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REVIEW

# Clinical Laboratory Biosafety Gaps: Lessons Learned from Past Outbreaks Reveal a Path to a Safer Future

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**SUMMARY** Patient care and public health require timely, reliable laboratory testing. However, clinical laboratory professionals rarely know whether patient specimens

contain infectious agents, making ensuring biosafety while performing testing procedures challenging. The importance of biosafety in clinical laboratories was highlighted during the 2014 Ebola outbreak, where concerns about biosafety resulted in delayed diagnoses and contributed to patient deaths. This review is a collaboration between subject matter experts from large and small laboratories and the federal government to evaluate the capability of clinical laboratories to manage biosafety risks and safely test patient specimens. We discuss the complexity of clinical laboratories, including anatomic pathology, and describe how applying current biosafety guidance may be difficult as these guidelines, largely based on practices in research laboratories, do not always correspond to the unique clinical laboratory environments and their specialized equipment and processes. We retrospectively describe the biosafety gaps and opportunities for improvement in the areas of risk assessment and management; automated and manual laboratory disciplines; specimen collection, processing, and storage; test utilization; equipment and instrumentation safety; disinfection practices; personal protective equipment; waste management; laboratory personnel training and competency assessment; accreditation processes; and ethical guidance. Also addressed are the unique biosafety challenges successfully handled by a Texas community hospital clinical laboratory that performed testing for patients with Ebola without a formal biocontainment unit. The gaps in knowledge and practices identified in previous and ongoing outbreaks demonstrate the need for collaborative, comprehensive solutions to improve clinical laboratory biosafety and to better combat future emerging infectious disease outbreaks.

**KEYWORDS** biosafety, disinfection, ethics, laboratory equipment, risk assessment, waste management, clinical laboratories, laboratory testing, personal protective equipment, specimen collection and transport

## INTRODUCTION

Patient care and public health in the United States depend on the reliability and quality of clinical laboratory testing, since laboratory tests account for the most frequently ordered diagnostic procedures in all patient encounters (1). Each year, it is estimated that one-third of the 500 million patient encounters in the United States within primary care or outpatient settings involve the ordering of one or more laboratory tests (1). Studies also suggest that at least 50 to 70% of today's medical decisions are influenced by laboratory test results (2, 3). Maintaining clinical laboratory services during an emerging infectious disease outbreak is essential to patient care.

Among the lessons learned from the 2014 Ebola outbreak were that policies and procedures need to be in place to safeguard health care workers and that consideration of Ebola should not delay diagnostic assessments, laboratory testing, and institution of appropriate care for other, more likely medical conditions (4). The 2016 outbreak of Zika virus presented another example of emerging infectious disease outbreaks that escalated to a public health emergency, and experts then suggested additional, new infections might appear in the not-too-distant future (5–7). In the midst of the Zika outbreak, the Department of Health and Human Services' Clinical Laboratory Improvement Advisory Committee (CLIAC), a federal advisory committee, recognized clinical laboratory biosafety as a "critical unmet national need" and called upon the U.S. government to substantially increase the amount of guidance, training, and outreach on biosafety to the clinical laboratory community (8). Therefore, strengthening biosafety management and preparedness in clinical laboratories, whose diagnostic work represents the tip of the spear against any disease outbreak in the United States, is of paramount importance for protecting the public's health. This has once again been reinforced by the COVID-19 pandemic that health care workers, laboratory personnel, and the public are grappling with (9). An in-depth discussion of the biosafety issues during the present pandemic is not the focus of this paper as we are in the midst of the pandemic at time of publication and a retrospective review is not

possible at this time. However, the gaps revealed during the Ebola outbreak continue to be relevant during the current pandemic.

In late 2014, during the height of the Ebola crisis in the United States, fears about safety in clinical laboratories had a direct impact on patient care. Unfortunately, many non-Ebola patients, who had symptoms, travel histories, or racial and ethnic backgrounds (10) that suggested they might have Ebola, suffered because there were concerns about handling specimens containing Ebola virus in diagnostic laboratories not designed as containment facilities. A Centers for Disease Control and Prevention (CDC) study showed that at least two persons, who tested negative for Ebola but had severely delayed diagnoses and treatment, died of other treatable causes (4). This study found several instances, reported by health departments or health care providers, where establishing alternative diagnoses were hampered or delayed due to Ebola-related infection control concerns. A subsequent study documented cases in which health care provider and laboratory concerns about risks for possible exposure to Ebola contributed to inadequate implementation of current malaria diagnostic and treatment guidelines, resulting in inappropriate practices in evaluation and management of patients (11).

In addition to a reluctance to test and treat patients whose symptoms seemed similar to Ebola patients, safety fears about Ebola led some commercial diagnostic laboratories in the United States to assert they would not process specimens from a patient who might have Ebola (11, 12). At about the same time, some laboratory equipment manufacturers recommended their instruments be incinerated after use with a specimen that came from a patient with Ebola, and refused to allow their technicians to service instruments that had been used with Ebola specimens (12).

During the Ebola outbreak response in the United States, wide discrepancies among the various guidelines for handling emerging infectious disease patients and their specimens resulted in confusion among health care workers (HCW), including laboratory professionals, about how to prepare and respond. For many, Ebola represented an "absolute risk" that transcended the duty to provide patient care (13). Confusion about how to protect themselves and their colleagues created ethical dilemmas for many health care and clinical laboratory professionals (13). Fortunately, this Ebola outbreak was limited to relatively few suspect patients in the United States (4), and state and national public health laboratories were able to handle the testing demands.

A well-established laboratory biosafety guidance in the United States is the CDC/National Institutes of Health's (NIH) *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), currently in its 6th edition (14). The BMBL focuses on biological research settings where the agent is almost always known before the work begins. This perspective differs substantially for clinical laboratory professionals, who generally do not know whether their specimens contain emerging disease or infectious agents. In addition, in contrast to diagnostic laboratories (15), research laboratories often work with agents in high concentrations and large volumes.

Recognizing these differences, a CDC-convened Biosafety Blue Ribbon Panel published the "Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories" in 2012 (15). While describing common hazards and providing guidance for safe work practices in diagnostic laboratories, it reinforced the paradigm that associates biological agents to biosafety levels. Both the BMBL and this publication indicate that work with Ebola should only occur in a biosafety level four (BSL-4) or maximum containment laboratory. Since most U.S. clinical laboratories operate at biosafety level two (BSL-2) (15), concerns about biosafety risks and possible exposure contributed, at least in part, to the reported reluctance and delays in providing laboratory testing to suspect Ebola specimens during the 2014 outbreak (4, 11, 12). However, testing a single specimen from a suspect patient, particularly a patient with an unknown—and possibly very low—likelihood of actually having Ebola virus disease (EVD), presents much different risks than working with Ebola in a research setting, perhaps in large volumes and high concentrations (13). Many clinical laboratories in 2014, both in the

**TABLE 1** Microbiologists and the disease they acquired during their research[c]

| Causal agent | Disease | Individual infected | Year |
|---|---|---|---|
| *Brucella melitensis* | Brucellosis | Florence Nightingale[a] | 1855 |
| | Brucellosis | Jeffrey A. Martson[a] | 1861 |
| | Brucellosis | Alice C. Evans[a] | 1922 |
| *Bartonella bacilliformis* | Carrion's disease | Daniel Alcides Carrión[b] | 1885 |
| | Carrion's disease | Ovidio García Rosell[a] | 1928 |
| | Carrion's disease | Maxime Kuczynski-Godard[a] | 1937 |
| *Vibrio cholerae* | Cholera | Louis Thuillier[b] | 1883 |
| | Cholera | Max von Pettenkofer[a] | 1892 |
| *Rickettsia prowazekii* | Epidemic typhus | Howard Taylor Ricketts[b] | 1910 |
| | Epidemic typhus | Stanislaus von Prowazek[b] | 1915 |
| | Rocky Mountain spotted fever | Thomas Bailey McClintic[b] | 1912 |
| | Rocky Mountain spotted fever | Henry Cowan[b] | 1924 |
| Yellow fever virus | Yellow fever | Eliju H. Smith[b] | 1798 |
| | Yellow fever | Jesse W. Lazear[b] | 1900 |
| | Yellow fever | James Carroll[a] | 1900 |
| | Yellow fever | Adrian Stokes[b] | 1927 |
| | Yellow fever | Hideyo Noguchi[b] | 1928 |
| | Yellow fever | Willian A. Young[b] | 1928 |
| EEE virus | Eastern equine encephalitis | Richard E. Shope[a] | 1959 |
| Lassa fever virus | Lassa fever | Jordi Casals-Ariet[a] | 1969 |
| | Lassa fever | Juan Roman[b] | 1969 |
| *Helicobacter pylori* | Gastric ulcer | Barry Marshall[a] | 1982 |
| SARS virus | Severe acute respiratory syndrome | Carlo Urbani[b] | 2003 |
| Ebola virus | Ebola virus disease | Antonina Presnyakova[b] | 2004 |
| *Yersinia pestis* | Plague | Malcolm Casadaban[b] | 2009 |

[a]Recovered from disease.
[b]Died from disease.
[c]Adapted from reference 18, which is published under an Attribution-NonCommercial–ShareAlike 3.0 Creative Commons License (http://creativecommons.org/licenses/by-nc-sa/3.0/).

United States and abroad, demonstrated they could appropriately mitigate those risks without relying on a maximum containment laboratory (16, 17). For an example of how one hospital accomplished this, see section "Real-life example of biosafety risk management—experience of a community hospital laboratory during an outbreak situation."

Issues around clinical laboratory biosafety are additionally complicated by the diverse nature of laboratories performing testing for medical care. These vary from national, state, and local public health laboratories, whose results are used for direct patient care (as well as disease surveillance and other public health and epidemiology purposes), to large national reference laboratories, to large and small hospital laboratories serving defined acute-care populations, to physician's office and waived-testing sites. Each of these serves different patient populations, performs different procedures with various risks, and has different levels of staffing and other resources. A mobile population and global food and other supply chains mean that disease can occur nearly anywhere. As such, smaller laboratories may be in a particularly difficult position. They can lack access to subspecialty expertise, and may have staff with multiple duties (such as microbiology testing and quality management or transfusion testing and laboratory safety) which can necessitate compromises in risk assessment and biosafety improvement practice.

Going forward in this document, "clinical laboratories" refers to laboratories whose primary mission is supporting direct patient care while "public health laboratories" refers to national, state, and local government laboratories tasked primarily with disease surveillance. We also distinguish between diagnostic laboratories, which may be either clinical or public health laboratories, and which perform testing for direct patient care, and research laboratories, which primarily develop new knowledge not used for direct patient decision making. Public health laboratories typically perform both research and diagnostic testing; in practice, all these distinctions necessarily blur.

