity are routinely done in private industry as part of their business management practices. All materials from an abandoned research project are destroyed. Research institutions and academia not only have internal inspections but they are also inspected externally by a number of federal agencies whose missions are based in environmental safety, worker protection, and security, if applicable. Examples of external review bodies include DHS, CDC, DoD, EPA, the Department of Transportation (DoT), the Federal Aviation Administration (FAA), USDA, the Occupational Safety and Health Administration (OSHA), NIH, and state departments of health.

Public health laboratories serve a more distinct function than research oriented institutions. Nearly all public health facilities, including hospitals, have a BSL3 laboratory or cabinets to mainly prevent accidental exposure of the laboratory worker and environment from common disease-causing agents, like tuberculosis. Since hospital and public health laboratories are at the forefront of disease detection, they have to have the capabilities to handle and detect known or unknown (novel) biological agents. In general, the CDC, USDA, OSHA, National Institute for Occupational Safety and Health


\textsuperscript{95} Select Agent Program and Biosafety Improvement Act, H.R.1225, 111th Cong. (2009); Select Agent Program and Biosafety Improvement Act, S. 485, 111th Cong. (2009).

(NIOSH), and EPA oversee the public health system. Since all public health laboratories work with clinical samples, they are all certified under Clinical Laboratory Improvement Amendments (CLIA) and subjected to similar oversight as clinical research laboratories. All state public health laboratories and some local laboratories are part of the CDC’s Laboratory Response Network and are therefore overseen by the CDC. Hospital laboratories are accredited by the Joint Commission.97 Central to public health preparedness and response are oversight of ready laboratories and personnel to initially diagnose, identify, and research the disease-causing agent, and if little or no medical interventions exist, develop vaccines and therapeutics against the disease-causing agent.

VI. MICROBIAL FORENSICS

Attribution of a biological attack is very difficult to assess, as the 2001 anthrax attacks and accusation of Bruce Ivins demonstrate. While DNA forensics has become well-established in the U.S. court system, many techniques used to identify pathogens and their strains have not been. The field of microbial forensics has blossomed since 2001. The anthrax attacks highlighted the differences between the public health community and law enforcement community on sample collection and investigations (i.e. evaluation of exposed or infected individuals for medical and public health purposes versus conducting a criminal investigation).98 Following the anthrax attacks, the FBI contacted well-known anthrax biologists to act as subject-matter experts to help develop techniques to identify signatures in the anthrax spores and/or evaluate the scientific data generated by these techniques.99 The technologies used were cutting edge and developed as the investigation evolved. However, the FBI interrogated these same scientists as suspects, which has resulted in a very distrustful relationship between the law enforcement and scientific communities.100

The public health community needs to be able to identify the infectious agent to properly provide the appropriate therapeutics to the infected individual(s) and conduct epidemiologic studies to determine who was exposed

---

and what public health actions should be taken.\textsuperscript{101} Law enforcement has different requirements. Law enforcement personnel need to be able to collect samples and victim accounts that will hold up in a court of law and conduct analyses to accurately determine the perpetrator. Since 2001, the CDC and FBI as well as some state departments of public health and law enforcement have developed plans for collecting and handling samples as well as questioning victims.\textsuperscript{102} DHS has established the National Bioforensic Analysis Center to conduct forensics analyses to identify the agent and perpetrator of a biocrime or bioterrorist attack.\textsuperscript{103} Recently, the intelligence community has been developing plans for microbial forensics, and the National Research Council released the report *Strengthening Forensic Science in the United States: A Path Forward*, which addresses the science of forensics in homeland security.\textsuperscript{104}

VII. **DECONTAMINATION**

The question of “how clean is clean” stems from the public’s need for no risk and the reality that no biological agent can be completely destroyed. Following the contamination of the Senate Hart Building, the EPA was called in to clean up the building and Senate staff wanted to know when it was safe to return to the building.\textsuperscript{105} Anthrax spores are hardy and common procedures like bleach treatment or heat will not destroy them, but as the decontamination efforts of the Senate Hart Office Building demonstrated, chlorine dioxide gas can be used as a decontamination agent against anthrax. There is a risk that the spore could germinate and grow to dangerous levels. There are now documented actions for decontaminating infrastructure if contaminated with the United States’ highest priority threat agents. Only recently has the issue of decontamination and how infrastructure, goods, and people can safely and effectively be decontaminated been considered.


\textsuperscript{104} *National Research Council of the National Academies, Strengthening Forensic Science in the United States: A Path Forward* (2009).

VIII. SCIENTIFIC RESPONSIBILITY IN INTERNATIONAL SECURITY

This paper has presented the many areas in which science plays a role in bioterrorism preparedness and response. Scientists may be asked to help in identifying infectious agents, developing medical countermeasures, or attributing a bioterrorism incident to a suspect. Modern history has demonstrated that scientists have acted responsibly and stepped up to the challenges they face. This section briefly documents major actions by scientists in international security and biosafety.

