Biosecurity: Progress and Challenges

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Bioscience facilities are essential to the efforts to combat both naturally occurring infectious diseases and bioterrorism. But both the general public and policy makers are questioning how bioscience institutions address the safety and security risks of handling infectious disease causing organisms. As a result, new regulations at the national level in many countries and international initiatives from the United Nations, World Health Organization, and others are having direct consequences for the operation of bioscience. In particular, laboratory biosecurity is a relatively new and evolving paradigm for bioscience facilities, which have an obligation to ensure their facilities operate safely and securely. However, although progress has been made in these areas, numerous challenges remain throughout the world, and much work remains. It is the responsibility of both the scientific community and policy makers to work collaboratively to ensure responsible use of pathogens and toxins, equipment, and expertise. (JALA 2009;14:141–7)

Introduction

Bioscience facilities face increased responsibilities for managing the risks associated with pathogens and toxins. These biorisks comprise both biosafety (accidental) and biosecurity (deliberate) risks. Recent high-profile biosafety breaches include the laboratory-acquired infections of Severe Acute Respiratory Syndrome (SARS)[1] and the foot-and-mouth disease outbreak in the United Kingdom.[2] The anthrax attacks of 2001 are the most well-known example of a breach in laboratory biosecurity; in that case, authorities believe that the perpetrator of the attack stole the anthrax bacteria from the U.S. government laboratory where he worked as a leading scientist.[3] These examples explain why policy makers and the public are increasingly scrutinizing how bioscience laboratories manage the safety and security of their operations.

According to the World Health Organization (WHO), laboratory biosafety is the term used to describe the containment principles, technologies, and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release, and laboratory biosecurity is the institutional and personal security measures designed to prevent the loss, theft, misuse, diversion, or intentional release of pathogens and toxins.[4] Laboratory biosecurity is more than simply physical security; it also includes personnel management, material control and accountability, information security, transport security, and program management.[5] A failure in either laboratory biosafety or biosecurity may affect the staff, community, and environment, and may jeopardize the institution's operations.

Although bioscience facilities that use pathogens and toxins must devote the necessary attention to managing laboratory biorisks, biosafety and biosecurity must be instituted in a balanced manner that preserves and supports an environment for legitimate and lifesaving microbiological research, diagnosis, and disease control activities. Pathogens and

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toxins are required in an array of activities, such as basic and applied research, education, quality control, pharmaceutical research and development, manufacturing, and food production. This paper aims to give readers an overview of the evolving norms for biosafety, and, especially, the dynamic field of biosecurity. The overview provides a foundation for an examination of significant biosecurity challenges that policy makers and bioscience institutions face in the coming years and demonstrates the need for partnerships between the technical and policy communities to address these challenges.

Although only in its infancy, biosecurity is already expanding beyond the control of pathogens and toxins to also address legitimate equipment and expertise that could be misused to construct a biological weapon or to conduct bioterrorism. Controlling "dual-use" equipment and knowledge in a manner that does not unduly jeopardize the science is extremely difficult, because user intent is often the only distinguishing factor between illegitimate and legitimate applications. Unfortunately, this is not simply an academic concern; although biological weapons are banned by international law, there is a long history of interest in and development of biological weapons by both state and nonstate actors.

Current biosecurity situation in the United States and internationally

Laboratory biosafety and biosecurity are now fundamental components of bioscience laboratory operations. They are based on many common principles, but biosafety is the more well-established discipline. Figure 1 shows examples of good biosafety. The first WHO *Laboratory Biosafety Manual* was published in 1983, but the initial WHO guidance on laboratory biosecurity was only released in 2006.[6] Likewise, *Biosafety in Microbiological and Biomedical Laboratories*,[7] the seminal biosafety guidance in the United States, was first issued in 1984, but only the fifth edition in 2007 included a section on the principles of biosecurity.

Another key difference in the United States and elsewhere is that biosecurity currently tends to be implemented through regulatory requirements, while the implementation of biosafety is primarily driven by worker safety, best practices, and guidance. For example, over the last decade, the U.S. government enacted extensive biosecurity legislation,[8] including criminal and civil penalties, giving the U.S. Department of Health and Human Services and the U.S. Department of Agriculture regulatory authority to establish controls on the possession, use, and transfer of select biological agents ("select agents"), and all U.S. bioscience institutions that possess those agents must be in compliance. Other U.S. federal agencies have their own regulations for the distribution of infectious materials, including the export control regulations of the Department of Commerce[9] and the Department of State.[10]