This review demonstrates the complexity and unique aspects of clinical laboratories and shows the challenges and difficulties of applying some of the currently available biosafety guidance in clinical laboratories, especially during responses to emerging infectious diseases. These challenges also reflect the gap demonstrating how previously published work has primarily focused on academic and industrial research-based practices, and not adequately considered the realities and safety risks associated with clinical laboratory operations. This review does not intend to solve all the challenges associated with clinical laboratory biosafety; it is not a guidance document. Instead, it highlights the complexity of the issues and the need to identify strategies and resources to focus collective efforts of the clinical laboratory community, the laboratory safety community, and all stakeholders, to develop reliable, consistent guidance and garner support needed to improve clinical laboratory biosafety.

Clinical laboratory safety has a direct impact on patient safety and public health, and thus deserves serious attention. The intent of this review is to characterize biosafety gaps and challenges in clinical laboratories and describe needs and opportunities for improvement. Clinical laboratories are unique environments that use instruments, procedures, and workflows not typically associated with research or academic laboratories. Clinical laboratory biosafety is different from research laboratory biosafety, clinical infection prevention and control, or general safety. The risks are different even if, occasionally, the biological agents are the same. In addition, clinical laboratories must always recognize their direct and immediate role in patient care—a concern that research laboratories generally do not need to consider. Not only must clinical laboratories carefully weigh their multiple needs, including the safety of their personnel and provision of patient care, but they must also recognize the inextricable link between laboratory safety and quality. Achieving accurate and reliable diagnostic test results ultimately depends on creating a system that can effectively manage risks to laboratory workers, the health care facility, the general population, animals, and the environment (4).

## BACKGROUND

### Biorisks in Clinical Laboratories

Since before the microbiological etiology of human illnesses was established, investigators who worked on infectious diseases often acquired them, due to accidental or voluntary exposure, in the course of their research (18, 19) (Table 1). Indeed, the discovery of a new etiologic agent was frequently followed shortly thereafter by the description of a laboratory-acquired case (19). Substantive studies on microbiological safety, including the potential risks of various laboratory procedures, date back to the 1950 (20). With the development of laboratory testing to support clinical care, and the evolution of clinical laboratories, there was recognition that workers in those laboratories were at risk for exposure to infectious pathogens. A review of laboratory-acquired infections (LAIs) published in 1979, with data culled from publications and derived from mail surveys, described infections by bacteria, viruses, fungi, and parasites. Although a lack of data for those who were not infected makes assessing the overall risk difficult, in the cases assessed in that review, approximately 34% (from 1,342 cases analyzed in 1951) and 17% (from 3,921 cases analyzed in 1976) of total LAIs were associated with clinical rather than research laboratories (21). These LAIs were caused by a wide variety of pathogens, with hepatitis particularly prevalent among clinical laboratory staff.

Exposure to infectious diseases represents a substantial public health burden, both in the United States and worldwide. In a 2017 study that did a global assessment of the incidence, prevalence, and years lived with disability, it was found that an estimated 43.2 million years living with disability were due to infectious diseases (22). Globally among HCW, it has been estimated that in the year 2000 there were 926,000 hepatitis C virus (HCV), 2,100,000 hepatitis B virus (HBV), and 327,000,000 human immunodeficiency virus (HIV) exposures due to percutaneous injuries; these exposures

resulted in 16,000 HCV, 66,000 HBV, and 1,000 HIV infections (23). In addition, bacterial and fungal (e.g., those caused by *Brucella* spp., *Neisseria meningitidis*, and *Coccidioides* spp.) infections represent a significant risk for acquired infection (24). Of the top three blood-borne pathogens (HIV, HBV, and HCV), postexposure prophylaxis, hepatitis vaccination, and low transmission rates, respectively, have helped mitigate the risks of exposures, but gaps remain, particularly for HCV (25, 26).

In the nonmicrobiology sections of clinical laboratories, a major issue may be a lack of awareness about possible infectious agents that a given specimen may contain and then working with little attention to risk for infection (15). This misunderstanding could be particularly problematic in laboratories that develop new testing procedures, such as molecular and biochemical assays, without fully considering the biorisks associated with the specimens, or in point-of-care (POC) testing settings where staff performing these tests may not have adequate training in laboratory procedures and biosafety practices (27).

**Laboratory Biosafety Guidelines and Requirements**

In 1974, CDC published "Classification of Etiologic Agents on the Basis of Hazard," which introduced concepts such as levels of containment and agent risk groups; with modifications, this classification of pathogens corresponds to those used today (28). Also in 1974, NIH published "National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses," which established three levels of containment based on a risk assessment for virally induced cancer in humans (29). In 1976, NIH published "Guidelines for Research Involving Recombinant DNA Molecules," which described the microbiological practices, equipment, and facility safeguards that correspond to the four levels of physical containment (30). In 1978 in the United Kingdom, a laboratory-associated outbreak of smallpox resulted in the death of Janet Parker, the last human to die of the disease. Her death led to a government inquiry that focused attention on safety practices in laboratories that conducted research on dangerous pathogens (31). This event arguably catalyzed the development of comprehensive guidance for laboratory biosafety. The World Health Organization (WHO) in 1983 (30) and CDC/NIH in 1984 (32) each published guidelines for laboratory safety. These guidelines lacked regulatory enforcement but established an evolving practice for biosafety. Notably, these foundational biosafety guidance documents primarily focused on biological research settings, where the safety risks were perceived to be most significant.

Starting in the 1980s, the HIV pandemic brought additional awareness to occupationally acquired infections, including clinical laboratory staff. Between 1985 and 2013, 16 confirmed and 21 possible HIV infections occurred in laboratory workers; nurses had 24 confirmed and 37 possible cases (33). In 1989, there were 1,304,880 registered nurses and licensed practical nurses, but only 140,730 medical technologists and medical laboratory technicians (34–36). When counting both confirmed and possible cases, a comparison between groups found laboratory workers acquired 26.3 HIV infections per 100,000, while nurses only acquired 4.7. Thus, laboratory workers' risk of accidental infection was more than five times higher than nurses. One explanation for this difference is that clinical laboratory professionals may handle hundreds of patient specimens a day, which may contain one or more infectious agents.

In 1985, CDC introduced "Universal Precautions," which were aimed at preventing the transmission of blood-borne pathogens due to exposure to blood and other potentially infectious materials (37–42). The Occupational Safety and Health Administration (OSHA) then promulgated a regulatory standard in 1991 to eliminate or minimize occupational exposure to blood-borne pathogens (43). In 1996, CDC's "Guideline for Isolation Precautions in Hospitals" combined Universal Precautions and previous recommendations on body substances isolation, now referred to as "Standard Precautions." The 1996 Guideline also introduced three "Transmission-Based Precautions," airborne, droplet, and contact. These updated guidelines apply to the care of all patients, irrespective of their disease state, or the potential route of exposure to the HCW (42). The OSHA blood-borne pathogen standard was revised in 2000 to require employers to

use controls to eliminate or minimize exposure to contaminated sharps (44). As a result of these governmental efforts, confirmed occupationally acquired HIV infections dropped precipitously from their peak of eight cases in 1992 to only a single case reported between 2000 and 2013 (33).

The events of September 11, 2001 and the subsequent anthrax attacks in the United States focused new attention on laboratory biosafety, and especially the new field of "laboratory biosecurity." The federal Select Agent Rule was revised in 2002 to require any facility that possesses select agents to register with the U.S. government, and to implement measures to ensure the security of those agents. In addition, the revised Select Agent Rule cited the BMBL, and set an expectation that select agent laboratories should follow that guidance (45). In 2012, the Select Agent Rule was modified to establish security standards for the select agents and to reduce the number of agents on the overall list. The Select Agent Rule was again modified in 2016 to add *Bacillus cereus* biovar anthracis. As of 2018, 253 entities were registered with the Federal Select Agent Program (46).

Despite the notable reduction in the number of occupationally acquired HIV infections in the 1990 and 2000, concerns remained that laboratory exposures occurred more than was generally suspected (33, 47). Due to the use of retrospective reviews, pathogen-specific studies, volunteer reporting, anecdotal reporting, and the lack of an official surveillance mechanism, data on exposures and LAIs remains elusive or incomplete (33, 48). This makes it impossible to accurately evaluate how best to prevent accidents, exposures, and infections in a clinical laboratory setting. Although in the 2012 "Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories" a recommendation was made for the federal government to create a "central site for surveillance and nonpunitive reporting of laboratory incidents/exposures, injuries, and infections" (15), such a surveillance system still does not exist today. Furthermore, a 2018 study by The National Academy of Sciences also identified the need for increased occupational safety and health surveillance for all workplaces (49). Recently, the American Biological Safety Association International (ABSA) created a searchable database that tracks LAIs that have been published in the literature (50). However, the number, environments, and characteristics of unpublished incidents nationwide still largely remain unknown.

Since 2012, laboratory biosafety has remained in the national consciousness, notably the debate over the appropriateness of research on gain-of-function of avian influenza, the shipment of improperly inactivated anthrax from the Army's Dugway Proving Ground, the discovery of smallpox virus at the NIH campus, and the two separate laboratory incidents involving *Bacillus anthracis* (the etiological agent of anthrax) and Ebola virus that took place at CDC in 2014 (51–53). Federal responses to these events have largely focused on high-containment (i.e., biosafety level three [BSL-3] or BSL-4) research facilities that work with select agents. In 2014, the White House asserted the government's "responsibility to ensure that infectious disease research in the United States is conducted safely and securely," and initiated a "safety stand-down" and an "immediate sweep" of federal facilities to identify select agents (54). A Federal Experts Security Advisory Panel (FESAP) was rechartered to evaluate approaches to enhance biosafety and biosecurity at high-containment laboratories that possess, use, or transfer select agents; a plan to implement the FESAP's recommendations was issued in 2015 (55). But those recommendations largely excluded consideration of diagnostic laboratories. This perspective is also evident in an extensive series of reports on the safety and oversight of high-containment laboratories that the U.S. General Accountability Office published between 2009 and 2017 (56).

