COMMENTARY

THE ROLE OF A NATIONAL BIOCONTAINMENT LABORATORY IN EMERGENCIES

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Over a decade ago, the National Institutes of Health awarded partial support for the construction and operation of 2 National Biocontainment Laboratories, with the condition that they would be available to assist in the event of public health emergencies—although how a biocontainment facility located on an academic campus might contribute was not defined. Here we offer examples of how one of these laboratories has contributed to a coordinated response to 2 recent international public health emergencies. Essential assets for success include highly trained and experienced staff, access to reference pathogens and reagents, cutting-edge knowledge of the field, appropriate biocontainment facilities, robust biosafety and biosecurity programs, and availability of modern instrumentation. The ability to marry the strengths of academia in basic and applied research with access to appropriate biocontainment facilities while drawing on a highly skilled cadre of experienced experts has proven extremely valuable in the response to recent national emergencies and will continue to do so in the future. Areas where additional planning and preparation are needed have also been identified through these experiences.

AFTER THE TERRORIST ATTACK OF September 11, 2001, and the subsequent use of anthrax in a domestic terrorist event, the National Institute of Allergy and Infectious Diseases (NIAID), in consultation with a blue ribbon panel, developed a strategic plan for biodefense research.¹ Their objective was to accomplish short- and long-term goals aimed at protecting the United States and the world population against biological attacks by a list of dangerous pathogens that were later defined as select agents. The NIAID strategic plan emphasized the need for both basic research and its application to the development of products such as diagnostics, therapeutics, and vaccines.

As part of the strategic plan, NIAID partially supported the construction of 2 comprehensive national biocontainment laboratories (NBLs): one at University of Texas Medical Branch (UTMB) in Galveston and the other at Boston University. The UTMB facility, known as the Galveston National Laboratory (GNL), was dedicated in November 2008. The Boston University NBL is known as the National Emerging Infectious Diseases Laboratories (NEIDL) and is just now beginning full operations. A condition of the award was that the national biocontainment laboratories be available to assist in the event of national, state, or local public

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health emergencies. Exactly how the labs might provide such assistance was not stipulated, and the possible roles that a biocontainment facility located on an academic campus might play were only alluded to in very general terms.

The GNL has had 2 opportunities to assist in public health emergencies. Here we offer case studies of how the GNL has contributed in coordinated responses to international public health emergencies and comments on other contributions of national importance.

THE 2009 INFLUENZA A:H1N1 PANDEMIC

The world was caught by surprise with the emergence of a novel influenza A:H1N1 virus, which first appeared in Mexico in 2009. Over the ensuing weeks, the new virus rapidly spread across the United States and internationally. Even though early fears of high mortality proved unfounded, the subsequent global pandemic nonetheless caused considerable disease and suffering and initially overwhelmed healthcare facilities around the globe, as had been the case previously when influenza viruses of sufficient antigenic novelty emerged. The laboratory was able to assist in the response to the new influenza virus by rapidly deploying experienced personnel to Mexico early in the epidemic to help with initial assessments and investigations by Mexican authorities.

As the demand for diagnostic testing grew, and the Texas state public health laboratory was overwhelmed with specimens, the national laboratory established rapid diagnostic testing capabilities at some scale. However, by the time the facility was able to gain CLIA (Clinical Laboratory Improvement Amendments) approval for testing, the surge in demand for diagnostic testing had generally passed. Nonetheless, the laboratory was able to provide rapid confirmatory testing at a rate of approximately 1,000 specimens per day.

This experience demonstrated the need for better advanced coordination with traditional public health laboratories before assistance is required, and the need to ensure that mandated regulatory requirements are in place before an emergency. Advanced coordination is possible; however, there are considerable challenges, including costs that are associated with establishing and maintaining CLIA certification in a research environment in the absence of a consistent demand for testing.

During the same epidemic, national biocontainment laboratories personnel were asked to assist the World Health Organization (WHO) in the production of reference reagents needed to support global diagnostic testing. While this was ultimately accomplished, delivery of the antigens was delayed substantially by administrative hurdles, again demonstrating the need for advanced coordination before the need arises. The experience demonstrated several challenges to be faced in anticipation of future

outbreaks and provided valuable lessons for future support efforts.

