

Are We There Yet? Laboratory Preparedness for Emerging Infectious Diseases

Moderators: Carey-Ann D. Burnham^{1*} and Jennie H. Kwon²

Experts: Eileen M. Burd,³ Sheldon Campbell,^{4,5} Peter C. Iwen,⁶ and Melissa B. Miller⁷

The West African Ebola virus epidemic of 2013–2016 was the most widespread epidemic of this disease in history; it is estimated that this occurrence contributed to more than 11 000 deaths. During the epidemic, health-care workers (HCW)⁸ (including laboratorians) were mobilized to care for individuals with suspected or confirmed Ebola virus disease (EVD). However, at the height of the epidemic, guidance on appropriate safety measures for laboratory workers manipulating specimens from EVD patients was sparse. This highlighted the need for data and guidelines for laboratories testing specimens not only for patients with EVD, but for any emerging infectious disease. During the Ebola epidemic, questions were raised about the roles and responsibilities of laboratories in responding to highly infectious diseases, and the burden of ongoing readiness for rare events. As the outbreak decelerates, laboratorians must regroup, gather data, and prepare for future outbreaks. We have asked 4 experts in this field to share their thoughts on contemporary challenges in laboratory preparedness for emerging infectious diseases.

During the recent Ebola epidemic, what laboratory testing did your hospital offer for patients with suspected EVD? Who performed this testing and where was the testing performed? Did you have dedicated equipment for laboratory testing or did you utilize existing core laboratory equipment?

Eileen Burd: Patients with clinical symptoms and appropriate epidemiologic risk factors for EVD were stratified as high, intermediate, or low risk by the provider seeing the patient. If evaluation revealed low risk or no identifiable risk, standard tests were generally ordered that included tests for diagnoses other than EVD including



complete blood count (CBC) with differential, complete metabolic profile (CMP), and malaria testing. Other tests that were ordered as indicated by the patient's symptoms included blood cultures, respiratory virus testing, urinalysis, urine culture, and molecular gastrointestinal panels. Blood and other specimens were collected and placed in specimen transport bags in the patient's exam room and transported to the main hospital laboratories per standard protocol.

If evaluation revealed that Ebola testing was indicated, the Emory Serious Communicable Disease Unit (SCDU) physician on call was contacted. If the SCDU physician agreed, the SCDU laboratory director on call was notified and the SCDU laboratory was activated. All specimens were packaged and transported under Category A precautions to the SCDU laboratory. Testing was limited to the tests available in the SCDU laboratory and no specimens were sent to the main laboratories in the hospital until EVD was ruled by PCR. Ebola virus PCR results were available in about 1.5 h after receipt of the specimen in the SCDU laboratory. Other tests available in the SCDU laboratory included CBC, CMP, magnesium, lactate dehydrogenase, γ -glutamyl transferase, amylase, lactate, phosphorous, venous/arterial blood gases, urinalysis, FilmArray[®] gastrointestinal panel, FilmArray[®] respiratory panel, BinaxNOW[®] malaria assay, and Alere Determine[™] HIV-1/2 Ag/Ab Combo test.

Testing in the SCDU laboratory is performed by staff medical technologists who volunteer on a rotating

Departments of ¹ Pathology & Immunology and ² Medicine, Washington University School of Medicine, St. Louis, MO; ³ Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA; ⁴ Department of Laboratory Medicine, Yale School of Medicine, New Haven, CT; ⁵ Pathology and Laboratory Medicine, VA Connecticut Health Care, West Haven, CT; ⁶ Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE; ⁷ Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, NC.

* Address correspondence to this author at: Department of Pathology & Immunology, Washington University School of Medicine, 660 S Euclid Ave., Campus Box 8118, St. Louis, MO 63110. Fax 314-362-1461; e-mail cburnham@path.wustl.edu.

Received October 15, 2016; accepted November 10, 2016.