Not many countries have implemented biosecurity regulations yet, but those that have typically take a similar approach,[11] with regulatory requirements for security based on schedules of pathogens and toxins. For example, Singapore,[12] Japan,[13] South Korea,[14] and Denmark[15] have all recently implemented biosecurity legislation, with specific lists of pathogens and toxins subject to controls. These exemplar national laws and regulations are important steps in securing dangerous pathogens and toxins worldwide, but they are only first steps. Many countries have yet to adopt laws specific to laboratory biosafety or biosecurity. Furthermore, some of the countries that have developed biosecurity regulations to date focus only on pathogens and toxins that impact human health, neglecting those that can impact animal and plant health (e.g., Japan and Demark). Agricultural facilities also regularly handle zoonotic pathogens and toxins. It is crucial that any biosecurity regulatory framework be extended to all institutions with materials of concern, including those in the health, agricultural, academic, and private sectors.

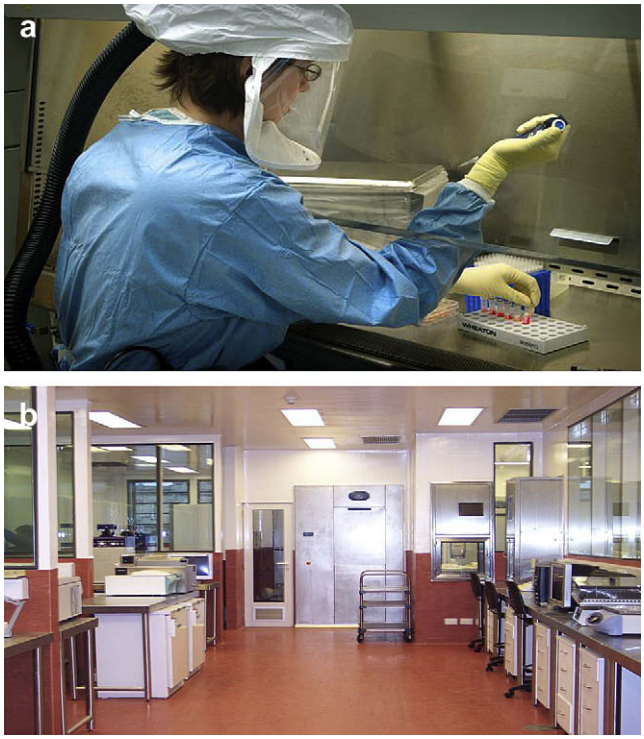

Figure 1. Many new domestic and international biosafety and biosecurity regulations, guidelines, initiatives, and legislation have successfully helped to mitigate the risks associated with pathogen research conducted in bioscience facilities around the world. 1a. A US Center for Disease Control's (CDC) researcher is following good laboratory practices pipetting specimens in a biosafety cabinet of a Biosafety Level 3-enhanced laboratory in Atlanta, GA. 1b. A well-designed Argentinean laboratory was constructed in 2008 using technical guidance provided by the US Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual, WHO Laboratory Biosecurity Guidance Manual, and the WHO Laboratory Biosafety Manual, among others.

Although national regulations are critical to enhancing biosecurity, the bioscience community needs to adjust to

this security paradigm because regulations impact day-to-day laboratory operations. Once regulations are enacted, laboratories typically must receive government approval to possess the listed pathogens and toxins, and to ship specimens to collaborating institutions. Laboratories will need to comply with specific detailed requirements for record keeping and may be subject to inspections. The bioscience community has not previously faced government oversight that limits where work is conducted or who does the work.

Recent international biosecurity initiatives

Realization of the threat of bioterrorism and biocrime has prompted many international and national initiatives on laboratory biosafety and biosecurity beyond regulations. International agreements, including the Biological and Toxins Weapons Convention[16] (BWC) and United Nations Security Council Resolution 1540 (UNSCR 1540), compel countries to strengthen their implementation of biosecurity. Since the 2003 Experts Group Meeting of the BWC, much attention has been devoted by the international community to raising awareness about the importance of laboratory biosecurity for bioscience laboratories.

On 28 April 2004, the United Nations Security Council unanimously passed UNSCR 1540, which established, for the first time, binding obligations on all UN member states under Chapter VII of the UN Charter, to take and enforce effective measures against the proliferation of weapons of mass destruction, their means of delivery, and related materials. One way that countries can demonstrate their compliance with UNSCR 1540 is through the implementation of laboratory biosecurity measures that secure biological weapons source materials in bioscience facilities. In fact, UNSCR 1540 specifically calls on countries to secure biological materials in production, use, storage, and transport, and implement physical protection measures, border controls, other law enforcement efforts, and end-user controls.