The nation's public health laboratories occupy a unique position in that most perform clinical and/or diagnostic testing and are subject to the Clinical Laboratory Improvement Amendments (CLIA) (57), and many of them form the backbone of the Laboratory Response Network (LRN), which is designed to respond to novel strains of disease, natural disasters, chemical spills, foodborne outbreaks, and other health

**TABLE 2** Clinical Laboratory Improvement Amendments of 1988 (CLIA) Requirements Related to Laboratory Safety

| Regulation | Description |
|---|---|
| Facilities | |
| §493.1101 (a) (1) | The laboratory must be constructed, arranged, and maintained to ensure the following: the space, ventilation, and utilities necessary for conducting all phases of the testing process. |
| §493.1101 (a) (2) | The laboratory must be constructed, arranged, and maintained to ensure the following: contamination of patient specimens, equipment, instruments, reagents, materials, and supplies is minimized. |
| §493.1101 (b) | The laboratory must have appropriate and sufficient equipment, instruments, reagents, materials, and supplies for the type and volume of testing it performs. |
| §493.1101 (c) | The laboratory must be in compliance with applicable Federal, State and local laboratory requirements. |
| §493.1101 (d) | Safety procedures must be established, accessible, and observed to ensure protection from physical, chemical, biochemical, and electrical hazards, and biohazardous materials. |
| Maintenance and function checks | |
| §493.1254 (a)(1)(2) | The laboratory must perform and document: (i) Maintenance as defined by the manufacturer and with the frequency specified by the manufacturer. (ii) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be within the manufacturer's established limits before patient testing is conducted. |
| Laboratory director responsibilities | |
| For moderate-complexity testing | |
| §493.1407 (e) (2) | The laboratory director must ensure that the physical plant and environmental conditions of the laboratory are appropriate for the testing performed and provide a safe environment in which employees are protected from physical, chemical, and biological hazards. |
| §493.1407 (e) (10) | Employ a sufficient no. of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report tests results in accordance with the personnel responsibilities described in this subpart. |
| §493.1407 (e) (11) | Ensure that prior to testing patient's specimens, all personnel have the appropriate education and experience, receive the appropriate training for the type and complexity of the services offered, and have demonstrated that they can perform all testing operations reliably to provide and report accurate results. |
| §493.1407 (e) (12) | Ensure that policies and procedures are established for monitoring individuals who conduct preanalytical, analytical, and postanalytical phases of testing to ensure that they are competent and maintain their competency to process specimens, perform test procedures and report test results promptly and proficiently, and whenever necessary, identify needs for remedial training or continuing education to improve skills. |
| For high-complexity testing | |
| §493.1445 (e) (2) | The laboratory director must ensure that the physical plant and environmental conditions of the laboratory are appropriate for the testing performed and provide a safe environment in which employees are protected from physical, chemical, and biological hazards. |
| §493.1445 (e) (11) | Employ a sufficient no. of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report tests results in accordance with the personnel responsibilities described in this subpart. |
| §493.1445 (e) (12) | Ensure that prior to testing patient's specimens, all personnel have the appropriate education and experience, receive the appropriate training for the type and complexity of the services offered, and have demonstrated that they can perform all testing operations reliably to provide and report accurate results. |
| §493.1445 (e) (13) | Ensure that policies and procedures are established for monitoring individuals who conduct preanalytical, analytical, and postanalytical phases of testing to ensure that they are competent and maintain their competency to process specimens, perform test procedures and report test results promptly and proficiently, and whenever necessary, identify needs for remedial training or continuing education to improve skills. |

emergencies (58). There are typically between 120 to 130 reference laboratories in the LRN network, and most of those have additional containment capacity (generally BSL-3) and are registered with the Federal Select Agent Program (58). To address the concerns about biosafety that were raised during the Ebola outbreak of 2014, CDC provided funding during 2016 to 2018 (including the Public Health Emergency Preparedness [PHEP] cooperative agreement) to enhance laboratory biosafety and biosecurity in state, local, and territorial public health laboratories (59). This funding enabled the recruitment of biosafety specialists and increased the amount of biosafety resources and training across the public health laboratories in the United States during the 2-year time frame. Aside from this temporary federal assistance, the nation's public

health and clinical laboratories in the United States have received limited specific support to strengthen laboratory biosafety (60).

The sections that follow describe the unique challenges that clinical laboratories have in applying currently available biosafety guidance to their operations. Further, the sections below identify specific gaps that remain to be addressed by the clinical laboratory community, the laboratory safety community, government regulators, and policy makers.

**Current Regulatory Oversight for Biosafety in Clinical Laboratories**

More than 260,000 clinical laboratories in the United States are certified under the CLIA regulations (61), although approximately 75% of these laboratories are subject to limited regulatory oversight since they test under a CLIA Certificate of Waiver and do not undergo routine inspections. The CLIA regulatory standards that apply to the other 25% of laboratories focus on the quality and reliability of clinical laboratory tests, and they include only general requirements for laboratory safety (57). The focus of CLIA inspections, during which a laboratory's regulatory compliance is reviewed by CLIA surveyors or inspectors, therefore, has also been laboratory quality rather than biosafety. Although CLIA requires that a laboratory's environment must be appropriate for the testing performed, and that personnel must be protected against hazards, CLIA does not refer to biosafety specifically or specify how laboratory safety systems should be designed or implemented. Table 2 lists the sections of CLIA regulations that include requirements for general laboratory safety. CLIA regulations hold the laboratory director responsible for providing a safe environment in which employees are protected from physical, chemical, and biological hazards, and for ensuring appropriate policies and procedures are in place, including the requirements for performing competency assessments of personnel. Table 2 also lists general CLIA requirements to ensure that laboratory personnel are following safety procedures, such as the safe use of equipment and safe handling of specimens when testing or otherwise handling potentially infectious materials. However, interpretation of these general safety requirements is subject to the expertise of laboratory professionals and the surveyors who conduct the inspections. As a result, clinical laboratory safety may not be applied consistently on a national basis.

As required by CLIA, surveyors inspect clinical laboratories every 2 years (62) and these inspections may be performed by the Centers for Medicare & Medicaid Services (CMS) or an accreditation organization approved by CMS as having standards that meet or exceed the CLIA regulations. Clinical laboratories in two states, New York (except for physician office laboratories) and Washington, are exempt from meeting CLIA regulations, as they are subject to state licensure requirements approved by CMS as meeting or exceeding CLIA regulations. Regardless of which agency or organization inspects clinical laboratories for quality purposes, ensuring the safety of laboratory and health care personnel is a critical component of laboratory testing quality and thereby patient safety (4, 11).

The on-site inspections conducted by CMS or state surveyors serve to ensure clinical laboratories have policies and procedures that comply with CLIA and state-mandated regulations, including those relating to laboratory safety. The CMS "State Operations Manual: Appendix C—Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services" provides guidance to surveyors and laboratories with respect to compliance with the CLIA safety requirements (63). Examples of the safety-related issues that surveyors are expected to review include checking for safety training records for the laboratory staff, maintenance stickers on chemical fume hoods and biological safety cabinets (BSCs), appropriately designated trash receptacles, proper disposal of biological or chemical waste, and the use of approved sharps containers (63). Surveyors also are expected to document observations such as staff not wearing gloves, storage of food in a laboratory refrigerator intended for specimens or reagents, or failure to perform testing of infectious agents at the appropriate biosafety level. If a laboratory is found to be out of compliance with CLIA safety requirements, the

**TABLE 3** Example of infection control precautions

| Precaution | Use | Requirement | Example infections/conditions that require precautions |
|---|---|---|---|
| Contact precautions | Patients known or suspected to have serious illnesses easily transmitted by direct patient contact or by contact with items in the patient's environment | Gloves; gown | *Clostridioides difficile*; gastroenteritis-rotavirus; human metapneumovirus |
| Droplet precautions | Barrier to stop infections spread by large (>5 $\mu$m), moist droplets generated when coughing, sneezing, or speaking | Contact precautions; well-fitting mask; eye protection | Mumps (infectious parotitis); *Mycoplasma* pneumonia |
| Airborne precautions | Patients known or suspected to have serious illnesses transmitted by airborne droplet nuclei | Contract precautions; droplet precautions; N95 mask; isolation room (in hospital) | Pulmonary or laryngeal tuberculosis; severe acute respiratory syndrome (SARS); smallpox |

laboratory is required to take and document corrective action. However, as surveyor trainings generally reflect the quality focus of the CLIA regulations, the extent to which safety-related policies, procedures, and practices in clinical laboratories are reviewed in conjunction with the inspections may vary widely depending on the surveyors' experience and expertise in laboratory safety and risk assessment.

Several of the deemed status-accrediting organizations, such as the College of American Pathologists (CAP) and The Joint Commission on Accreditation of Healthcare Organizations (Joint Commission), have included safety and biosafety-related requirements as part of their accreditation programs. The CAP accreditation program includes a Laboratory Safety checklist in addition to safety and biosafety requirements for laboratories in their General Laboratory and Microbiology checklists (64). The Joint Commission has accreditation programs for both the hospital and the laboratory (www.jointcommission.org), which include standards for biosafety and biosecurity, risk assessments relating to infection control and emergencies, as well as evaluation of environmental risks associated with equipment, space, or facilities (65). However, while the accreditation standards of these and other organizations may be more specific for laboratory safety than CLIA requirements, they are not uniform across all programs or all Certificate of Accreditation laboratories, since each accrediting organization has the latitude of establishing requirements that are equal or more stringent than CLIA. In addition, because laboratory inspections by accrediting organizations are generally peer-based, the extent to which adherence to the safety requirements is reviewed also varies widely depending on the peer inspectors' expertise in laboratory safety or biosafety.

CLIA also mandates that laboratories must be in compliance with applicable federal, state, and local laboratory requirements. These include safety regulations administered by OSHA, NIH, the Environmental Protection Agency (EPA), the Department of Transportation (DOT), the Department of Health and Human Services, and other federal, state, and local agencies. Some of the topics covered under these regulations and discussed later include the Blood-borne Pathogens Standard, personal protective equipment (PPE), hazardous waste management and disposal, transportation of hazardous materials (including infectious substances), occupational exposure to hazardous chemicals in the laboratory, hazard communication, recombinant DNA, and select agent regulations. On occasion, CLIA surveyors may observe or obtain information regarding potential safety violations that are not applicable under CLIA but are subject to OSHA or other regulations. If this occurs, the surveyors are required to notify CMS and the appropriate state or local authority and may notify other applicable federal agencies.

In summary, while clinical laboratory testing is highly regulated in the United States, national regulations specific for clinical laboratory safety are limited. The majority of laboratories, those operating under a Certificate of Waiver or a Certificate of Provider-Performed Microscopy, are not routinely inspected and therefore lack an external mechanism to monitor the quality and safety of their testing practices.

Overall, there is a lack of uniformly implemented and routinely monitored systems in place for laboratory safety and biosafety nationwide.

## ISSUES COMMON ACROSS THE CLINICAL LABORATORY

Clinical laboratories are at the vanguard when it comes to infectious diseases and outbreaks. They are charged with identifying the etiological agent that causes the disease as well as maintaining vigilance to recognize an outbreak (66). The biosafety concerns of clinical laboratories are distinct from research or public health facilities because each specimen presents an unknown hazard and the suspected diagnosis is often not shared with the laboratory. Thus, there are significant threats to public health when clinical laboratories cannot safely process specimens from patients with, or suspected to have, highly infectious diseases.