© 2016 American Association for Clinical Chemistry

⁸ Nonstandard abbreviations: HCW, healthcare workers; EVD, Ebola virus disease; CBC, complete blood count; CMP, complete metabolic profile; SCDU, Serious Communicable Disease Unit; PCR, polymerase chain reaction; PUI, person(s) under investigation; SLPH, State Laboratory of Public Health; BSL2+, biosafety level 2+; PPE, personal protective equipment; POC, point of care; BSC, biological safety cabinet; ICU, intensive care unit; FDA, Food and Drug Administration; BBP, bloodborne pathogen; SARS-CoV, severe acute respiratory syndrome coronavirus; LDT, laboratory-developed tests; pdmH1N1, pandemic H1N1; EUA, Emergency Use Authorization; MERS-CoV, Middle East respiratory syndrome coronavirus; ASM, American Society for Microbiology; PHL, public health laboratory.

on-call schedule so that laboratory services can be provided around the clock. The equipment in our SCDU laboratory is dedicated for use only in that laboratory. The major drawback of using dedicated equipment is the expense, including the initial purchase and the cost of maintaining equipment and space that is rarely used. In addition, backup instruments are not available if an instrument becomes disabled.



Melissa Miller: Our initial plans focused on a person under investigation (PUI) likely presenting to our emergency department or an outpatient clinic with the assumption that either the laboratory would be notified by the clinical team, or in the laboratory's travel history review for malaria testing, we would identify

a potential PUI. We developed plans for the appropriate collection and transport of specimens to the clinical microbiology laboratory for Ebola testing performed by our State Laboratory of Public Health (SLPH) and the CDC, as well as the essential tests to support patient care without undue risk to laboratorians. The on-site microbiologic testing offered for PUI was limited to blood cultures (collected in plastic bottles) and malaria smears (thin smear only), as indicated. All specimen processing performed before inactivation procedures was performed in our mycobacteriology suite [biosafety level 2+ (BSL2+)] by personnel trained in donning and doffing personal protective equipment (PPE). Laboratory personnel were on call 24/7 to provide this service.

Inherently problematic was the assumption that the laboratory would be notified of these cases. Extensive education, signage, and computer alerts (i.e., hard stop for required travel history and symptom review) were developed in an attempt to mitigate this risk. Unlike many past infectious disease epidemics, the impact to the clinical laboratory extended beyond microbiology. Core laboratory services, including chemistry and hematology, were also challenged. Due to the concerns of contamination of laboratory equipment and potential exposure of laboratorians in a high-throughput laboratory, our institution elected to develop dedicated point of care (POC) services for PUI. We worked with local experts who had treated EVD patients in Africa and our infectious disease and critical care colleagues to determine the "minimal necessary testing" for a critically ill PUI until they had been ruled out for EVD by the SLPH/CDC. Based on this list, POC instruments were reallocated and/or acquired for the sole purpose of testing PUIs. These instruments were placed in a dedicated room with

a biological safety cabinet (BSC) adjacent to an isolation room in an intensive care unit (ICU). Laboratory personnel were trained and on call to staff the POC laboratory, as needed. Until this laboratory was ready, our plan specified that specimens be transported to Microbiology for centrifugation and processing, as needed, before delivery to the Core Laboratory for essential testing on designated devices that would then be decontaminated using routine protocols.

What is the current status of your emerging pathogens laboratory?

Melissa Miller: The POC laboratory used during the EVD epidemic has been decommissioned. However, we have maintained procedures for ready deployment of the laboratory should the need arise. The EVD epidemic and risk to laboratorians was unique in that it impacted multiple areas of the clinical laboratory, including anatomic pathology. Most of our epidemics and emerging pathogen concerns to date have relied primarily on the readiness of the clinical microbiology laboratory. Our microbiology laboratory maintains a secure, camera-monitored "Emerging Pathogens Room" with a BSC and small incubators and supplies. This dedicated room, along with our mycobacteriology suite, provides continuous readiness and security for most emerging pathogens.

Eileen Burd: The Emory SCDU Laboratory is at "ready state." An on-call schedule is generated each month with 2 medical technologists (1 testing technologist, 1 safety technologist) and 1 laboratory director on call each 24-h day, separate from their routine laboratory duties. The instruments in the laboratory are maintained by the technologists who are trained to run tests in the SCDU laboratory. Quality control, calibration, and proficiency testing are performed as appropriate for each assay or instrument.

What are some of the challenges that clinical laboratories encounter that hinder preparedness for emerging infectious diseases?