The passage of the World Health Assembly Resolution 58.29 in 2005 is another landmark measure that recognizes the importance of laboratory biosafety and biosecurity. This resolution specifically urged member states of the WHO to implement an integrated approach to laboratory biosafety, including containment of microbiological agents and toxins. Member states were advised to review protocols for ensuring the safe handling of harmful biological agents. States were also instructed to establish biosafety practices in accordance with WHO guidance. Mobilization of national and financial resources sufficient to accomplish these goals, as well as the requisite international support and cooperation, were also recognized as important components. The WHO has also developed a number of benchmark documents, including the third edition of the *Laboratory Biosafety Manual* in 2004.[14] This document serves as a global resource that offers practical guidance on biosafety for all types of laboratories and biosafety levels; the third edition includes a chapter that introduced, for the first time, laboratory biosecurity. Other influential WHO documents include *Biorisk management: Laboratory Biosecurity Guidance*,[17] which promotes the protection and control of laboratory biological materials to prevent intentional misuse, and the *Guidance on Regulations for the Transport of Infectious Substances*.[18]

In 2007, the Organization for Economic Cooperation and Development (OECD) published the *OECD Best Practice Guidelines for Biological Resource Centers*.[19] This comprehensive report describes a rationale for establishing a global network for biological resource centers (BRCs), and contains four sets of best practice guidelines, including the *Best Practice Guidelines on Biosecurity for BRCs*. Other organizations, such as the World Organization for Animal Health, have also recently published guidelines that endorse good biosafety and biosecurity practices in laboratory environments. Three of the most important include *The Terrestrial Animal Health Code (2007)*, *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (2004)*, and *Quality Standard and Guidelines for Veterinary Laboratories: infectious diseases (2008)*.[20] All of these publications are available online, and have been translated into multiple languages.

These international initiatives are designed to strengthen the implementation of biosafety and biosecurity at the laboratory level. In particular, UNSCR 1540 should compel more countries to enact national legislation that addresses biosecurity. And the guidance from WHO and other international organizations should help establish a new international norm, setting the expectation that laboratories will implement needed changes to ensure that pathogens and toxins are handled safely and securely.

Looking ahead: biosecurity challenges

Despite these international initiatives and national regulations, biosafety and biosecurity problems continue to arise (e.g., Fig. 2), perhaps indicating the need for stronger partnerships between the scientific and policy communities to help create a culture of safety and security in the bioscience community. For example, the laboratory-acquired infections of SARS in 2003 occurred in biosafety level 3 (BSL3) and BSL4 (maximum containment) laboratories. A WHO investigation attributed these infections to negligent program management (e.g., poor laboratory practices, insufficient training). Similarly, even the most sophisticated security systems can be circumvented if the people with access to dangerous pathogens are not trustworthy, reliable, and trained to abide by the security protocols. In 2007, the Associated Press noted that there had been more than 100 biosafety and biosecurity incidents at laboratories in the United States since 2003.[21] For example, Texas A&M University received a $1 million USD fine, and had to suspend all of its select agent research because of failures to properly and accurately report incidents.[22] Pirbright Laboratory in the United Kingdom inadvertently released foot-and-mouth disease virus into the community through a leak in its effluent pipes, which were known to need maintenance.[2]

Figure 2. Although substantial progress has been made in generating biosafety and biosecurity awareness, numerous challenges remain throughout the world, and much work remains, in both developed and developing regions. It is not uncommon to identify numerous biosafety and biosecurity violations in the daily operation of both US and international bioscience facilities, such as the easy identification and accessibility of dangerous pathogens (Figure 2a and 2b), the lack of appropriate physical security to protect pathogens from theft (2c), and substandard laboratory equipment (2d).

As a result of these and other incidents, public and political concerns about the safety and security of high-containment bioscience facilities have intensified in recent years. For example, the Oversight and Investigations Subcommittee of the U.S. House of Representatives Committee on Energy and Commerce held hearings in October 2007 and May 2008 "to examine the risks associated with the recent proliferation of high-containment biological research laboratories."[23] And, in December 2008, the Congressionally mandated Commission on the Prevention of Weapons of Mass Destruction (WMD) report, *World at Risk*,[24] recommended that the United States "conduct a comprehensive review of the domestic program to secure dangerous pathogens, …tighten government oversight of high-containment laboratories, and promote a culture of security awareness in the life sciences community." This increased attention places bioscience facilities in the proverbial fishbowl as everyone watches how the facilities address current and emerging biosecurity challenges.