### Biosafety Gaps in the Clinical Laboratory Testing Process

This section reviews the biosafety-related issues in the total testing process, consisting of the preanalytic, analytic, and postanalytic phases in clinical laboratory testing and services. Analytic issues are discussed in more depth in the section "Issues in Specific Areas of the Clinical Laboratory." Risks of exposure and other biosafety challenges are discussed with an emphasis on issues related to patient specimens from collection to completion of testing in the laboratory, also referred as "the specimen management chain."

**Biosafety risks in the preanalytic phase.** The preanalytic phase of clinical laboratory testing usually encompasses the collection, handling, and transport of patient specimens to the testing site after the test selection and ordering by a health care professional. While laboratories are responsible for providing guidance (written, electronic, and oral) to nonlaboratory personnel (nurses, medical assistants, nurse practitioners, physician assistants, and physicians) regarding the collection and transport of specimens, such guidance is primarily focused on ensuring specimen adequacy and integrity. Laboratories often lack direct control over how specimens are collected and transported to the laboratory, may have difficulties in achieving standardized procedures for specimen collection, and rarely know whether and what infectious pathogens or other hazards might be present in the specimens (67). Therefore, the preanalytic phase is particularly challenging to the laboratory in assessing not only the quality but also the safety aspects, including assessing the risk of exposure of personnel, the patient, and the environment to hazardous materials such as infectious agents, toxins, and chemicals (62).

**(i) Specimen collection.** Laboratories typically adhere to Infection Control Precautions as specified in guidelines provided by the institutional Infection Prevention and Control Program (Table 3) (68). For emerging and highly contagious pathogens, additional precautions may evolve and be required (69). Free-standing and independent laboratories, however, may lack this level of guidance.

It is essential that hospitals receiving patients at risk for emerging infections be able to identify and place them under appropriate management and precautions (70–72). Specimen collection is the first phase in which laboratory biosafety risk occurs because some specimen collection processes can involve high-risk activities, such as being in the presence of a patient harboring an infectious agent who is actively coughing, sneezing, vomiting, bleeding or otherwise producing bodily fluids. CDC recommends when collecting specimens from potentially infected patients, to adhere to Standard Precautions and, if necessary, Transmission-Based Precautions (42, 70). In these situations, precautions beyond those routinely taken may be needed and should be considered and delineated in risk assessments and procedures developed by either the health care system, the hospital, or the laboratory (70). For rare, high-risk pathogens, special labeling is frequently done, but in widespread outbreaks, Standard Precautions becomes the model, with additional mitigation as risk assessment dictates. It is unclear how practical additional mitigation will be if a high-prevalence pathogen requires extensive precautions. Ideally, involving laboratory personnel in hospital-wide team

**TABLE 4** Example safety risk assessment for collection and transport of a respiratory specimen

| Process | Risk(s) identified | Approach(s) to mitigation |
|---|---|---|
| Specimen Collection | Infection of collecting staff | Proper use of personal protective equipment (PPE) and engineering controls; proper patient identification and placement with appropriate precautions; adherence to isolation precautions and routine hand hygiene; use of proper collection procedure(s); access to specimen collection guidelines and educational material |
| | Contamination of environment | Proper patient identification and placement with appropriate precautions; adherence to isolation precautions and routine hand hygiene; attention to environmental cleaning protocols |
| | Contamination of specimen container, paperwork, or transport bag | Decontamination of container after collection; placement of secondary container (e.g., bag) outside of isolation area; use of secondary containers (bags or shipping containers depending on nature of transport) |
| Specimen Transport | Loss of specimen in transit | Appropriate tracking mechanisms |
| | Spillage from primary container | Attention to tight-fitting lids and tops; appropriate choice of container for specimen types; avoidance of leak-prone designs; utilization of durable leak resistant secondary container |
| | Disruption of primary container and bag with widespread contamination | Avoidance of pneumatic tubes for high-risk specimens; for shipping via courier or public carrier, secondary shipping containers meeting international guidelines |

discussions around labeling specimens from patients under investigation (PUI) and in removing such designations and labels as the clinical situation evolves improves communication and safety of the team.

**(ii) Specimen transport.** In order to protect patients, staff, and the environment, WHO provided recommendations for personnel who work with specimens, which include but are not limited to: packaging specimens appropriately for transport, decontaminating spills, cleaning and disinfecting working areas for future use, decontaminating nondisposable equipment/materials according to protocols, placing waste in leak-proof biohazard bags to ensure safe final management of waste, and protecting cleaning/decontamination personnel using gloves with a thick rubber protective coat (73).

(*a*) *Pneumatic tube transport.* Many institutions have policies to determine if a specimen should be transported by manual delivery or is eligible for transport through a pneumatic tube system (if present). This information can usually be found in the guidelines from each institution's Department of Infection Prevention and Control (74). The major concern in transporting clinical specimens, blood, or medications in a pneumatic tube system is leakage into the carrier component of the system (via container leak or breakage) and the potential for introduction into the tubing system, which can result in the spread of material through the tube system, contamination of the building or environment, and ultimately the exposure of personnel to hazardous material. As part of mitigating these risks, carrier inserts can be utilized to provide a "soft delivery" of the carrier as a means to lower the likelihood of breakage and leakage. OSHA recommends padded carrier liners and specifically designed pouches to protect transport in order to maintain the integrity and containment of specimens (75, 76). Additional measures to reduce risk may include: opening carriers in a BSC, having laboratory personnel wear gloves when opening pneumatic tube carriers that contain patient specimens, decontaminating the outside of tube carriers before returning them to patient-care areas, and decontaminate, according to manufacturer's instructions, the inside of the carrier if a leak occurs in the specimen container (77).

The Clinical and Laboratory Standards Institute (CLSI) provides guidance regarding clinical specimens transported via a pneumatic tube system (77). This guidance recommends that for specimens transported via pneumatic tube, the primary and secondary

containers should be tested and shown to be leak-proof under the conditions present in the pneumatic system. If a spill or leakage occurs, it is recommended to decontaminate the container and affected surfaces according to the system manufacturer's instructions. CLSI recommends institutions establish a policy to identify specimens that should never be transported through the pneumatic tube system, for example, specimens of increased volume, irreplaceable specimens (e.g., cerebrospinal fluid, biopsy specimens), and flammable materials (77). During the Ebola outbreak, CDC recommended against pneumatic-tube transport of specimens from PUI (78).

(*b*) *Off-site transport*. Biological materials that require transfer to off-site location(s), defined as transport in commerce to another location by aircraft, rail, highway, or vessel, pose special risks and are subject to regulatory requirements (79–81). Some best practices for shipping and transport of clinical specimens are important for biosafety, as well as preservation of specimen integrity and fit-for purpose (such that specimen integrity is maintained to prevent compromising downstream purpose[s]). These practices include cold chain and chain of custody procedures and documentation, use of reliable couriers and vendors, and, in particular, good communication between the senders and recipients of specimens. There is a regulatory distinction between specimens that might, by virtue of being from a PUI, contain high-risk pathogens and specimens that are known to contain such pathogens. The line between these cases, both scientifically and practically, is indistinct.

In discussing these activities and potential sources of exposure within the specimen management chain, the importance of performing formal risk assessments of each procedure and the development of a risk-based biosafety plan are also highlighted. Table 4 is an example of a safety risk assessment associated with the collection and transport of a respiratory specimen (sputum). Further discussion on risk assessment in clinical laboratories is provided under the "Biorisk Management" section.

**Biosafety risks in the postanalytic phase: specimen storage, retrieval, and archiving.** Specimen storage, retrieval, and archiving are postanalytic activities that are part of the specimen management chain. Specimens may be stored, retrieved for additional testing, and then either destroyed or archived for continued retention. Improperly stored specimens pose a risk to the safety of personnel and the environment and may compromise the quality of specimens resulting in erroneous or misleading test results.

Materials in the laboratory include primary specimens, subspecimens (aliquots), and processed derivatives (products) that may be stored in the laboratory or transferred to other locations. It has been recommended by the Association of Public Health Laboratories (APHL) that laboratories develop and implement procedures that specify, in detail, how different types of specimens and products should be handled and stored, to help minimize risk to personnel (82).

There is risk for exposure to laboratory personnel during retrieval of specimens from storage (15) or from packages shipped from other locations for retention (80). While DOT Hazardous Materials Regulations dictate the precautions required to reduce risks to personnel shipping/receiving specimens that may contain hazardous materials, they do not address specimen storage or retrieval activities (80).

The following areas, along with risk assessment and mitigation considerations, are discussed in this section: storage conditions and space; inventory controls: tracking and retention; and preparedness and emergency planning. The risks associated with storage of specimens and products related to the Surgical Pathology Laboratory, including the potential for incomplete inactivation of some agents by fixation is addressed in the section "Anatomic Pathology."

**(i) Storage conditions and space.** (*a*) *Storage containers*. The CDC-convened Biosafety Blue Ribbon Panel found that potential risks associated with specimen containers during storage and retrieval of specimens include breakage, leakage, and contaminated external surfaces (15). Preventive measures include choosing the appropriate containers for storage conditions, correct size to avoid overfilling, container materials compatible with the

storage temperature based on the specifications of manufacturers for plastic packaging (avoiding glass containers when possible), leak-proof closures, seals compatible with the storage temperature and conditions, and routine disinfection of the exterior of containers prior to storage to protect handlers retrieving specimens. When shipping specimens, hazardous material regulations mandate the use of leak-proof durable secondary containers, sufficient packaging materials to protect the integrity of containers during shipping, and maintaining the required temperature. Establishing good communication between senders and recipients, along with chain of custody processes (80), can also help mitigate risks associated with transport of potentially hazardous biological materials.

(*b*) *Storage temperature.* Laboratories have guidelines for required retention periods and appropriate storage temperature and duration for different types of specimens to maintain stability of analytes. Some specimens can be stored for short periods at 4°C but require freezing at lower temperatures for longer storage. Uncontrolled or unscheduled thawing of frozen specimens may require additional precautions as there may be unrecognized leakage, contamination, and risk to anyone who accesses or retrieves from the storage area, especially if the integrity of specimen containers is compromised (83, 84). Several options used by clinical laboratories to maintain stable storage conditions for specimens include: temperature monitoring, equipment maintenance schedules, back-up equipment in case of breakdown, and use of liquid nitrogen units for long-term archiving (85, 86).

(*c*) *Storage space.* An important consideration for laboratory safety (and management) is the availability of sufficient and appropriate storage space for short-term and long-term retention of specimens. Clean, well-lit, and well-organized storage units and areas, such as walk-in units or long-term archiving locations, can improve safety and lessen potential mistakes during retrieval.

Restricting access to patient specimens is an important safety consideration. CDC recommends locating specimens away from high traffic areas, separating specimen storage from frequently accessed reagents, and availability of lockable secure storage units when needed (10).