Sheldon Campbell: The biggest challenge is the unknown, intermittent, and dynamic nature of the risk. Emerging infections come in different types—viral, bacterial, fungal, parasitic; by definition they appear unexpectedly, and the outbreaks vary from a dozen cases to global pandemics. Routes of transmission, duration of risk before, during, and after symptoms, specificity of the clinical syndrome, quantitative risk of a given

duration of risk before, during, and after symptoms, specificity of the clinical syndrome, quantitative risk of a given

source-patient actually being infected, and level of infectious risk in a given specimen type vary between outbreaks, and our understanding of them evolves within the span of a new outbreak. Secondly, clinical laboratories, like all parts of the healthcare system, are under continuous pressure to reduce costs and improve outcomes in documentable ways. The efforts we make to prepare for the latest outbreak tend to erode and be gone by the time the next thing happens.



Peter Iwen: Major challenges for clinical laboratories include inadequate facilities for handling specimens that might contain a high-risk pathogen, outdated or lack of appropriate equipment, and insufficient number of trained laboratorians. The high cost to validate new testing platforms that

might only be used rarely to assess specimens from a highly infectious patient must be considered. Finally, the need to provide for a proficiency and quality management program over the long term along with the availability of staffing that can meet competency assessments for this specialty laboratory will be an ongoing financial challenge for hospital and laboratory administrators.

How can laboratories ensure that personnel maintain competency with enhanced PPE and/or special equipment or procedures outside of an epidemic setting?

Eileen Burd: All of the HCWs in the Emory SCDU are required to demonstrate competency in using PPE each quarter during routine periods when the SCDU is not activated. Any changes in PPE equipment or procedures are reviewed during the competency sessions. In addition to quarterly competency, annual no-notice drills are held that involve only the SCDU personnel on call that day. Annual drills are organized and observed by the SCDU Medical Director and Program Coordinator. These are “real-life” exercises in which the SCDU is activated and a volunteer “patient” is transferred by ambulance. The volunteer patient is admitted to the SCDU and evaluated. Specimens are taken and laboratory tests are performed as ordered. As in a real event, a conference call is held in the afternoon to discuss patient status, review expectations, schedules, and Just-in-Time Training. All members of the SCDU team, even if they are not participating in the drill, are encouraged to join the conference call or appoint a designee.

Sheldon Campbell: The only possible approach is to practice and drill the procedures. This is very difficult to

sustain in the absence of an imminent threat; there’s always something more urgent to do. It might make more sense for the rest of us to create skeletal procedures and mechanisms that we build on when an event occurs, then activate our training and procedures when an emerging infection hits some threshold. But then, what’s the threshold to activate the planning and start training? What if you’re the first place hit?

In the setting of an outbreak of an emerging infectious disease, how do clinical laboratories balance the risks to patients and the risk to laboratory workers?

Eileen Burd: Outbreak situations generate a certain amount of fear among hospital and laboratory staff. Having emerging infectious disease protocols in place helps lessen that fear. Individuals caring for, or testing, specimens from known or suspected infected patients are under additional stress and using the greatest protective methods available is justified. Because initial symptoms of emerging infectious disease may be nonspecific, as is the case with EVD, it is not always possible to identify infected patients early. It is crucial that standard precautions are used consistently by all HCWs at all times.

Patients suspected or known to be infected with certain epidemiologically important pathogens such as Ebola virus require additional control measures to protect HCWs and other patients. The goal is to provide care as needed, but to minimize unnecessary contact with patients and avoid procedures that increase the risk of exposure to infectious material. Some of the recommended measures include limiting the number of people exposed to the patient, isolating the patient in a room with the door closed, implementing standard, contact, and droplet precautions, limiting invasive procedures to those essential for patient care, using PPE, and appropriately decontaminating surfaces and equipment, etc.

The laboratory should provide a minimum menu of tests for the diagnosis and evaluation of the patient, with results available as quickly as possible. Risk of exposure from spills or aerosols generated when testing patient specimens can be minimized by limiting the number of staff performing the tests and use of appropriate PPE. Consideration should be given to segregating equipment used for testing and performing laboratory tests in a dedicated space.