THE 2014-15 EBOLA EPIDEMIC

Several characteristics of the West African Ebola epidemic allowed for significant contributions by NBL personnel and resources to the international Ebola response. GNL personnel are members of the WHO Global Outbreak Alert and Response Network (GOARN), the international consortium of partners that assist in the control of outbreaks of international consequence, and they contributed extensively to coordinating the global response. As the magnitude of the epidemic became apparent, the director general of WHO created an International Health Regulations Emergency Committee for Ebola, and an individual from the GNL was invited to serve on the emergency committee that determined that the Ebola epidemic met the conditions of a public health emergency of international concern.² As the epidemic progressed, there was a need for experienced personnel to assist in coordinating the on-the-ground response, and a senior scientist was deployed for nearly 2 months to serve as country coordinator for the US Centers for Disease Control and Prevention (CDC) team in Sierra Leone.

Texas was the site where the only West African national reached the United States and suffered onset of clinical Ebola after his arrival. He was hospitalized in Dallas and unfortunately transmitted Ebola to 2 nurses who treated him. In response to the case, Texas Governor Rick Perry rapidly convened a special task force charged with providing experts and evidence-based assessments related to the Ebola response and with developing a comprehensive plan to ensure future preparedness for infectious disease emergencies.³ Experts from the national biocontainment laboratory were selected for the task force and continue to serve on the committee even as the demands of the Ebola epidemic are waning.

A large volume of infectious medical waste was generated during the hospitalization of the Ebola patients, and its accumulation and disposal became problematic as entities that normally dispose of medical waste were unwilling to handle waste generated from the care of an Ebola patient. Fortunately, UTMB has a fully licensed medical waste incinerator, and the university was able to dispose of the waste safely and efficiently.

All of these examples demonstrate the value of engaged, highly qualified, and experienced personnel being available to provide both technical advice and practical leadership in response to a major international epidemic as well as the importance of flexibility of laboratory resources in a national emergency.

As the response to Ebola progressed, it became apparent that the national capacity to manage severely ill patients suffering from transmissible infectious diseases was

insufficient, and in response some medical centers, including UTMB, were designated as referral sites for the care of such patients.⁴ In preparation, members of the UTMB National Biocontainment Training Center, which provides extensive training at all levels of biocontainment, provided training in the appropriate use of personal protective measures for clinical and support staff who might be involved in the management of an Ebola patient. Leveraging these existing resources and expertise to rapidly address this emergency need proved quite valuable.

The NBL, through the World Reference Center for Emerging Viruses and Arboviruses, a NIAID-supported activity, maintains access to virus isolates from virtually all past Ebola outbreaks as well as the critical reference reagents needed to quickly identify an infected individual. Early in the course of the outbreak, before diagnostic capabilities had been made widely available, a small number of suspected Ebola infections were seen among travelers returning from West Africa. Working in close partnership with the Texas Department of State Health Services, the NBL was able to rapidly (within 12 hours of receipt of specimens) provide preliminary results to rule out Ebola infection. While the tests were research assays, they had been used in the past on literally hundreds of specimens from experimentally infected animals, and there was great confidence in their accuracy to detect Ebola virus in blood. The testing provided provisional results that were quickly delivered with appropriate caveats to concerned attending medical staff and state health officials, allowing them to focus their attention on alternative diagnoses and to reduce anxiety in both the patient and the attending medical staff.

RESEARCH AND DEVELOPMENT

Prior to the West African Ebola outbreak, NBL investigators were actively involved in research to develop improved vaccines, drugs, and diagnostic assays for Ebola under the sponsorship of NIH, the Department of Defense (DOD), and others. A number of the vaccine and drug candidates were in advanced preclinical testing to demonstrate efficacy in animal models, and with the emergence of Ebola in West Africa, the ongoing work took on a more practical and immediate significance.