**Inventory controls: tracking and retention.** Informatics systems such as Laboratory Information Management Systems (LIMS) that generate labels with unique identifiers, assign a storage location (room, unit, shelf, box, and box position), and securely link specimens to case information can track specimens from draw to disposal. It may be helpful to pretest labels for compatibility with temperature and storage conditions, as some materials (specifically the adhesives) are not compatible with low temperatures and can separate from the containers during storage. The resulting unlabeled specimens may need to be destroyed, as specimens with unknown content pose a biosafety risk. Tracking stored subspecimens and derivatives can be challenging if the aliquots and derivatives (nucleic acid, cells, isolates) are not assigned and labeled with unique identifiers that unequivocally link them to the original parent specimen. For large volume specimen storage and archiving, quality audits are beneficial to ensure that locations indicated in the database (or LIMS) match the physical location of specimens, to facilitate efficient and accurate retrieval. Automated systems are available that can perform all storage functions, including recapping and retrieval using barcoded information. However, there is insufficient information about the risks associated with automated storage systems for infectious specimens (87).

In addition to accurate tracking and retrieval of specimens, inventory controls may be critical when, based on new information (test results or pathogen identification), all remaining specimens, subspecimens, and products related to a patient need to be quickly identified, removed from an existing location, and transferred to higher containment. In one documented instance, poor inventory controls coupled with poor housekeeping practices in a storage area resulted in hazardous, misplaced, and unaccounted for specimens that were left behind when a laboratory moved to a new location (53).

Specimen management includes regularly scheduled inventory audits for removing (culling) specimens that have exceeded their usefulness, and retention requirements to free up valuable space and reduce risk; this practice can benefit many laboratories

when included in standard operating procedures (SOPs). Useful information on the retention periods for different specimen types can be found on APHL's website (82).

**Preparedness and emergency planning.** Laboratory contingency plans can have measures to ensure that stored specimens will not be compromised due to loss of power or equipment failure, and include plans for adequate future storage and archiving capacity (88, 89). When collection and testing of specimens occur in low resource settings, as may happen in some outbreaks, contingency planning for storage is even more critical, as such locations may not have reliable, uninterrupted power supply or access to adequate inventory management systems for tracking specimens (90). Proactive planning for natural disasters may also be a concern. For example, specimen archiving is often located on basement floors that could be vulnerable to flooding, which could result in loss of valuable and irreplaceable specimens and pose biosafety risks for emergency and cleanup personnel.

An example of an often-encountered gap in the implementation of emergency plans for specimen storage is availability of backup equipment (91). Cold storage or freezer space intended to serve as backup in case of equipment failure is often repurposed for routine use due to storage space constraints. This results in urgent and often chaotic scrambling for alternative space to transfer affected specimens in case of equipment failure, creating potentially hazardous situations such as dropped or "lost" specimens, partial thawing, and disruption of inventory tracking procedures.

Some laboratories have developed biosafety and preparedness plans, SOPs, and training to address where specimens will be stored in case of outbreaks or new emerging disease situations, as well as how alternative secure storage options will be identified (92). These SOPs can include procedures for the safe transfer and shipping to public health, reference, and specialty laboratories or approved archiving locations. In addition, biosafety plans and SOPs often include procedures for sequestration of specimens suspected or confirmed to contain high-impact pathogens, and define exceptions to standard storage, retrieval, and retention policies to facilitate safety. When such plans and procedures are not in place or cannot be safely executed, patient specimens may need to be destroyed immediately after testing is complete.

**Planned archiving for future laboratory needs.** Archiving specimens beyond testing may not be a primary concern for clinical laboratories. However, including unused or residual specimens in the laboratory's retention plans, especially unique specimens obtained during outbreaks, can be useful toward building future reference material(s) (93, 94). Communication with public health laboratories may be helpful in this regard. In addition to the need for reference materials, access to patient specimens is critical and often limiting for development of new or improved tests and their validation, or for the development of new vaccines and other prevention and treatment methods. In the absence of proactive plans, or needed infrastructure for archiving in low resource settings, extremely valuable specimens could be destroyed to ensure biosafety. Following the initial response to the 2014 Ebola outbreak, tens of thousands of specimens were shipped from West Africa to other countries for safekeeping, but an unknown and likely greater number of specimens were destroyed (95, 96).

**Biosafety gaps and future needs.** Activities conducted within the specimen management chain, if not performed correctly, are potential sources for endangering personnel, patients, and the environment. Each activity affects both the quality of the specimen (and could lead to erroneous or misleading laboratory test results that could have a negative impact on patient management, outcome, and safety) and the personnel involved in the specimen management chain (97). Patient specimens and derivatives, when not stored appropriately, may pose significant risk upon retrieval, but storage and archiving are not perceived as high-risk activities and are often omitted in published studies. One opportunity to mitigate risks associated with specimen storage is the development of improved containers that are durable, leak-proof, appropriate for a wide range of analytes and conditions, and better suited for small quantities of specimens needed for future analysis methods. The introduction of new

instrumentation and technologies coincides with the need for additional evidence-based guidance on the safe storage of specimens, such as uncapped specimen containers, or specimens and derivatives on various matrices (i.e., blood spots and nucleic acid).

### Equipment and Instrumentation Safety

Standard Precautions recommend cleaning and disinfection of patient care equipment, instruments, and devices (70). Laboratory equipment and instrumentation used to test patient specimens have the potential to generate percutaneous, droplet, and aerosol risks, and these risks may be under appreciated particularly when obvious signs of contamination are absent from otherwise clean and well-controlled laboratory environments. The CDC-convened Biosafety Blue Ribbon Panel published the "Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories" and identified laboratory equipment and procedures associated with aerosol exposure, which include: (i) centrifugation; (ii) mixing, blending, grinding, shaking, sonicating, and vortexing specimens; (iii) pouring, splitting, or decanting liquid specimens; (iv) removing caps or swabs from culture containers; (v) opening lyophilized cultures; (vi) opening cryotubes; and (vii) filtering specimens under vacuum (15). One study that investigated aerosol risks associated with common clinical laboratory activities evaluated how different centrifuges generated aerosols in the laboratory setting and identified the use of sealed containers, addition of an air filter into the centrifuge, and following the manufacturer's guidance on equipment usage, as important measures for reducing the amount of aerosols associated with using centrifuges (98). While the risks of contamination are low for common blood-borne pathogens when Standard Precautions and Transmission-Based Precautions are used, even low-level residual contamination of instrumentation and the surrounding workplace raises concern when processing specimens that contain pathogens associated with high morbidity and mortality. While the CDC advises clinical laboratories to follow manufacturer-installed safety features (70), when these features are not systematically assessed, designed, or installed for all possible pathogens, the opportunity for accidental infection remains.

Important components of equipment and instrumentation safety that encourage safe workplace practices are workflow assessment and human systems engineering. The importance of these components was demonstrated by a recent survey where a majority of LAIs in BSL-3 and -4 laboratories were the result of human error (99). However, workflow assessments and systems engineering are not relevant to only high-containment laboratories. Clinical laboratories (BSL-2) also can have poor safety practices, and often have clean workspaces in or directly adjacent to contaminated workspaces, increasing the risk of cross-contamination. There are few published studies that evaluate laboratory equipment hazards, and most of the available studies have investigated contamination without documenting transmission of infectious agents (87). Conversely, studies that document laboratory-transmitted infections rarely detail specific instrumentation or manufacturers (20, 21, 24, 100). As such, the interpretation of risks associated with specific instrumentation may include consideration of laboratory workflows, procedures, and PPE used with these instruments.

**Studies on laboratory contamination.** Studies that have examined contamination of laboratory equipment have identified several potential hazards. One study used mouse liver homogenates in conjunction with recombinant herpes simplex virus to evaluate laboratory contamination using an ultrasonic processor and a tissue dispenser (101). This study found that these devices, under normal use, generated aerosols that contain live virus. Another study looked at clinical laboratory contamination with human rhinovirus during normal work practices (102). They collected samples from PPE and laboratory equipment used for virus collection and preparation. Viral contamination was detected on the glove and cuff of protective clothing as well as inside the BSC windows, trash handles, the centrifuge inner walls, and the inner surface of the centrifuge rotor. A separate study investigated HBV and HCV contamination by collecting swab samples from a total laboratory automation system in a clinical laboratory (87).

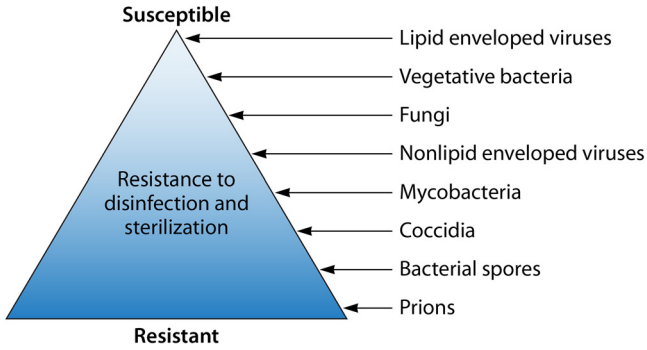


**FIG 1** Hierarchy of resistance to disinfection and sterilization. The hierarchy of microbial resistance to disinfection and sterilization. Selection of disinfectants for pathogens should be based on a well-established hierarchy of susceptibility to chemicals as determined by the microbes' biophysical characteristics (adapted from reference 114).

The swab samples were analyzed and the highest pathogen contamination levels were found in tube manipulation sites and at the decapper waste chute. Additionally, a study that used fluorescent dye and bacteriophage to assess contamination of laboratory staff, test devices, and a BSC identified a high degree of contamination, including 16% of technologists' bare hands, despite the use of gloves (103). They specifically tested the use of a commercial instrument that offers rapid cartridge-based assays to detect nucleic acid, including Ebola RNA; a rapid malaria antigen assay; and a POC instrument that is a frequent component of containment laboratories designed to handle Ebola virus-infected specimens. Notably, they were able to substantially reduce, but not eliminate, contamination by modifying their procedure and by instituting double gloving (103).

**Sources for laboratory equipment incidents.** The risk of instrument-related contamination is likely highest when accidents happen, but can also occur during routine use. While catastrophic instrument failures that involve broken specimen containers or centrifuge rotors clearly pose risks, more subtle failures, such as blocked peristaltic pumps, partially blocked filters, or missing centrifuge "O"-ring seals have also been shown to generate aerosols that contain bacterial spores (104). In particular, specimens that contain *Mycobacterium tuberculosis* are challenging because aerosols generated by processing and culturing are common causes of LAIs (47). However, *M. tuberculosis* aerosols have also been associated with false-positive results due to laboratory cross-contamination (105, 106). Routine laboratory procedures, such as tissue homogenization and pipetting, have been shown to generate influenza aerosols (107) and low-level surface contamination of automated chemistry instrumentation with HBV and HCV during routine use (87). Together, these data identify a need for instrument-specific risk assessments, manufacturer-installed safety features, and workflow assessments that could result in changes in routine laboratory practice.