Sheldon Campbell: There’s no “right” answer to this. Ideally, the impact on mortality of delayed or absent laboratory testing could be balanced against the risk to laboratory personnel and some greatest-good-for-the-greatest-number calculation applied; in practice there’s no way to make that calculation. I think the “abundance of caution” formulation used in Ebola was unhelpful; “abundance of caution” for whom, the laboratory or the

patient? Laboratorians frequently mention what a large fraction of medical decisions involve laboratory results; with that in mind, we cannot consistently argue that “the laboratory results don’t matter that much in this case.” There needs to be a more robust dialogue, both within the laboratory community, and between laboratories and clinicians, about what levels of risk are acceptable, and what impact delaying or restricting laboratory testing will have on patients. Ideally this would be an evidence-driven discussion; that may be another part of the research agenda.

How do laboratories decontaminate laboratory equipment used for testing clinical samples from patients with highly virulent infections?

Melissa Miller: To my knowledge, this is still largely an unanswered question. The CDC has provided guidance for surface decontamination, but defer to the manufacturers’ operator’s manuals for decontaminating internal components of equipment. The CDC states they are in consultation with the Food and Drug Administration (FDA) and manufacturers to address these unanswered issues. Since there is no recommended method(s) for decontamination, or a validated method for assessing effectiveness of any method, an instrument may have to be decommissioned if it becomes contaminated. These issues, in part, led to our decision to implement POC testing devices for the essential laboratory tests needed to support the care of a critically ill PUI.

Peter Iwen: A wide range of methods have been described by manufacturers to decontaminate equipment used to test specimens containing Ebola virus, ranging from minimal processes such as bleach wiping, to incineration of the instrument after utilization. In many instances where laboratories are being developed for the patient care biocontainment units, equipment is being dedicated to an in-unit or remote laboratory location that will be devoted to this unit. Scientifically validated standardized protocols for environmental disinfection have shown that fresh 10% bleach at a minimal contact time of 5 min is highly effective to inactivate Ebola virus and most likely the other high consequence viral pathogens. To reemphasize, laboratory safety practices are not new concepts for the laboratory with blood-borne pathogen (BBP) safety standards that are already a standard of practice in the laboratory, which include barrier protection, gloves, gowns, and goggles.

What evidence, guidance, and diagnostic tools are needed for future outbreaks with emerging infections?

Melissa Miller: Each outbreak is unique in terms of the type of guidance needed, data available to inform recom-

mendations, and the diagnostic tools desired. Nonetheless, with each new outbreak, we improve our readiness on both a national and local scale for the next emerging infectious disease. For example, the severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic took months to identify the infectious agent and make its viral sequence publicly available. At the time, this seemed astoundingly rapid compared to previous emerging infectious agents (e.g., HIV). The rapid availability of sequence data facilitated development of laboratory-developed tests (LDTs) and epidemiologic studies that informed an appropriate public health response. The laboratory protocols that many of our institutions developed for SARS were readily adapted in 2009 when we were faced with the influenza pandemic. The pandemic H1N1 (pdmH1N1) viral sequences were publicly available in weeks, which allowed for in silico analysis of FDA-cleared laboratory tests, development of LDTs, and submission and approval of Emergency Use Authorization (EUA) tests. Likewise, we drew upon the lessons learned from SARS and pandemic influenza to guide our preparedness for the Middle East respiratory syndrome coronavirus (MERS-CoV), and outbreaks with multidrug-resistant *Acinetobacter* helped inform our preparedness for carbapenem-resistant *Enterobacteriaceae* outbreaks.

However, the EVD outbreak was more challenging because most US laboratories did not have previous experience managing a highly virulent, BBP outbreak. But we do have extensive experience in working with BBPs and relied on our knowledge of transmission to guide our laboratory practices. Nonetheless, the highly virulent nature of the Ebola virus led to more fear and enhanced precautions since the risk associated with improper procedures or simple mistakes was increased. The laboratory needs associated with the next outbreak are unpredictable, but unifying needs for every outbreak are (a) rapid, consistent communication from public health and federal entities, (b) data-driven recommendations, and (c) adequate, sustainable funding to quickly mobilize local, regional, and national responses.