Changes in three main areas, in particular, are likely to have major repercussions on the future operations of bioscience facilities: ensuring that the increasing number of individuals who work in bioscience laboratories are adequately screened, qualified, and trained; ensuring that rigorous biorisk management programs are implemented at bioscience facilities across the globe; and understanding and managing the rapid advances in bioscience to ensure adequate control of dual-use pathogens, equipment, and expertise. The following section will explore these three areas in additional detail.

The people who work with the pathogens and toxins are the most important aspect of the laboratory biosafety and biosecurity systems; the best engineered controls only work if people use the equipment correctly.[25] For example, a biosafety cabinet provides little to no protection to a user who does not follow the proper procedures, and electronic card key access controls do not prevent someone from opening the door for an individual who does not have approved access. Because individuals are the linchpin for controlling biorisks in facilities, ensuring that individuals are properly qualified, screened, and trained to have access to pathogens or toxins is the most important task facing managers of bioscience facilities. There are many factors to consider before qualifying such individuals, such as their technical qualifications, technical experience, medical clearance, mental health, and training.

From a biosecurity perspective, mechanisms must be in place to provide some level of assurance that individuals are trustworthy. As more individuals work in the biosciences, the odds of a biologist becoming a terrorist or an individual intent on causing harm increase.[26] When the Federal Bureau of Investigations (FBI) publicly identified a scientist at the U.S. Army Medical Research Institute of Infectious Diseases as the perpetrator of the anthrax letters, Congress

immediately began to question whether the current screening process for granting individuals access to select agents is sufficient.[27] There will undoubtedly be more attention devoted to the issue of personnel reliability for individuals who work in containment laboratories or otherwise have access to pathogens and toxins. Trustworthy persons are also fundamental to the integrity of the scientific process. Recent high-profile cases of scientific fraud,[28] such as the discredited papers on embryonic stem cell lines by Woo Suk Hwang, highlight another reason that institutions should have mechanisms in place to provide some degree of confidence in the personal integrity of their employees.

Managing personnel is only one aspect of bioscience laboratory management. Ultimately, if an incident where a pathogen or toxin accidentally escapes from a facility or is misused and can be traced back to a specific institution with reasonable certainty, that institution could be liable if it has not implemented best practices in biosafety or biosecurity. How does an institution demonstrate that it is implementing best practices? To address this question, several efforts are underway to create professionally developed standards for managing laboratory biorisks. Laboratories could voluntarily seek accreditation to these standards to demonstrate that they are implementing best practices. In 2007, a collaborative effort by biosafety and biosecurity professionals used the European Committee for Standardization (CEN) process to develop the Laboratory Biorisk Management Standard.[29] The American Biological Safety Association has also proposed to develop an independent laboratory accreditation program based on the CEN standard and the U.S. biosafety guidelines.[30] Accreditation initiatives such as these may also eventually provide a framework for better biorisk management, which will help maintain citizens and investors confidence in the bioscience facilities that are critical in the continued work with infectious diseases.

Recognizing the need for improving laboratory biorisk management, the American Society for Microbiology (ASM) made a series of recommendations to improve biosafety training, oversight, resources, reporting, and biosecurity in their recent testimony to the U.S. House of Representatives Energy and Commerce Committee Subcommittee on Oversight and Investigations.[31] ASM specifically called for mandatory, periodic training through formal training programs for all personnel who work in containment laboratories. ASM also urged for the creation of a harmonized system of oversight for all pathogens in the United States. Furthermore, the U.S. Government recently established a Trans-Federal Task Force on Optimizing Biosafety Oversight, which is tasked with analyzing the current U.S. system for biosafety oversight and developing options to address any identified gaps.[32] The Task Force is just beginning their analysis, but, similar to the *World at Risk* report, the Task Force study will likely highlight the lack of a single regulatory authority for biocontainment laboratories in the United States, and the lack of clear implementation standards for biosafety and biosecurity.

Although there are a variety of studies underway that examine how oversight of high-containment bioscience laboratories should be improved, the experts overwhelmingly agree that existing biosafety and biosecurity training programs need to be expanded, and new programs need to be developed. The current training programs do not have the capacity to train workers for all of the existing facilities, and, yet, the growing numbers of these facilities will require increasing numbers of workers.[33] New training programs intended to help fill these gaps include the National Biosafety and Biocontainment Training Program,[34] Emory University's Science and Safety Training,[35] Sandia National Laboratories' Controlling Laboratory Biorisks Training Course,[36] and the Canadian Science Center's International High Containment Biosafety Workshop.[37]

