The Laboratory Response Network: Before, During, and After the 2001 Anthrax Incident

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Abstract

The Laboratory Response Network (LRN) was established in 1999 in response to the worldwide concern for the potential use of biological or chemical agents in the commission of acts of terrorism. One such example was the numerous “hoax” letters allegedly containing the agent of anthrax that were mailed to a variety of agencies, including family planning clinics. As a result of this realistic threat, the Centers for Disease Control and Prevention, in partnership with the Federal Bureau of Investigation and the Association of Public Health Laboratories, created the LRN for the purpose of strengthening the nation’s capacity to provide immediate and sustained laboratory testing and communication in the event of public health emergencies, particularly in response to acts of bioterrorism. From the time of its establishment to the present, the LRN has been successful in integrating the public and private health laboratory communities, in addition to expanding its original focus of medical laboratories to military laboratories, veterinary laboratories, agricultural laboratories, food and water testing laboratories, and international laboratories. The original designation of laboratories as Levels A, B, C, and D was revised to Sentinel, Reference, and Federal laboratories. They now function as an integrated network, with the major goal being to ensure that the nation’s public health and private sector laboratories, along with other select laboratories, are prepared and equipped to respond to a biological or chemical act of terrorism in an appropriate and integrated manner. The lessons learned during the anthrax investigation in 2001 clearly demonstrated the need for an integrated network of laboratories, education, and training of technical personnel and the development of rapid detection and confirmatory technology. The American Society for Microbiology is one of many partners in the LRN and is responsible for maintaining and developing sentinel level testing protocols to either “rule out” or refer possible agents of bioterrorism. The mission of the LRN has been expanded to include not only biological and chemical terrorism, but also emerging infectious diseases and other public health threats and emergencies.

Introduction

The Laboratory Response Network (LRN) was created nearly 6 years ago. Its inception was in response to the 1995 Presidential Directive 39, in which national antiterrorism policies were outlined and specific missions were assigned to federal departments and agencies. In 1999, following a mandate from Congress to establish and coordinate laboratory resources for preparedness and response to biological terrorism, the Centers for Disease Control and Prevention (CDC), in partnership with the Association of Public Health Laboratories (APHL) and the Federal Bureau of Investigation (FBI), created the LRN. The primary mission of the LRN and its partners was to maintain an integrated network of laboratories that were equipped to respond quickly to acts of biological terrorism targeting the civilian population. Within 3 years following the establishment of the LRN, the United States encountered its first bioterrorism attack. The scale of the public’s response to this attack was not anticipated and threatened to overwhelm the ability of the LRN to process and test environmental and human samples. The overall response to this attack was generally regarded as successful,
but many of the lessons learned from the attack resulted in several modifications of the LRN, including the reclassification of laboratories, expanding the number and types of laboratories, and what constitutes membership in the network. This review focuses on the evolution of the LRN since 1999 and its current structure, including revisions in its mission, participation of public and non-public health laboratories, expansion of laboratory capacity, and the current challenges that confront the network.

**The LRN: Pre-Anthrax Attack**

From the period of December 1999 to October 2001, the primary focus of the LRN was to create a network designed to integrate federal, public health, and private clinical laboratories, including commercial laboratories, and define their respective responsibilities when confronted with a suspected or confirmed act of biological terrorism. The ultimate purpose of the LRN was to strengthen the nation’s capacity to rapidly detect biological and chemical agents that could be used as terrorist weapons. The goal was to ensure that there were a sufficient number of clinical laboratories that possessed the capacity and technical expertise necessary to respond to a bioterrorism event. As a result, the LRN was configured as depicted in Fig. 1 (1). Laboratories were classified as Level A, B, C, or D. Level A laboratories consisted primarily of private and commercial clinical laboratories, in addition to many metropolitan and military laboratories, which functioned at Biosafety Level (BSL) 2. The primary responsibility of Level A laboratories was to limit testing to human specimens and “rule out or refer” suspected bioterrorism-associated agents by following standardized testing protocols developed by the American Society for Microbiology (ASM) in partnership with the CDC (2-6).

In addition to the development of standardized protocols, a major effort was undertaken by the CDC, in conjunction with the APHL, to develop and provide training and education for laboratory personnel at the national and regional levels in the areas of biosafety, specimen selection, preservation, and transport; the recognition of clinical manifestations; and the characterization of targeted microbial agents. Additional training and education were also provided by ASM, which sponsored workshops and symposia at its annual meeting. Many of the regional clinical microbiology associations also provided training and education at the regional and local levels. Although Level A laboratories had access to the LRN, they were not considered to be official members and did not have access to the CDC secure website. This decision was primarily driven by the need to maintain the highest level of safety and the concern that many of these laboratories did not possess, at a minimum, a biological safety cabinet and thus could not fully practice BSL-2 safety procedures.