Sheldon Campbell: We need templates for risk assessment, reviewed and vetted by authoritative bodies. Guidance during evolving events tends to be fragmented and inconsistent, coming from multiple sources with different recommendations. I’m not sure there’s a cure for that; bright people working with limited data will arrive at disparate conclusions, but it’s rough on the folks trying to decide what to do. Regulatory support for ongoing preparedness is necessary. In particular, the Joint Commission has tremendous power to drive the agenda of health-care systems. Nothing happens without administrative support and resources, and absent financial incentives; regulatory support is essential. We also need a research agenda which includes laboratories. There are a tremen-

dous number of unique unanswered questions out there, particularly with regard to risks associated with laboratory systems and instrumentation.

What is the most important lesson for clinical laboratories from the recent Ebola epidemic?

Melissa Miller: One important lesson I learned both as a laboratory director and as a member of the American Society for Microbiology (ASM) Committee on Laboratory Practices is the need for timely, effective communication. Communication was critical in every aspect of EVD readiness planning. Reciprocal communication with public health colleagues, coordination of efforts among sections of the clinical laboratory, and discussions with a wide variety of services (including infection control, emergency preparedness, waste management, critical care, transport services, and shipping companies, among others) required clear, effective communication to organize a cohesive readiness plan.

Peter Iwen: Many important lessons were learned during the recent Ebola epidemic that were not originally anticipated. One lesson learned while caring for patients with EVD in the US was the critical requirement to have safety protocols in place to process and test specimens that potentially might have a high-risk pathogen. In addition, open lines of communication between in-house medical staff and external collaborators to include those at the jurisdictional public health laboratory (PHL) were essential. Individuals in the PHL can provide guidance on the screen assays available, provide for transportation of specimens from the medical facility to the PHL, and interact directly with the CDC laboratories when additional testing is required. Finally, although many laboratories have a program for the deposition of clinical specimens that might include decontamination or the archiving of excess clinical material, the “cradle to grave” concept of specimen tracking was recognized as an important issue that all laboratories needed to consider. The ability to determine where high-risk specimens have been handled in the laboratory, and to recognize individuals who may have come in contact with the specimen, was important to determine who may be at risk for a laboratory-acquired infection and the potential for community exposure. Ultimately, the lesson learned from the recent Ebola outbreak is that all laboratorians need to be prepared to handle any specimen that could potentially harbor a high-risk pathogen, that administrators need to be flexible and provide appropriate protocols to make sure that a safe environment exists for the laboratorians, and that the laboratory be able to provide support for optimal management in the care of the patient.

Sheldon Campbell: That it’s just one blasted thing after another; we can never be certain what’s in that tube, so continuous, minute-to-minute and day-to-day and month-to-month attention to standard precautions and continuous safety improvement is essential, not just when there’s a high-profile outbreak, but all the time. Like a sports team, we have to drill the fundamentals, whether or not we’re going to get to the Big Game.

Eileen Burd: EVD is extremely hazardous because of the high mortality, lack of proven therapeutics, and potential for transmission. Very early after our first patient arrived, it became obvious that in situations like this you have to be flexible. The course of EVD is remarkably varied and testing needs to be varied accordingly. Extra effort was focused on communication between the care providers and the laboratory. Our most severely ill patient required many of the features of intensive care and the dynamics and testing needs shifted, sometimes by the hour. Treating 2 patients at a time is different from treating only 1, and laboratory personnel had to plan to spend longer periods of time in the containment laboratory to accommodate the larger number of specimens. Throughout the care of each patient every team member needed to be able to respond to change and adapt quickly. Flexibility allowed our teams to adapt to the difficult task of caring for these patients more adeptly.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors’ Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: M. Miller, American Society for Microbiology.

Consultant or Advisory Role: C.-A.D. Burnham, Monsanto and Thermo Fisher Scientific; M. Miller, Cepheid.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: C.-A.D. Burnham, Cepheid, Accelerate Diagnostics, bioMérieux, and Theravance; M. Miller, Hologic and Lumindex Molecular Diagnostics.

Expert Testimony: None declared.

Patents: None declared.

Previously published online at DOI: 10.1373/clinchem.2016.265850
