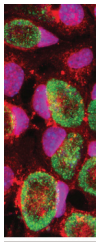

COMMENTARY

Containing infectious disease

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Since 2001, the threat of intentional release of biological agents capable of severe human disease has been a clear and present danger. At the same time, natural outbreaks of emerging infectious diseases have become almost routine: 2003, SARS (Peiris *et al.*, 2003); 2005, H5N1 influenza virus (Beigel *et al.*, 2005); 2009, H1N1 pandemic influenza virus (Neumann *et al.*, 2009); 2012, MERS-CoV (Zaki *et al.*, 2012); and 2013, H7N9 influenza virus (Gao *et al.*, 2013). In addition, previously as well as recently established infectious agents continue to flare with some regularity: hantavirus (Jonsson *et al.*, 2010), West Nile virus (Murray *et al.*, 2010), dengue (Adalja *et al.*, 2012), etc. Even those infectious diseases (e.g. measles, mumps) long regarded as having been 'taken off the table' due to effective vaccines have seen resurgence due to evolving public perceptions of vaccination risk/benefit trade-offs (Serpell & Green, 2006; Berger & Omer, 2010). Finally, long-standing, but treatable traditional infectious agents have continued to demonstrate slow, but steady and relentless progression to greater resistance to available therapy: tuberculosis, malaria, multiple gram-negative bacterial agents, etc. (Boucher *et al.*, 2009).

Analysis of recent infectious disease outbreaks has revealed hundreds of newly recognized infectious agents in the latter half of the 20th century alone (Jones *et al.*, 2008). Factors influencing this explosion are varied. Clearly, technological advances in microbiological isolation and characterization have been critical to the rapid identification of novel etiologic agents of outbreaks. Overall population growth, human encroachment into long-standing wildlife communities, larger and more crowded urban centers, greater global mobility patterns and increased pressure on agricultural output all contribute to a higher likelihood of infectious agent outbreaks as well as their potential establishment in favorable ecological niches resulting in persistence. As a result of an ever increasing interdependent global community, there is an ever increasing potential for significant morbidity and mortality, overall societal disruption, and even national security concerns due to large infectious disease outbreaks.

Our ability to rapidly recognize an emerging infectious disease and/or public health emergency as well as respond with appropriate public health and biomedical interventions, in the form of surveillance, infection control, contact tracing, diagnostics, vaccines and therapeutics relies on a basic understanding of transmission dynamics, microbiology, host defenses and disease pathogenesis. The deliberate release of anthrax spores in 2001 highlighted substantial vulnerabilities in terms of a coordinated public health response, but also underscored the lack of fundamental knowledge concerning this as well as other exotic infectious agents. While an immediate response was to address shortcomings in terms of available medical countermeasures, a longer-term goal was to expand and strengthen the fundamental basic science knowledge base concerning those infectious agents for which previously little information had been obtained to be better prepared for the future as well as expand the pool of trained investigators.

At the same time that biodefense funding by the National Institute of Allergy and Infectious Diseases (NIAID) was focusing on the scientific and medical gaps related to bioterrorist threat agents, construction of Biocontainment Laboratories, both BSL-3 (Regional Biocontainment Laboratories – RBLs) and BSL-4 (National Biocontainment Laboratories – NBLs), was undertaken to provide adequate research infrastructure and capacity for these efforts as well as not displace existing research projects on other important, but nonbiodefense agents that also require containment (Hirschberg *et al.*, 2004). There was also recognition of evolving engineering standards that precluded simply renovating existing facilities. In addition, with an appreciation of the value of animal models for a greater understanding of disease pathogenesis as well as their critical role in the ability to advance candidates countermeasures, these facilities were designed to handle space requirements for the safe conduct of animal studies, from rodents through nonhuman primates. These facilities were also designed to establish workforce training, which would complement the engineering controls to provide for skilled laboratory workers to conduct state of the art research to the highest standards for safety toward laboratory workers as well as the general public.

Another consideration was the newly announced Food and Drug Administration (FDA) regulatory pathway known as the 'Animal Rule' (Burns, 2012), which allows for certain categories of medical countermeasures to be approved on the basis of animal efficacy with supporting human safety data in those instances when life-threatening diseases are extant, but traditional human Phase III testing for efficacy is neither ethical nor technically feasible. As animal studies performed to support this regulatory pathway would require good laboratory practices (GLP) conduct and the majority of academic research is not specifically conducted with GLP compliance, the BSL-3 RBLs and the BSL-4 NBLs were designed to accommodate GLP animal studies. The FDA is working with a NBL to design a curriculum specific for GLP 'best practices' under containment. This activity will address regulatory issues for medical countermeasure development that require animal model testing under containment conditions.

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The bulk of laboratory capacity in these facilities came online in the 2008–2010 timeframe; however, since that time, their impact on the scientific field encompassing this neglected category of infectious agents has been substantial. Novel vaccine concepts have applications beyond the initial biodefense agent with the potential to impact the wider repertoire of infectious disease (Garufi *et al*., 2012). From the identification of a novel disease risk factor for an attenuated vaccine strain (Quenee *et al*., 2012) to the characterization of viral activity of public health significance geographically adjacent to the United States (Adams *et al*., 2012), these facilities are directly contributing to a greater level of preparedness to intentional as well as natural future outbreaks of known human pathogens. In addition, the facilities have also contributed to newly emerging pathogens such as the recent H1N1 pandemic (Ljunberg *et al*., 2012) and even fungal meningitis from contaminated injectable drugs (Zhao *et al*., 2013). Finally, with the emergence of MERS-CoV as a potentially more dangerous sibling to SARS, these facilities have assisted in defining species restriction and moving quickly to a relevant animal model for the evaluation of potential medical interventions (de Wit *et al*., 2013; van Doremalen *et al*., 2014).

These facilities provide a resource for the country and the world to continually push back the frontiers of dangerous and poorly characterized infectious agents and provide for a greater degree of preparedness in expectation of recognition of currently unknown infectious agents. At the same time, they offer the potential to assist in the midst of public health emergencies involving serious infectious agents such as may arise as a result of newly emerging infectious diseases or due to intentional release. They represent a critical component of our overall public health preparedness for infectious diseases. They directly contribute to the application of fundamental basic scientific research into improvements in the health and well-being of the public, while addressing current public health threats and standing ready to assist with emerging infectious disease threats in the future.

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