Laboratories designated Level B and C were comprised of state and selected military laboratories. Their primary mission was to accept and test environmental specimens and serve to “rule in” isolates that had been referred by Level A laboratories. Level C laboratories were selected state health laboratories that possessed additional testing capacity, such as botulism testing. Level B and C laboratories constituted the core
of the LRN and had direct access to the secure CDC website, which contained testing protocols and technologies designed to confirm organism identification and, when necessary, perform or confirm results of susceptibility testing. These laboratories were required to practice and adhere to BSL-3 containment standards, and personnel were required to complete a formal training program and participate in proficiency testing conducted and monitored by the CDC before being certified as a Level B or C LRN laboratory.

Only two Level D laboratories were in operation during this time period, CDC and the United States Army Institute for Infectious Disease Research (USAMRIID) at Ft. Detrick, Maryland. Both laboratories followed strict BSL-4 containment practices and utilized the highest level of diagnostic technology, in addition to conducting research, development, and validation of new diagnostic technology, and they continue to do so. In addition, the CDC facility is also responsible for fully characterizing biological agents. In the event of a public health emergency, such as a bioterrorism attack, the CDC facility was expected to conduct the majority of testing, with USAMRIID serving in a support capacity in the event that the CDC exceeded its surge capacity.

LRN: During the Anthrax Attack

Although most laboratories had been preparing for the possibility of a bioterrorism attack against the civilian population, there did not exist a genuine belief that such an attack would occur, and in general, there was a false sense of security. Furthermore, it was generally accepted that in the event of an attack, the public health sector, specifically the LRN laboratories, would be the major source of response while the private sector would play little, if any, role. However, these perceptions and preparation plans were changed forever following the 12 October, 2001 release of anthrax spores by means of the United States Postal Service. Before the letters containing Bacillus anthracis spores were mailed, the planned role of the LRN had not been fully validated, nor was the need for extensive environmental testing fully appreciated or anticipated (7). Instead, the scenario envisioned a sharp increase in hospital admissions caused by one of the targeted bioterrorism agents (8). By the time the symptoms and bioterrorism agent were identified, the disease would most likely be established within the local population. Thus, laboratory response would be focused primarily on collecting, processing, and analyzing human clinical specimens.

In actuality, non-member and member LRN laboratories were inundated with both human and environmental samples, with the latter outnumbering the former. Although the anthrax attack was concentrated on the East Coast, public panic was such that many clinical laboratories throughout the United States were faced with the challenge of accepting and analyzing environmental samples referred by first responders who were unfamiliar with the LRN and its operational structure. As stated previously, Level A laboratories were not intended to accept environmental specimens, but many law enforcement personnel and first responders, unaware of this provision, transported specimens to the most conveniently located laboratory within their geographical area. A major concern was the potential for false-positive results that would result in undue anxiety and unnecessary medical interventions for exposed individuals, including the administration of prophylactic antibiotics or vaccines (9). For example, the University of Louisville Hospital Microbiology Laboratory examined over 300 environmental specimens during a 4-week period following the initial release of the anthrax spores in Florida. In addition, hundreds of local residents (the worried well) presented to the emergency room demanding the collection of nasal swabs because “that is what is being done in Florida and everyone is being given ciprofloxacin.” Although our laboratory was classified as Level A, it functioned as an LRN laboratory as a result of public pressure and a sense of responsibility to provide a public service to the metropolitan population, law enforcement, and first-responder community. During this period, the Kentucky State Health

Figure 2. Laboratory Response Network (2002-present). National reference and sentinel laboratories work as an integrated network that builds upon individual laboratory capacity in order to respond to public health emergencies.
Laboratory was overwhelmed with environmental specimens and, because of staffing shortages and the inability to provide services on a 24-hour basis, experienced over a month delay in completing specimen analysis. Similar experiences were reported throughout the U.S., but the most representative description of laboratory response has been described for the New York City Bioterrorism Response Laboratory (7). The effort described for this facility was largely successful, even though the attack was unforeseen and threatened to overwhelm the laboratory’s ability to process and test environmental specimens. Since the anthrax attack was concentrated in the Washington, D.C., and New York City areas, the ability of the New York City and Virginia State Health Laboratories to respond effectively to the situation was enhanced through a joint effort with the CDC and the Department of Defense (DOD). Through this joint effort, these laboratories were capable of sustaining a laboratory response that resulted in the release of test results in a timely fashion. Furthermore, scientists at the CDC had successfully developed a number of PCR assays for detecting agents of bioterrorism. The anthrax assay played a significant role during the response to the attack by rapidly confirming the identity of the agent.