However, even if managers of bioscience facilities ensure that their staff who have access to pathogens and toxins are appropriately qualified, screened, and trained, and also implement robust biorisks management programs for laboratory biosafety and biosecurity, steady advances in biotechnology pose clear challenges to the notion of laboratory biosecurity. Practicing the current state of the art, leading laboratories can create organisms through de novo synthesis, and modify the pathogenic properties of wild-type strains through site-directed mutagenesis, directed evolution, and other techniques.[38] Already some experts are concerned about terrorists creating pathogens that are not found in nature.[39] Perhaps, as the technology advances, it may eventually become easier for a terrorist to synthesize a pathogen than to steal it from a laboratory. The Industry Association of Synthetic Biology recently announced that its members would review DNA orders for dangerous sequences,[40] but standards for determining how to review sequences and databases of sequences of concern have not yet been created. In 2004, the U.S. National Academies of Science published *Biotechnology in an Age of Terrorism*, which examines biological research in light of U.S. national security concerns.[41] The publication, also known as the *Fink Report*, noted that those with malicious intent could misuse the tools and intellectual advances produced by the growing global bioscience industry. One outcome of this report was the creation of the U.S. National Science Advisory Board on Biosecurity[42] to support the development of oversight mechanisms and increase awareness and collaboration in an effort to minimize the risks and harm that could result from malevolent use of legitimate research.

Conclusions

In essence, laboratory biosecurity (pathogen control) is now a subset within the larger emerging field of biosecurity. To implement biosecurity broadly defined in an effective, sustainable manner will require policy makers and bioscience institutions to work in partnership to develop solutions to the challenges that emerge in parallel with the growth and advances in bioscience. Already, it is difficult to define or measure the advancement of laboratory biosafety and biosecurity. Although there has clearly been a significant increase

in the number of leading publications and national legislation to address biosecurity in the last 5 years, there have been no studies demonstrating that these efforts have led to direct improvements in laboratory biosafety and biosecurity at bioscience facilities. Furthermore, there is very little information available in the open-source literature that reports the number of biosafety accidents or biosecurity breaches worldwide. Better data on laboratory biosafety and biosecurity incidents and "near misses" would help policy makers assess and ultimately improve their ability to address these risks.

The concept of laboratory biosafety and biosecurity internationally is still in its infancy, and the international community faces many challenges in achieving comprehensive implementation in a manner that does not unduly constrain the bioscience efforts that are critical to advancing public and agricultural health. Do resources for strengthening biosafety and biosecurity come at the expense of research resources? Do more rigorous requirements for training and background screening make it more difficult for laboratories to attract the best technical personnel? How will any biosecurity regulatory regime keep pace with the rapid advance of bioscience? Although stricter regulations have been enacted by some countries, the absence of global norms constitutes a vital security risk, because those with malicious intent can simply seek out the weakest control points globally in their search for materials, equipment, and expertise. Developing effective global norms will require both bottom-up efforts at individual laboratories and top-down national and international efforts. Even UNSCR 1540, which requires countries to enact national biosecurity legislation, has had only limited success in facilitating the establishment of these global norms. As of November 2008, 159 countries had submitted a report on the status of their national legal infrastructure concerning WMD-related materials. Yet far fewer, if any, are in compliance with all of the components of UNSCR 1540. Commonly cited reasons for noncompliance are the "insufficient understanding of their obligations," and the lack of capacity to fulfill the requirements. These excuses for poor compliance with UNSCR 1540 could be addressed at least in part if countries' policy makers relied on the technical expertise inherent in their bioscience technical communities.

Better partnerships between the policy and technical communities are needed to develop effective strategies for addressing current and emerging concerns. Policy makers play a vital role in this by setting norms, which create a minimum standard for bioscience institutions, and allocating research priorities and resources. Bioscience institutions need to help policy makers understand the operational and technical realities to ensure that policy mandates address the realities of the laboratory. And this need for laboratory scientists, technicians, and other technical experts to convey the capabilities and limitations of biological science and related technologies to policy makers will become ever more critical as the science and its applications advance and expand. Although countries adopt biosecurity regulations primarily because of concerns about bioterrorism, and to meet international obligations, such as the BWC and UNSCR 1540, bioscience facilities have additional motives for enhancing the management of laboratory biorisks. In today's world, bioscience research requires the support of the public, so bioscience laboratories must do what they can to establish and maintain public confidence in their work. Even in the absence of concrete direction from policy makers, bioscience facilities can individually take steps to be open, transparent, and implement best practices for work with pathogens and toxins, dual-use equipment, and expertise, demonstrating good corporate citizenship to the community.

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