Scientists have played a critical role in national security since the days of the Manhattan Project and atomic bomb. In 1939, Leo Szilard, a Hungarian-American physicist, convinced Albert Einstein to sign a letter describing advancement in nuclear physics—in particular, their military application—to President Roosevelt. This effectively started the Manhattan Project. The fear that Nazi Germany was developing their own nuclear bombs drove scientists to support the United States developing equal arsenal to counteract Germany's potential capability. Following the defeat of Germany, many of the same scientists working on the atomic bomb signed a petition, authored by Szilard, stating that the threat of nuclear bombs no longer existed and that unless absolutely necessary, nuclear bombs should not be used against Japan. Following the end of World War II, physicists were intimately involved in reviewing the societal consequences of nuclear weapons and shaping nuclear weapons policy. Notable activities in which scientists played a major role include establishment of the Pugwash Conferences and the Bulletin of the Atomic Scientists, the Treaty on the Non-proliferation of Nuclear Weapons, and a series of test ban treaties, the latest being the Comprehensive Test Ban Treaty. At international conferences, American and Soviet physicists engaged in scientific discussions that contributed to the disclosure or perception of United States and Soviet nuclear capabilities. These revelations, then, informed U.S. and Soviet leadership about nuclear weapons advancements and fueled the policies of deterrence. Throughout this Cold War period, groups like the JASON Defense Advisory Group (an independent group of accomplished scientists)

and the National Academy of Sciences Committee on International Security and Arms Control addressed key science and security issues and were vehicles for policy development or international engagement.

While much of the Cold War era was spent deterring the nuclear arms race, the threat of chemical and biological weapons (CBW) was present. However, scientists seemed to have been less engaged in policy discussions regarding CBW than their physicist counterparts. While the major world powers had active CBW programs following World War II, the urgency with which to consider the societal implications of this research (as was the case with the atomic bomb) may not have existed, since the use of CBW was banned by the 1925 Geneva Protocol. In 1969, President Nixon ended the U.S. bioweapons program and initiated international discussions on a treaty banning the development and stockpiling in types and quantities of biological substances intended to do harm; the Biological Weapons Convention (BWC) was signed in 1972. The two notable biologists who were very active in policy discussions regarding biological weapons were Joshua Lederberg and Matthew Meselson. After the fall of the Soviet Union and revelation of an enormous and covert Soviet bioweapons research complex, the international community, with input from the academic scientific community (not the biotechnology or pharmaceutical industry), began negotiating a verification protocol for the BWC. In 1993, the Chemical Weapons Convention was successfully negotiated and contained within it a verification protocol. The chemical industry was integral to the success of the CWC negotiations and scientists rallied to persuade the United States ratify the treaty before it went into force in 1997. This offered hope to those seeking a verification protocol for the BWC, but after seven years of negotiation, the protocol failed.

Although not directly related to biological weapons, the U.S. scientific community called for a moratorium in the 1970s on the newly emerging

---

recombinant DNA (rDNA) technology until its risks (including its potential to be misused for malicious purposes) could be assessed and guidelines were formed regarding its safe use. Preeminent American scientists, government officials and journalists discussed the risks and potential guidelines at the 1975 Asilomar Conference. Institutional Biosafety Committees (IBC) were created as a result of these discussions to oversee rDNA research. Since the 2001 terrorist attacks, the biosecurity community has become increasingly concerned about the misuse of legitimate research by individuals with malicious intent. Throughout the world, scientists have been involved in policy discussions about oversight and education of dual-use research; the U.S. government has created the NSABB to provide recommendations to the U.S. government on oversight and education of dual-use research. Current recommendations include biosecurity review by the IBC and biosafety officers, as well as vetting laboratory personnel seeking to work in high-containment labs. Most recently, biosafety and biosecurity have been used interchangeably; there are ongoing biosecurity policy discussions about oversight of high-containment laboratories and biosafety training.

IX. Conclusion

The discovery of the extensive Soviet bioweapons program, the unsuccessful Aum Shinrikyo bioweapons program, acquisition of dangerous biological agents by a member of the Aryan Nations, the events of September and October 2001, the West Nile outbreak, and the SARS outbreak have contributed to the current state of preparedness and response to biological threats—whether natural, accidental, or intentional. Unlike other forms of weapons of mass destruction, biological agents are readily found in nature and nearly all cause natural disease outbreaks throughout the world. Policies to prevent a bioterrorist incident may impair scientists’ ability to respond to the incident. Science plays a major role in preventing and mitigating a bioterrorist attack. A careful analysis of the impact of the United States’ security policies on national security and scientific advancement and public health, as well as fostering a trusting relationship between the security and scientific communities, are sorely needed to effectively prepare for the next biological incident.