COMMENTARY

BIOCONTAINMENT LABORATORIES: A CRITICAL COMPONENT OF THE US BIOECONOMY IN NEED OF ATTENTION

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A UNIQUE AND CRITICAL COMPONENT of the national bioeconomy is that which deals with biodefense and the risk to national health and security arising from especially dangerous emerging infectious diseases caused by pathogens such as Ebola virus and antibiotic resistant microbes. An essential element in the critical national infrastructure required to safely and securely address these dangerous threats is the existing national network of academic biocontainment laboratories developed by NIH in cooperation with states and constructed over a decade ago.¹ The value of these labs to medical research is well established; however, there is concern about the sustainability of the network as facilities age and cost of operations continues to rise.

ESPECIALLY DANGEROUS PATHOGENS

In the United States, dangerous pathogens are grouped by the severity of the diseases they cause, their ease of transmission, and the availability of vaccines to prevent infection and therapeutics to treat those who become infected. Pathogens are classified as biological safety level (BSL) risk groups 2, 3, or 4, with BSL-4 reserved for the most dangerous pathogens for which no effective treatment or vaccines are available. BSL-4 laboratories are specially constructed to protect the welfare of the workforce in-

involved in research and development, and to ensure the safety and security of the surrounding community and environment against possible release due to a breach in containment. BSL-3 laboratories have only slightly less rigorous infrastructure requirements and handle pathogens such as plague and anthrax, among many others.

The safety and security of the entire dangerous pathogen research and development enterprise is overseen by the US Centers for Disease Control and Prevention (CDC), Division of Select Agent and Toxins, under the Federal Select Agent Program (FSAP), mandated by federal law. Those pathogens that are of agricultural importance are managed by the Department of Agriculture (USDA) Animal and Plant Health Inspection Service, Agriculture Select Agent Services, and microbes that may cause disease in both humans and animals are jointly managed by both CDC and the USDA.²

CRITICAL NATIONAL INFRASTRUCTURE

The critical national infrastructure established to support research on especially dangerous pathogens currently includes 9 BSL-4 biocontainment laboratories in the United States, with others now under construction. Historically, the few biocontainment laboratories in operation were located only in the federal sector; however, following the

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9/11 attacks and the anthrax mailings, the National Institutes of Health (NIH), working in partnership with states, invested approximately \$1 billion for the construction of 12 regional BSL-3 biocontainment laboratories and 2 national maximum containment facilities (BSL-4) on academic campuses across the nation (Figure 1). The goal was to harness the strengths of the academic sector for basic and applied research by providing selected academic centers with the critical infrastructure required to safely and securely investigate the most dangerous pathogens.

In addition to the network of academic biocontainment laboratories, today there are 5 BSL-4 laboratories managed by the US government, 1 by a private foundation, and 1 BSL-4 agriculture laboratory is under construction (Figure 2). A small BSL-4 laboratory on an academic campus pre-dates the development of the National Institute of Allergy and Infectious Diseases (NIAID) network. A large number of BSL-3 laboratories were also independently constructed by both the commercial and academic sectors, usually with limited federal government investment.

PERSONNEL

Personnel handling select agents in biocontainment laboratories undergo background checks by the Department of Justice; they must be enrolled in an occupational health program, and they require extensive training in biosafety and biosecurity prior to gaining access to the laboratory. They may work in various aspects of research and development, from basic discovery research to advanced product preclinical testing and evaluation. Basic and applied research often depends on having access to highly specialized equipment, instrumentation, and continuously evolving technology. Similarly, the need for comprehensive documentation, record keeping, and complete external audit of records that is required by the Food and Drug Administration (FDA) makes the conduct of well-documented studies to demonstrate the efficacy of candidate vaccines and therapeutics in laboratory animals both challenging and expensive from a study design and personnel standpoint. Successful operation of biocontainment laboratories requires skilled building engineers and safety officers adept at managing the unique requirements of these complex facilities. Veterinarians and animal

Figure 1. The Network of Academic Biocontainment Laboratories for Biodefense and Emerging Infectious Diseases

National Biocontainment Laboratories (BSL-3 and BSL-4 capabilities)