**Challenges in equipment and instrumentation-related risks.** With the exception of POC instrumentation and efforts to place high-risk instrumentation in BSCs (108, 109), it remains a challenge for clinical laboratories to prepare for unanticipated high-risk pathogens in all routine workflows (14). Small splash shields, unsealed centrifuge rotors, and improper use of PPE when handling laboratory equipment remain common, emphasizing a need for clearer manufacturer guidance, better training of staff, and harmonization of safety features and processes. Maintenance of instruments often involves accessing internal systems that contain sharp mechanical components, increasing risk of percutaneous injury if procedures are not properly followed. However, maintenance staff may be unaware of the safety policies and procedures required in clinical testing and thus less aware of infectious hazards. Systems engineering approaches that maximize safe instrument use and reduce cross-contamination could mitigate these risks (110).

The majority of published studies that involve laboratory equipment are the result of case investigations into LAIs. Reviewing published studies provides an opportunity to increase awareness, reinforce training, and strengthen biosafety efforts. To make peer-reviewed cases more accessible, ABSA created a searchable LAI database (my.absa.org/LAI) (111). Additionally, the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM) contains reports of adverse events and other issues with medical devices, including clinical medical equipment reports. Reporting is required by device user facilities, importers, and manufacturers; additional reports can be submitted by consumers and health care professionals.

### Disinfection of Laboratory Equipment and Instrumentation

Laboratory equipment and instruments that contact infectious agents or are contaminated with blood or any other potentially infectious materials should have instructions for their routine cleaning and disinfection (112). During the 2014 Ebola outbreak, many equipment manufacturers could not provide guidance on the care of their equipment and the only disinfection strategy they would advise was to incinerate their instruments after use (12). Unlike other medical devices, which include methods for cleaning and disinfection in their instructions for use, many *in vitro* diagnostic test systems lack guidance for decontamination. These issues revealed not only numerous flaws in safety of instruments used in clinical laboratory settings, but also a lack of understanding about disinfection of pathogens (33).

Environmental disinfection is crucial to interrupt the spread of many pathogens, and this strategy is being applied to new and emerging viruses. Selection of disinfectants for these pathogens, including Ebola virus, Middle East respiratory syndrome-related coronavirus, and Zika virus, should be based on a well-established hierarchy of susceptibility to chemicals as determined by the viruses' biophysical characteristics (113); this approach has been adopted by CDC and EPA (Fig. 1) (114). Ebola is an enveloped virus that can be inactivated by a wide variety of disinfectants and detergents (112, 113, 115, 116). However, during the 2014 Ebola outbreak, a slightly more conservative approach was taken by CDC, and decontamination guidance also included methods known to inactivate nonenveloped viruses (EPA List L), as well as pasteurization (temperatures between 60 and 80°C) procedures (117) and germicidal UV light (118). Currently, the CDC Ebola guidance recommends health care systems decontaminate surfaces using an EPA-registered disinfectant with a label claim for nonenveloped virus (119, 120). Recently, CLSI has convened a workgroup that is working with federal agencies and manufacturers on developing consistent recommendations for instrument disinfection (QMS27 Decontamination of Laboratory Equipment and Instrumentation).

**Methods to decontaminate instruments.** According to CDC guidance, exterior surfaces of equipment should be routinely cleaned and disinfected with an EPA-registered disinfectant (114). In addition, the interior parts of the instrument which come into contact with patient specimens, including fluid pathways and interior surfaces, should also be cleaned and disinfected. Some manufacturers recommend the use of a sodium hypochlorite solution for blood contact surfaces and fluid flow-paths (121, 122). In these cases, following the manufacturer's instructions for cleaning might be considered sufficient to decontaminate the instrument. There are also EPA-registered products that are noncorrosive and leave no residues that are marketed for the decontamination of clinical analyzers. As an alternative, surface disinfection of medical equipment (dialysis machines, pulse oximeters, blood pressure monitors, etc.) in patient rooms has been accomplished using "no touch" methods, such as devices that use UV or hydrogen peroxide mist/vapor (123–125).

**Biosafety gaps and future needs.** Our knowledge of instrument contamination during routine use, or during use with highly pathogenic microbes, is quite limited. Laboratories usually have limited ability to evaluate decontamination procedures prior to purchase, and often receive limited assistance from manufacturers regarding instrument decontamination during routine usage. More studies of different types of laboratory equipment and

**TABLE 5** Federal regulations that impact waste management in clinical laboratories

| Regulatory entity[a] | Regulatory standard | Description |
|---|---|---|
| EPA | The Federal Clean Air Act of 1955 and revisions (1963, 1977, 1990) | Addresses emissions from laboratories; in 2000 the Environmental Protection Agency began enforcement of new standards for hospitals, medical and infectious waste incinerators |
| | Clean Water Act, 1977 and Water Quality Act, 1987 | Protect the nation's water from physical, chemical, and biological contamination and preventing point and nonpoint source pollution |
| | Solid Waste Disposal Act, 1965; Resource Recovery Act, 1970; Resource Conservation and Recovery Act (RCRA) 1976; Hazardous Solid Waste Amendments, 1984; Medical Waste Tracking Act, 1988 | Regulation of hazardous chemical wastes; Regulation of municipal solid waste landfills; medical waste |
| DOT | Hazardous Materials Transportation Act, 1977; Hazardous Materials Regulations, 49 CFR 171-180 | Transportation of hazardous substances, including infectious substances |
| NRC | Atomic Energy Act, 1990; NRC 2011-18767 | Radioactive wastes; protection of cesium-137 chloride sources |
| OSHA | 29 CFR 1910.141 (a)(4) (i-ii): 1998 | Sanitation/waste disposal |
| | 29 CFR 1910.132;1998 | Personal protective equipment |
| | 29 CFR 1910.145;1998 | Specifications for accident prevention signs and tags |
| | 29 CFR 1910.1200;1998 | Hazard communication |
| | 29 CFR 1910.1030;1998 | Bloodborne pathogens |
| | 29 CFR 1910.1450;1998 | Occupational exposure to hazardous chemicals in the laboratory |
| Department of Agriculture; CDC | 7 C.F.R. Part 331: Agriculture; 9 C.F.R. Part 121: Animals and Animal Products; 42 C.F.R. Part 73: Public Health | Federal Select Agent Program: destruction of agents, laboratory cultures; wastes generated during delivery of care to patients with Ebola would not be subject to federal Select Agent regulations if transferred or decontaminated within 7 days post patient care (See the exclusion provision in sections 3(d) and/or 4(d)) |
| Department of Homeland Security | | Controls applied to laboratories with technology that contains certain radiological sources; FBI background checks to approved individuals |

[a]EPA, Environmental Protection Agency; DOT, Department of Transportation; NRC, Nuclear Regulatory Commission; OSHA, Occupational Safety and Health Administration.

instrumentation, as well as protocols and research on decontamination procedures, would help address gaps in this knowledge (126). In addition, instrument contamination/decontamination is not, at present, specifically considered in regulatory determinations and approval processes. Advancements in decontamination science would aid users and manufacturers in addressing the lack of protocols that ensure nonobvious points of contamination are not missed, and there is a need for industrial design and decontamination science to help inform future regulations in this area. Clinical laboratories lack training and certification in environmental sampling needed to verify instrument decontamination, and this is an additional area for a needs assessment.

### Laboratory Waste Management

All clinical laboratories generate nonhazardous and hazardous or potentially hazardous waste. Thus, it is important for laboratory directors, managers, supervisors, and staff to be familiar with federal, state, and local regulations that govern the generation and handling of various types of waste (regular solid waste, liquid waste, etc.). Clinical laboratories may generate hazardous waste that contains chemical, infectious, radioactive, sharps, or multihazardous (contains multiple types of) materials (14, 127–130) whose handling is regulated by the Code of Federal Regulations (CFR). The federal agencies that have regulatory oversight over hazardous wastes in the United States include the EPA, DOT, OSHA, Nuclear Regulatory Commission (NRC), and the Department of Homeland Security (Table 5). In addition to federal laws and regulations, clinical laboratories

may have to operate under more restrictive state and local legislation (www.epa.gov/home/health-and-environmental-agencies-us-states-and-territories). The EPA is no longer primarily responsible for regulating medical waste; instead, the states have the primary responsibility for regulating clinical laboratory waste, and these regulations are diverse (131). The Healthcare Environmental Resource Center summarizes state-specific requirements and approved treatment options (www.hercenter.org/rmw/rmwoverview.php). Additionally, a more detailed reference document is CLSI GP05-A3 Clinical Laboratory Waste Management (132).

**Laboratory waste management program.** A "Laboratory Waste Management Program" can be designed so an organization can control and monitor the production, segregation, storage, and disposal of all waste generated by the laboratory, thus making the waste generator responsible from "cradle to grave," i.e., from waste generation to treatment to final disposition (132). This program ensures the waste stream would not pose a public health risk to employees, the general public, or a threat to the environment. There are liabilities associated with handling, transport, and disposal of hazardous waste; mishandling of waste, even if disposal occurs by a contracted waste management service, could result in laboratories being responsible for fines and damages (80).

CLSI provides guidance on establishing an effective Laboratory Waste Management Program which includes identification of all applicable federal, state, and local regulations, as well as any accreditation standards (Joint Commission, CAP, etc.) and identification of waste management options (e.g., contract off-site treatment, on-site treatment options if available, contract hauler, etc.). It also includes identifying the needs and expectation of employees, performing a cost/benefit analysis and assessing liabilities of the waste disposal methods, and associating risk assessment with each waste management option (132).

The EPA provides general recommendations for laboratories that include minimizing the amount of waste (133). Inventory control can also be a part of the overall waste minimization plan to prevent waste of reagents, media, and supplies due to expiration.

Laboratory waste can be subdivided into different categories, segregated at the point of generation, then removed to a waste-specific storage area to prevent accumulation at the point of generation and minimize the risk of spills that could result in exposures. For some types of waste, EPA sets time limits and stipulates engineering controls (e.g., lead shielding, proper ventilation, refrigeration, etc.) that should be in place (133). Some potentially infectious waste, if not treated on site, can be considered regulated medical waste (RMW). It is important to note that the regulation of RMW was delegated to the states after the expiration of the Medical Waste Tracking Act of 1988 (134). RMW is the portion of the waste stream that may be contaminated by blood, body fluids, or other potentially infectious materials, including cultures, and has the potential of posing a significant risk by transmitting infection (135, 136). RMW includes sharps (discarded needles, scalpels, glass Pasteur pipettes, broken glass, broken petri dishes, rigid plastic tubes, flasks, beakers, broken vials, broken or unbroken glass slides, and other laboratory materials that contain infectious agents), cultures, stocks, human blood, blood products, pathological wastes, and animal wastes. There are some exceptions, which depend on state regulations, especially if waste is collected by a licensed and permitted medical waste hauler (131). The laboratory should also determine the composition and quantity of the waste being generated, as some of this waste (e.g., Category A Infectious Substances), if transported off site, requires special packaging and handling. In addition to packaging requirements, the waste hauler may need special permits issued by DOT (80, 137).