LRN: Post-Anthrax Period

Based in part on the lessons learned from the anthrax outbreak and the realization that the LRN is a dynamic and still-evolving program, the original structure, mission, and membership in the network have undergone significant revisions. Today, the LRN is a national network of approximately 120 laboratories. The original classification of laboratories as Levels A, B, C, and D has been revised as follows: Level A laboratories are now designated Sentinel laboratories and consist of hospital-based, commercial, and most military laboratories that are on the front lines. Sentinel laboratories are restricted to testing only human specimens, do not have access to the CDC secure website, and are to follow standard testing protocols designed to “rule out” or, if necessary, refer suspicious samples or isolates to the nearest Reference laboratory (formerly Levels B and C). Reference, or “confirmatory,” laboratories are equipped to perform tests to detect and confirm the identity of a threat agent. These laboratories ensure a timely local response in the event of a terrorist incident and reduce the need to rely on laboratories at the CDC. The majority of Reference laboratories are located at state and some local health departments. In addition to being able to identify Category A biological agents, a few public health laboratories can measure human exposure to toxic chemicals by testing clinical specimens. Reference laboratories have been expanded to include (i) selected military laboratories operated by the DOD, including USAMRIID; (ii) food-testing laboratories, such as those within the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), and others responsible for ensuring the safety of the food supply; (iii) environmental laboratories with the ability to test water and other environmental samples; (iv) veterinary laboratories, namely, those run by the USDA, that are responsible for animal testing; and (v) international laboratories, which are currently located in Canada, the United Kingdom, and Australia. The former Level D laboratories are now designated Federal laboratories and include facilities located at the CDC, USDA, FDA, and other federal agencies. The revised and current mission of the LRN and its partners is to maintain an integrated national and international network of laboratories that can respond quickly to acts of chemical or biological terrorism, emerging infectious diseases, and other public health threats and emergencies. In its role as a confirmatory testing resource, the LRN serves an important complementary function to Sentinel laboratories, which provide lower-level testing for institutions directly involved in patient care (5). The current structure of the LRN is depicted in Fig. 2.

In addition to the redesignation of the roles and expansion of LRN laboratories, a structure has been created to address chemical terrorism. Currently, 62 state, territorial, and metropolitan public health laboratories are members of the chemical component of the network. A designation of Level 1, 2, or 3 defines network participation, and each level builds upon the preceding level. Level 1 laboratories are responsible for (i) working with hospitals in their jurisdictions; (ii) maintaining competency in clinical specimen collection, storage, and shipment; (iii) ensuring that the necessary evidence control measures, including proper taping of specimens and chain-of-custody guidelines, are followed; (iv) being familiar with chemical agents and their health effects; (v) training on projected clinical sample flow and shipping regulations; and (vi) working to develop a coordinated response plan for their state and jurisdiction. Level 2 laboratories (currently 41 laboratories) are capable of detecting exposure to a limited number of toxic chemical agents in human blood or urine, such as cyanide and toxic metals. Level 3 activities are currently performed by five laboratories, in which personnel are trained to detect exposure to an expanded number of chemicals in human blood or urine, including all Level 2 agents, in addition to testing for mustard agents, nerve agents, and other toxic chemicals.

Membership in the LRN has been clearly defined for public health laboratories, but not for Sentinel laboratories. The LRN Working Group is in the process of developing criteria for admitting Sentinel laboratories to membership in the LRN. Currently, state health laboratory directors determine whether public health laboratories in their states should be included in the network. Membership is not automatic, and prospective Reference laboratories must possess equipment, trained personnel, and facilities properly designed to meet BLS-3 containment criteria and must demonstrate testing accuracy. State laboratory directors have been directed by the APHL to conduct either site visits or surveys of all clinical laboratories within their respective states to determine which laboratories meet the criteria for Sentinel membership. The LRN Working Group has proposed that each state develop a registry method to formally designate sentinel laboratories as “Registered Sentinel laboratories.” Inclusion in this proposed registry requires the following: (i) being a licensed (state) or accredited (CLIA, CAP, or JCAHO) laboratory that receives human, animal (American Association of Veterinary Laboratory Diagnosticians [AAVLD]), food (USDA, FDA), agricultural, or chemical specimens for analysis; (ii) routinely using
FDA-approved methods for the complete analysis, identification, and susceptibility testing of common etiologic agents or fully identifying toxic chemicals; (iii) being able to fully comply with the safety standards as outlined in the fourth edition of the manual *Biosafety in Microbiology and Biomedical Laboratories* (10); (iv) filing a successfully completed LRN capacity audit; (v) receiving training specified by the state public health laboratory; and (vi) agreeing to the provisions for preparation and response outlined by the state public health laboratory. The LRN Working Group is also considering the provision of a certificate to those Sentinel laboratories that have successfully met LRN membership standards. Until the issue of membership in the LRN for clinical laboratories is resolved fully, it is recommended that the APHL or the state health laboratory be contacted for information and questions.

Efforts are also being made to identify criteria for advancing selected Sentinel laboratories to Reference laboratory status. The LRN Working Group has developed criteria for a laboratory to become a designated Reference laboratory. Any laboratory that is interested in or desires to receive Reference status should contact its state health laboratory director.

As the LRN continues to evolve, it is important to recognize that the LRN is a partnership between government and private organizations with responsibility in the areas of biological and chemical preparedness. The CDC officially directs and coordinates the LRN but welcomes and receives recommendations from the following agencies and organizations: APHL, FBI, AAVLD, USDA, DOD, FDA, Department of Homeland Security, the Environmental Protection Agency, and ASM (the author serves as the ASM Public and Professional Affairs representative to the LRN Working Group). Each agency and organization is represented at the quarterly meetings of the LRN Working Group. Thus, the LRN is a national asset that coordinates laboratory resources for preparedness and response to biological and chemical terrorism. Its success is dependent on the interaction and participation of all laboratories throughout the U.S. regardless of their individual specialties and current classification.

References