- Galveston National Laboratory, University of Texas Medical Branch, Galveston, TX
- National Emerging Infectious Diseases Laboratory, Boston University, Boston, MA
- Georgia State University, Atlanta, GA*

Regional Biocontainment Laboratories (BSL-3 capabilities only)

- Colorado State University, Fort Collins, CO
- Duke University, Durham, NC
- George Mason University, Fairfax, VA
- Rutgers University, New Brunswick, NJ
- Tufts University, Boston, MA
- Tulane University, New Orleans, LA
- University of Alabama, Birmingham, AL
- University of Chicago, Chicago, IL
- University of Louisville, Louisville, KY
- University of Missouri, Columbia, MO
- University of Pittsburgh, Pittsburgh, PA
- University of Tennessee, Memphis, TN

*Not part of the NIH-constructed network of biocontainment laboratories for biodefense and emerging infectious diseases.

Figure 2. Federal and Foundation BSL-4 Biocontainment Laboratories (affiliation) Independent of the NIAID Academic Network

- Centers for Disease Control and Prevention, Atlanta, GA; includes new laboratory planned for construction (DHHS/CDC)
 - United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD; includes new laboratory under construction (DOD)
 - Integrated Research Facility, Fort Detrick, Frederick, MD (DHHS/NIH)
 - National Biodefense Analysis and Countermeasures Center, Fort Detrick, Frederick, MD (DHS)
 - Rocky Mountain Laboratory, Hamilton, MT (DHHS/NIH)
 - Texas Biomedical Research Institute, San Antonio, TX (independent nonprofit institution)
 - National Bio- and Agro-defense Facility, Manhattan, KS; an agriculture research facility now under construction (DHS for construction and commissioning; ownership to be transferred to USDA following commissioning)
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care staff also require extensive training prior to working in a high-containment laboratory. Collectively, the workforce that exists today in the biocontainment laboratory network is uniquely skilled and represents a major investment by universities that are home to this critical national infrastructure.

DEMONSTRATED SUCCESS

Over the past decade, the network of academic biocontainment laboratories has repeatedly proven its value to the nation and the world through scientific advances in the understanding of the most dangerous pathogens and development of products needed for their prevention and control. For example, the academic network of BSL-4 laboratories contributed to the development of the vaccines, therapeutics, and diagnostics now in use to diagnose, treat, and prevent Ebola virus infections among healthcare workers and exposed persons in the Democratic Republic of the Congo.^{3,4} Similarly, network scientists rapidly worked to understand the devastating disease seen among pregnant women following infection with Zika virus and helped lead the effort to advance a vaccine for this terrible disease.⁵ Many other success stories exist involving globally important diseases and biodefense threats, such as glanders, tuberculosis, anthrax, plague, influenza, West Nile, eastern equine encephalitis, and infections due to antimicrobial resistant microbes.⁶

SUSTAINING INVESTMENTS FOR PREPAREDNESS AND RESPONSE

The network of academic regional and national biocontainment laboratories (the NIAID biodefense laboratory

network) faces grave challenges regarding the sustainability of this critical national infrastructure. The network is threatened by high operating costs that cannot be met through traditional facilities and administrative costs typically associated with extramural research grants and contracts; the increasing regulatory burden associated with the FSAP; and the demands for a highly trained workforce. The business model originally envisioned to sustain the network through facilities and administrative costs associated with extramurally funded research and development projects has simply failed to meet the extraordinary operations costs of these unique facilities.

Further, several biocontainment laboratories are currently being built or contemplated around the world, many in countries that lack the rigorous oversight, the specially trained workforce, or the engineering controls needed to ensure their safe and secure operations. The NIAID network of BSL-3 and BSL-4 laboratories on US academic campuses has the infrastructure and experience that positions these facilities and their personnel as resources for global collaborators who are less experienced with the critical operation and management of biocontainment labs. By facilitating collaborations, personnel exchanges, and training opportunities, partnerships between the network and international biocontainment laboratories can reduce the potential for accidental release of dangerous pathogens and the risk of misuse by nefarious actors interested in developing biological weapons.