Results were reviewed intensely and used to rapidly advance the most promising candidates to field testing. Once the West African Ebola virus was available, further challenge experiments were rapidly scheduled and done to assure efficacy of countermeasures against the epidemic virus strain.^{5,6} The technical capabilities, available reagents, and access to relevant specimens from experimentally infected laboratory animals allowed for effective collaborations with commercial partners to quickly assess and field rapid diagnostic assays and reference diagnostic systems; at least 1 Ebola rapid diagnostic assay was approved for use in West Africa by both WHO and the US Food and Drug Ad-

ministration (FDA), based in part on validation testing done at the NBL. As part of the validation of the rapid diagnostic assay, an NBL scientist was deployed to Sierra Leone to test the prototype assay on specimens from acutely ill Ebola patients and appropriate uninfected controls. These partnerships between NBL scientific staff and commercial partners from the biotech industry contributed significantly to making the essential tools required to combat the Ebola epidemic rapidly available.

IDENTIFICATION OF UNKNOWN PATHOGENS

In addition to the threats raised by naturally occurring outbreaks or epidemics, the risk of misuse of infectious diseases for nefarious purposes is of constant concern. When an outbreak of an unknown pathogen arises, an early step in an emergency response is to determine the cause of the outbreak. In the United States, this is generally in the purview of the CDC; however, given access to infectious material from acutely ill patients, the NBLs are able to assist in the initial identification and characterization of the pathogen. Importantly, at least 1 NBL has an extensive reference collection of strains and reagents that serves to assist in the identification of pathogens and provides access to near-neighbor pathogens that can contribute to the characterization of the pathogen and serve as reference material to facilitate the recognition of deliberately modified organisms. In the instance of a novel viral pathogen, actually having the virus and then rapidly developing efficient testing procedures both in cell culture and in animal models are high priorities that supplement and potentiate efforts to identify countermeasures that may be effective in treating disease. This requires access to the appropriate level of biocontainment, essential equipment, instrumentation, and trained personnel with the ability to grow and assay the virus as well as experience in the rapid development of the assays and animal models required to make the assessments, all of which are made available through the NBLs.

LESSONS LEARNED AND RECOMMENDATIONS

The NIH investments in construction and operations support for the NBLs has created a new resource in the national defense against emerging infectious diseases and the threat of bioterrorism. Recent events have provided clear examples of how the NBLs benefit the nation. Common themes of these case studies were: (1) a need for in-depth technical expertise and highly trained personnel; (2) access to appropriate biocontainment facilities; and (3) the ability to address urgent research demands to better characterize the etiologic agents, rapidly evaluate potential therapeutic interventions, provide diagnostic assistance, and contribute to development of preventive measures. These key assets may serve as examples of how the NIAID

investment in the NBLs is meeting the original vision to assist in the event of a national, state, or local public health emergency. Several challenges were also identified, including the need for greater coordination with local, state, and national public health officials before an emergency occurs, and the need to address regulatory requirements for human diagnostic testing before the need arises.

What do the NBLs bring that is different from NIH, CDC, or DOD federal facilities? The laboratories have strengths in basic research and the ability to develop concepts on to products, all within a single facility. They are agile and able to respond rapidly to emergent situations. Their investigators have a broad and diverse network of colleagues and collaborators who are working at the leading edge of discoveries in their field, and they have the ability to engage these collaborators in research on pathogens requiring biocontainment, drawing on intellectual resources that might otherwise not be applied to studies on dangerous pathogens. The initiation of collaborations may be less bureaucratic as compared to some government facilities, especially with international partners, and, finally, the NBLs provide added surge capacity to assist in emergencies at times when government laboratories may be overwhelmed.

To ensure that the full potential of the NBL network continues to be met, sustained funding will be required to offset the significant costs associated with security, maintenance, and operation of these highly specialized facilities, and continued attention paid to appropriate comprehensive training of personnel in biosafety and biosecurity related to the investigation of highly virulent pathogens. Finally, NBL investigators need to maintain reference strains of pathogens, relevant reagents, and timely access to clinical specimens resulting from outbreaks of known or novel infectious diseases. Challenges associated with the movement of infectious material, especially internationally, continue to affect optimal use of the NBLs. Nonetheless, the ability to marry the strengths of academia in basic and applied research with access to appropriate biocontainment facilities while drawing on a highly skilled cadre of experienced experts has proven to be extremely valuable in the response to recent national emergencies and will continue to be useful in the future.

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