**Storage and transport.** Infectious waste needs to be properly stored in appropriate containers, which may include properly labeled bags that meet American Society for Testing and Materials (ASTM) International D1709 requirements (138), such as rigid sharps containers, leak-proof stoppered bottles/flasks, or containment tanks (132). CDC and CLSI recommend that waste transported within the facility to the treatment site

**TABLE 6** Examples of Category A infectious substances (not inclusive) (79, 146)

| Microorganism | Form |
|---|---|
| *Bacillus anthracis* | Cultures only |
| *Brucella abortus* | Cultures only |
| *Brucella melitensis* | Cultures only |
| *Brucella suis* | Cultures only |
| *Burkholderia mallei* | Cultures only |
| *Burkholderia pseudomallei* | Cultures only |
| *Chlamydia psittaci* (avian strains) | Cultures only |
| *Clostridium botulinum* | Cultures only |
| *Coccidoides immitis* | Cultures only |
| *Coxiella burnetii* | Cultures only |
| Crimean-Congo hemorrhagic fever virus | Patient material, items contaminated with other potentially infectious material (OPIM[a]) |
| Dengue virus | Cultures only |
| Eastern equine encephalitis virus | Cultures only |
| Verotoxigenic *Escherichia coli* | Cultures only |
| Ebola virus | Patient material, items contaminated with OPIM |
| Flexal virus | Patient material, items contaminated with OPIM |
| *Francisella tularensis* | Cultures only |
| Guanarito virus | Patient material, items contaminated with OPIM |
| Hantaan virus | Patient material, items contaminated with OPIM |
| Hantavirus causing hemorrhagic fever and renal syndrome | Patient material, items contaminated with OPIM |
| Hendra virus | Patient material, items contaminated with OPIM |
| Herpes B virus | Cultures only |
| Human immunodeficiency virus | Cultures only |
| Highly pathogenic avian influenza | Cultures only |
| Japanese encephalitis virus | Cultures only |
| Junin virus | Patient material, items contaminated with OPIM |
| Kyasanur forest disease virus | Patient material, items contaminated with OPIM |
| Lassa virus | Patient material, items contaminated with OPIM |
| Machupo virus | Patient material, items contaminated with OPIM |
| Marburg virus | Patient material, items contaminated with OPIM |
| Monkeypox virus | Patient material, items contaminated with OPIM |
| *Mycobacterium tuberculosis* | Cultures only |
| Nipah virus | Patient material, items contaminated with OPIM |
| Omsk hemorrhagic fever virus | Patient material, items contaminated with OPIM |
| Poliovirus | Cultures only |
| Rabies and other lyssaviruses | Cultures only |
| *Rickettsia prowazekii* | Cultures only |
| *Rickettsia rickettsii* | Cultures only |
| Rift Valley fever virus | Cultures only |
| Russian spring-summer encephalitis virus | Cultures only |
| Sabia virus | Patient material, items contaminated with OPIM |
| *Shigella dysenteriae* type I | Cultures only |
| Tick-borne encephalitis virus | Cultures only |
| Variola virus | Patient material, items contaminated with OPIM |
| Venezuelan equine encephalitis virus | Cultures only |
| Vesicular stomatitis virus | Cultures only |
| West Nile virus | Cultures only |
| Yellow fever virus | Cultures only |
| *Yersinia pestis* | Cultures only |

[a]See OSHA's Bloodborne Pathogen Standard (29 CFR 1910.1030) for additional information (43).

be contained in clearly labeled, dedicated leak-proof containers or carts (132, 139). These carts and containers should be disinfected frequently. When transporting waste, public areas should be avoided to minimize risk of exposure to patients, staff, and visitors. If waste is transported off site, then one must follow DOT specifications for the packaging and transport of waste (80, 137). According to DOT, waste must be bagged or double bagged and then placed in semi-rigid or rigid containers that contain the appropriate labeling and transported to the appropriate storage area for pickup.

Sharps containers should be closed and brought to an area for storage until pickup (137). The facility is required to ensure that the waste meets DOT regulations by packaging and providing appropriate storage, as well as transportation documentation for the waste hauler who transports the waste to a certified medical waste treatment facility.

**Decontamination.** Generators of infectious waste have the option to treat waste on site at the generating facility or off-site at a cooperative regional facility or a commercial treatment facility. However, on-site treatment (e.g., autoclaving, chemical disinfection, incineration, or another validated decontamination method) is recommended by both CDC and NIH (BMBL) (14). Treatment of RMW is enforced at the state level and the primary methods are either incineration or autoclave; however, autoclaving is currently the method of choice for the decontamination of laboratory infectious wastes (114). Incineration using a hospital/medical/infectious waste incineration unit is also an option; however, because medical waste incinerators are expensive to operate while meeting the requirements of the Clean Air Act, their use continues to decrease. Alternative decontamination methods, often designated in state regulations and permitted by the state, include high-vacuum autoclave with rotating drum and shredder, high-vacuum autoclave with compactor or shredder, chemically enhanced continuous feed autoclave and shredder, microwave heat-generating unit with shredder, and electrothermal deactivation with shredding (140–144).

**Lessons learned.** The Ebola outbreak created several challenges with regard to waste management. The DOT defines an infectious substance as Category A if it is in a form capable of causing permanent disability, life-threatening, or fatal disease in healthy humans or animals upon exposure; materials contaminated with Category A infectious substances are Category A waste (145). All waste generated in the care of or during the diagnostic testing of specimens from an Ebola patient, as well as patients infected with any hemorrhagic fever virus, is designated a Category A infectious substance (Table 6) that requires special packaging for transportation (146). This includes PPE, used supplies, bedding, single-use items, patient materials and laboratory waste, and any supplies or linens not meant to be reprocessed. However, packaging for Category A infectious substances was originally designed for laboratory specimens, as hospitals were expected to dispose of large amounts of Category A waste on site. In addition, hospital capacity for treating its own infectious waste on site has diminished since the mid-1980s, a decrease that coincided with the rise of the Medical Waste industry (147). Transporters of Category A waste were required to go through a permitting process and have established packaging and procedures for hauling waste to a treatment site (148). Due to these requirements, an additional issue encountered with packaging for waste was that it limited off-site autoclave options, since there were no validated autoclave cycles for processing waste in Category A packaging. Many of these issues were realized during the Ebola outbreak, as several clinical microbiology laboratories had eliminated the autoclaving of waste and relied on vendors to haul waste off site (149, 150). Unfortunately, some vendors refused to accept untreated medical waste from suspected Ebola patients. This issue highlights the potential risks associated with streamlining laboratory processes, when fear and public perception might limit where waste can be treated and disposed (149). If more facilities had the capacity to treat their waste on site, many of these problems might have been minimized. There may be a need to revisit the Category A infectious substance list (151, 152), to reevaluate whether medical waste contaminated with blood and other potentially infectious materials needs specialized packaging, and to establish industry standards for appropriate autoclave cycle times.

### Clinical Laboratory Personal Protective Equipment

PPE is defined as specialized clothing or equipment worn by clinical laboratory personnel for protection against infectious and hazardous materials (153). While essential to and widely used within the biosafety community, the availability of PPE in clinical laboratories is often insufficient, as are systems (in place) for ensuring it is appropriately

employed (154, 155). Due to this, many clinical laboratories have followed guidance from CDC (156) and other organizations (157) when developing a plan to manage PPE that includes training regarding the use of the equipment and the assessment of competency.

CDC outlined the principles of PPE use when in direct patient contact with suspected infectious fluids in the Ebola health care guidance (156), but of course these principles are applied to other hazards as well. This guidance provides recommendations for donning PPE, PPE during patient care, and doffing PPE. When donning, CDC recommends observation by a trained observer of appropriate order of assembly so that modifications do not occur after entry into the patient care area. When caring for patients, retaining PPE throughout the duration of work is necessary. If a breach in PPE occurs, the health care provider should move to the doffing area immediately to assess exposure.

The practice of double gloving and removing contaminated outer gloves compared to the practice of disinfecting gloved hands have both been suggested however, there is inconsistency in guidance regarding the effectiveness of each (42, 158, 159). Due to this lack of consensus in the literature, and because institutions may have different risk tolerance, conducting a comprehensive risk assessment may determine which practice is appropriate for the specific situation. When doffing, CDC recommends removal of PPE to reduce risk of exposure from PPE using a structured procedure performed in the presence of a trained observer in a designated area. Furthermore, doffing should be completed upon departure from a patient area that is clearly separated from the donning area, with appropriate placement of a biohazard bin. Disposable PPE should be discarded into a biohazard bin after potential exposure to patient tissue or fluids, even if not visibly contaminated and never reused. Biohazard containment bin(s) are often located adjacent to the immediate work area but should be separate from storage and donning areas. Any required decontamination of equipment can be performed adjacent to the doffing areas. An example would be decontamination of face shields or safety glasses that have been contaminated by a splash from a patient specimen.

**PPE in clinical laboratories.** PPE used in direct patient care is typically different from that used in clinical laboratories, and that used in surgical pathology and autopsy may differ as well. CDC recommends clinical laboratories develop a robust plan to manage PPE that applies to all laboratory activities (160). This management plan would account for all laboratory functions inside and outside the laboratory (e.g., phlebotomy) and indicates the best approach for clinical laboratories is to comprehensively assess specific laboratory sites and activities. Industry (e.g., manufacturers) also has guidelines and policies regarding the use of PPE that can inform clinical laboratories in organizing their approach to PPE management. Additionally, the Consultation Section of the Department of Labor and Industries has sample PPE policies that include responsibilities of supervisors and employees, hazard assessment and PPE selection, and employee training, as well as cleaning and maintenance of PPE (161).

**Personnel responsibilities for PPE management.** A clinical laboratory supervisor, safety officer, or designated personnel is the individual most likely responsible for management of PPE. Their responsibilities can include: (i) performing a hazard/risk assessment to determine the likelihood and consequence of receiving/handling hazards requiring PPE; (ii) selection and purchase of PPE; (iii) reviewing, updating, and conducting PPE assessments when a job changes, new equipment is acquired, in review of an accident, and when requested (such review should be performed at minimum annually); (iv) maintaining documentation of hazard/risk assessments; (v) maintaining documentation of PPE assignments and training; (vi) providing training, guidance, and assistance to supervisors and employees regarding PPE; (vii) reevaluating previously selected PPE; and (viii) reviewing and analyzing the overall effectiveness of all PPE-related activities. The OSHA blood-borne pathogens standard states the general supervisor is usually responsible for ensuring or implementing the use of PPE by employees (43). However, each

laboratory employee is also responsible for wearing appropriate PPE, receiving training, maintaining PPE, and following PPE policies. The employee also has a responsibility to report new risks, problems with equipment, and comply with PPE maintenance and cleaning.