To ensure the sustainability of the NIAID biocontainment laboratory network, the US government should consider several issues. Specifically:

- *Operations Costs.* The safety and security of modern biocontainment laboratories rest on a complex foundation of facility infrastructure and physical security.

Physical security is provided by police and guards, restrictive card key and biometric access, and tech-based surveillance systems, leading to controlled access to ensure that only approved, appropriately trained individuals are allowed entry to the facilities. Mechanical systems include sophisticated air handling to create directional airflow within the facilities and ensure that exhaust from all BSL-4 and many BSL-3 containment labs is filtered and free of pathogens. Solid and liquid wastes are treated before leaving the facility, with solid wastes often disposed of through specialized incineration. Biocontainment laboratories require higher air changes than ordinary laboratory environments, because air flow is directional, often single pass, filtered, and may employ redundant systems. As a result, the energy costs for biocontainment laboratories greatly exceed those of a traditional research laboratory. In addition, the network labs have been in operations for over a decade, and essential equipment is reaching end of life and requires replacement as technology advances.

The costs of maintaining these laboratories greatly exceeds the financial support provided by research sponsors for facilities and administrative cost recovery, resulting in a significant financial burden on the universities where these facilities are located. While the 2 national biocontainment laboratories housing BSL-4 capabilities receive limited federal support to help offset their BSL-4 operational costs, the BSL-3 laboratories at both the national and regional facilities receive none. An independent assessment funded by NIAID in 2017 found that *annual* operational costs for biocontainment laboratories were approximately 5% to 8% of the original multimillion dollar construction costs of the facilities. The current approach to financing this important national resource network is insufficient to meet operational needs.

- *Regulatory Burden.* Oversight of biocontainment laboratories handling select agents is mandated in federal law and provided by CDC and by the USDA through FSAP. Certain pathogens are further designated as tier 1 agents and require additional special documentation, enhanced access control to laboratory spaces where they are handled, and additional personnel monitoring. Federal oversight includes documentation that all individuals having access to select agents have undergone a background check by the Department of Justice, have been enrolled in an entity-specific occupational health program, and are appropriately trained for their duties. Files that document training must be maintained for each individual involved in work with select agents or others who must enter select agent spaces (eg, maintenance personnel), and all records must be maintained for 3 years.

Facilities are approved to handle and store specific select agents, and although these microbes can be easily grown at any time, FSAP nonetheless requires an accurate inventory of individual vials containing each registered pathogen, thereby adding a significant accounting burden for investigators. Inter-entity transfer of select agents requires prior approval from FSAP, and the shipping permit is valid for only 30 days. All shipments must be documented by both the sending and receiving entities, and records must be maintained for a minimum of 3 years. BSL-4 laboratories are inspected annually, during which pathogen inventories, personnel training files, pathogen transfer records, building maintenance records, and other items are reviewed. BSL-3 facilities are inspected at least every 3 years, and there are often unannounced inspections in between. All audits are to the same level of detail.

The compliance burden placed on universities to meet the FSAP requirements is substantial and growing. Each select agent inspection requires preparation by all staff handling select agents prior to the visit, then time spent with inspectors to review records and document inventories during the inspections. The accounting burden of documenting the use of each vial of a pathogen used in an experiment or the increase in the number of vials when new stocks are grown is substantial. Documentation requirements for the removal of specimens from biocontainment are likewise burdensome. Communications with the select agent program before, during, and after each site visit is time consuming, and failure to meet any requirements may force the removal of an individual from the laboratory, closure of a specific program, or removal of select agent registration approval for the entire entity.

As the select agent program continues to evolve, more of the administrative burden is placed on the regulated entities. There is no program in place to allow universities to recoup the expenses of maintaining compliance with the select agent program; consequently, universities are forced to sustain the costs of this mandatory program using already limited institutional funds.

- *Skilled Labor Force.* Personnel working in biocontainment are uniquely trained and represent a wide range of technical skills. Entities managing biocontainment laboratories are required to maintain extensive records that document not only formal education degrees, but also specialized training in biosafety and biosecurity appropriate for the work their employees undertake. Requirements for independent entry to biocontainment are not standardized across the nation, but rather are established by each individual entity. In addition to formal university training and advanced degrees providing the essential skills needed to conduct their individual research or development project, each individual is usually required to have some level of general and specific training to work at the level of biocontainment appropriate for their

duties. This often includes a period of formal mentorship at the side of a more experienced individual and represents a significant training burden.

Maintenance personnel and those involved in ensuring the safe and secure operations of the facility may have different specific training requirements, but nonetheless must complete demanding and time-consuming biocontainment-specific training and orientation. Support personnel, particularly those from equipment suppliers involved in providing equipment and instrumentation installation, calibration, service, and repairs often are not willing to enter into biocontainment spaces, leaving programs with few options to sustain these essential resources. For personnel safety, there are few options for biosafety training by commercial vendors or partner universities; thus most universities of the national network maintain their own independent training programs. This represents yet another unfunded mandate assumed by the universities to sustain this critical national infrastructure.

- *International Engagement.* The United States has been a global leader in research and development involving especially dangerous pathogens. We were among the first to construct dedicated biocontainment facilities, and we pioneered the development of biosafety and biosecurity equipment and programs required to ensure the safety of our workforce and the surrounding community. Our preeminence in the field is, however, dwindling. Today there are more than 50 BSL-4 laboratories in operation or under construction around the world. In the past, we were able to offer new facilities assistance to establish best practices for safe and secure operations of their facilities. Unfortunately, funding for such activities is no longer available, leaving a massive gap in global security as more and more biocontainment facilities obtain dangerous pathogens and begin their own independent investigations, often without the benefit of adequate training or the experience and good counsel that US experts traditionally provided. The risk of accidental releases or purposeful misuse of dangerous pathogens is greater without meaningful engagement between US labs and our colleagues working in biocontainment around the world.

SPECIFIC ACTIONS

The US government should consider the following specific actions, which will help sustain the bioeconomy's critical national infrastructure that deals with biodefense and the risk to national health and security arising from especially dangerous emerging infections.

Strategically Targeted Funding for Biocontainment Laboratory Operations: We must create a sustained funding

mechanism for maintenance and operations costs of the critical national infrastructure that exists in the network of academic BSL-3 and BSL-4 biocontainment laboratories.

Policy and Regulatory Opportunities: We should explore ways to reduce the regulatory burden on entities handling select agents.

- Entities should be held accountable for the dangerous pathogens under their control; however, they should not waste time and effort accounting for individual vials of replicating agents.
- Scientific progress requires efficient specimen transport and sharing between entities. The regulatory burden placed on entities and the commercial transportation sector should be reviewed, recognizing the critical role they play in facilitating research on especially dangerous pathogens.

Training and Continued Development of a Skilled Workforce: We need to invest in ways to sustain and enhance the uniquely trained workforce essential to the successful operations of biocontainment laboratories and the implementation of cutting-edge research. Development of coordinated training programs for both domestic and foreign talent working in biocontainment should be explored. Academia has a proven track record of success in providing such training for national and international partners; however, funding to support this critical endeavor has eroded and novel strategies must be developed.

International Opportunities: We should establish a formal program to support international engagement with foreign biocontainment laboratories to ensure their safety and security by (1) providing training in best practices in biosafety and biosecurity, and (2) conducting collaborative research activities to enhance mutual transparency and reduce the potential risk of intentional misuse of dangerous pathogens.

The NIAID network of biocontainment laboratories provides a unique resource to the nation by marrying cutting-edge discoveries with the ability to test novel concepts and products with the real pathogen, not a surrogate model system. The students educated at these facilities graduate with unparalleled experience working in biocontainment and know firsthand the challenges and opportunities facing the biodefense community. They are a critical resource for the future.

The risk of bioterrorism and the emergence of novel, highly dangerous pathogens are real threats to our nation. The NIAID network of biocontainment laboratories was created to contribute to the national defense against these threats, and their contributions to our security and well-being are undeniable. As the network completes a decade of service, we as a nation need to pay attention to the maintenance and sustainability of this critical resource in the bioeconomy. With relatively minor investments and modifications to overly burdensome regulations, we can sustain this national treasure for years to come.

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