**Selection of PPE.** HCW wear protective clothing (e.g., surgical gowns, isolation gowns, and coveralls) to protect both the patients and themselves from the transfer of microorganisms spread by blood and body fluids as well as other hazardous materials. A common misunderstanding among many HCW is that they are protected from blood, body fluids, and other potentially infectious materials when they wear any type of fluid-resistant garment (162). However, the selection and use of PPE is informed by the hazards and the risk of exposure. While a thorough risk assessment will identify potential exposures to blood and body fluids, employers may need to consider that the risk of exposure sometimes depends on the stage of the disease and severity of symptoms (14). For example, for EVD, severe symptoms are strongly associated with high levels of virus production (163). CDC and CLSI recommend additional factors to consider when assessing the risk of exposure in health care facilities include source, modes of transmission, positive and negative air pressure within facilities, types of contact, and duration and type of tasks (77, 162). Thus, a laboratory's site-specific risk assessment will consider many external factors when determining the infectious-agent-specific body protection that is required, e.g., impermeable gowns, laboratory coats, or coveralls. In addition to the factors mentioned above, there are other intrinsic aspects of garments related to their design, integrity, durability, comfort, and functionality to consider, as well as the potential limitations of each type of PPE. The selection of body protection can be confounded by terms (e.g., fluid-resistant, fluid-proof, impermeable, and impervious) used in the industry to define barrier resistance properties of garments. Furthermore, a microorganism's ability to penetrate protective clothing depends upon several factors, e.g., physical and chemical properties of the material/fabric, and the shape, size, and other characteristics of the microorganisms.

Understanding how protective clothing materials provide protection against microorganisms in blood and body fluids guides proper selection of PPE. Body protection needs to meet American National Standards Institute (ANSI), the International Organization for Standardization, ASTM International, the National Institute for Occupational Safety and Health (NIOSH), or other standard requirements as determined by the level of risk. The CDC website provides information on national and international standards, test methods, and specifications for fluid-resistant and impermeable gowns and coveralls used in health care (www.cdc.gov/niosh/npptl/topics/protectiveclothing/default.html). Additional guidance for PPE and/or surgical drapes includes the Association for the Advancement of Medical Instrumentation technical report on selection of protective apparel and surgical drapes (164) and OSHA 29 CFR 1910.132. NIOSH conducts tests and evaluates PPE, and if it meets with NIOSH standards than the product is labeled as such. They also provide training guides and videos that are well known to infection prevention and control departments who work with clinical laboratory mangers and biosafety officers (165).

**PPE from head to toe.** Selection of PPE is determined by an understanding of what hazards and what level of protection each piece of equipment provides (162, 164). Protective clothing and equipment should meet regulatory standards, where applicable, as they apply to eye and face protection, head protection, body protection, foot protection, respiratory protection, and hand protection (43, 153).

There is a wide range of commercially available respiratory protective equipment available to clinical laboratory professionals. Surgical masks are worn by clinical and laboratory professionals and can be used to provide protection from hazards such as splashes or sprays of large droplets of blood or body fluids. They protect the mouth and nose from contaminated hands and fingers and also prevent contamination of patient wounds and laboratory samples (166). However, a NIOSH-approved N95 respirator, or equivalent, may be required when aerosols are generated. OSHA requires

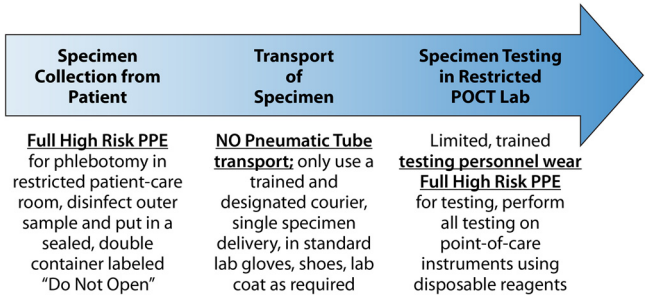


**FIG 2** Proposed PPE for specimen collection, transport, and specimen testing: high to moderate risk patients. PPE associated with specimen collection, transport, and testing of patients designated high to moderate risk for a highly infectious agent.

employees wearing tight-fitting respirators be fit tested prior to use (153). Fit testing must be performed by personnel knowledgeable in respiratory protection, qualified to follow an OSHA-accepted protocol, and able to train employees on donning and doffing respirators. More extensive coverage, such as a hooded respirator with face shield and helmet, or filter/blower units, i.e., powered air purifying respirator (PAPR), may also be warranted, such as when personnel cannot wear a tight-fitting N-95 respirator. The requirements for a respiratory protection policy as outlined in the OSHA Respiratory Protection Standard will need to be implemented by the employer. All respiratory protection deemed necessary by the risk assessment should meet the OSHA Respiratory Protection Standard 1910.134 (153).

Typical face and eye protection include face shields, eye shields, safety glasses, or use of a bench barrier that is impermeable to splash and infectious materials. Depending on the infectious agent, head protection may be optional, except in surgical pathology or autopsy.

In many clinical laboratories, closed toed shoes made of impermeable materials are sufficient foot protection (15). However, CDC also recommends impermeable shoe covers or booties as alternative solutions when splashes are significant, especially in areas such as surgical pathology, areas where surgical pathology frozen sections are prepared, and autopsy suites.

Hand protection is designed to protect against hazards ranging from biological agents to harmful chemicals. CDC recommends glove selection be based on the risk assessment and OSHA recommends selection be task specific and based on the performance as well as construction characteristics, as one type of glove does not protect against all possible hazards (15). Additionally, a double-glove approach is an option for procedures with high potential for exposure. For more information regarding the various types of gloves, please refer to ASTM International standards.

**Employee training.** According to OSHA requirements, any employee required to wear PPE must receive training in the proper use and care of the equipment (156). Training should be specific to individual sites within clinical laboratories that require PPE and should include when to wear PPE, which PPE to wear, how to properly don, doff, adjust, and wear the PPE, the limitations of PPE, and proper care, maintenance, life span, storage, decontamination, and disposal of PPE.

If a clinical laboratory does not have a dedicated safety officer, a designee may develop training modules and deliver training. However, supervisors are typically responsible for ensuring staff competency for using PPE (43). Training is typically repeated on an annual basis or when upgrades/changes are made in PPE. Competency assessment, as required by CLIA and its approved accreditation organizations, such as CAP, includes: documentation of initial training, review of competencies at 6 months into the first year of employment, and review of competencies annually thereafter. The CLIA regulations require certified laboratories to maintain training and competency records for each trainee (167).

**Supply management and storage.** CDC provides guidance regarding PPE management and storage. In short, PPE should be stored in a clean area, according to vendor recommendations (156, 160). For equipment that has an expiration date, a process for purchasing and cycling in new equipment would prevent use of expired materials. Important to the process of PPE distribution is the designation, with appropriate signage, of PPE storage and donning areas. Signage that identifies specific areas for equipment storage, donning, and doffing is an effective procedure for preventing contamination of clean areas. While institutional policies will vary, the minimum signage typically identifies clean areas; this is a consideration for clinical laboratories that have multiple storage areas or travel routes to and from sites requiring PPE. In some cases, donning may be required prior to entry into a working laboratory, i.e., BSL-3 facilities. In such cases, laboratory gowns and all other required PPE should be directly adjacent to entry areas. Segregating contaminated equipment away from clean PPE storage sites, and locating PPE storage sites adjacent and accessible to work areas, may help reduce risk to users.

**PPE challenges in response to an infectious outbreak: exposure control.** The Ebola outbreak in the United States drew attention to the need for high-risk PPE (Fig. 2) and stepwise procedures for donning and doffing PPE when there was potential exposure to highly infectious agent(s). One of the questions causing confusion for clinical laboratories at the time was how the processes for using PPE for direct patient care were applied to, or differed from, PPE needed for processes in the clinical laboratory and testing environment.

In order to address this gap, Emory University, working closely with CDC, created modules for consideration of patient management, including clinical laboratory testing (168), and the following is a brief description of how Emory currently handles management of a patient with possible/confirmed EVD. Infectious Disease Service and Infection Control personnel are responsible for designating a patient as high or intermediate risk. Appropriate PPE is determined by risk assessment as recommended by the Infectious Disease Service, the Clinical Microbiology Laboratory, and the Department of Infection Prevention and Control. For drawing blood from high-/intermediate-risk patients, the phlebotomist is directed to don appropriate PPE and bring only the necessary supplies when entering the patient care room. Prior to leaving the room and entering the doffing area, collection tubes will be wiped with disinfectant and labeled legibly. PPE is removed in the adjacent doffing area and phlebotomy waste disposed of in a biohazard receptacle. The phlebotomist then dons a new pair of gloves and places the specimens into a biohazard bag, wiping the outside of the bag with disinfectant. Gloves are removed prior to exiting and new gloves donned before leaving the room. Outside the patient room, the phlebotomist places specimens in a second biohazard bag. The bag is placed into a secondary container which is sealed and marked "Do Not Open." Personnel who transport specimens follow standard procedures and avoid public areas and elevators to the testing area. Furthermore, specimen transport should adhere to standard procedures and should perform site- and activity-specific risk assessments to determine if enhanced biosafety precautions are warranted based on situational needs; transport by pneumatic tube is NOT allowed. Testing locations can range from POC testing using disposable reagent packets to tests performed in specialized negative-pressure laboratories. Testing personnel wear appropriate PPE and all biological and reagent waste should be disposed as RMW. For patients subsequently determined to be low risk or negative for the specific infectious agent, a reduction in the level of PPE may be deemed appropriate depending on the location, procedures, and personnel performing the testing. One example of possible PPE for testing specimens from high- to moderate-risk infectious patients is shown in Fig. 2. This approach may not be feasible for many hospitals, and specimen handling will be determined by institutional risk assessment/mitigation.

**Evaluation of Clinical Laboratory Biosafety Competencies and Training**

Biosafety competencies are a critical component of the laboratory biosafety plan, and when incorporated with biosafety risk assessments, mitigation strategies, training, audits, and other tools, can enhance a culture of safety in the laboratory. Three guidance documents, "Guidelines for Biosafety Laboratory Competency," "Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories," and "Competency Guidelines for Public Health Laboratory Professionals" (15, 169, 170) guide biosafety practices for individuals who work in clinical and public health laboratories. These guidelines are also useful for identifying gaps that can be filled by further training.

Regulations that require the incorporation of biosafety competencies into laboratory operations may help to ensure compliance with safe work practices. The use of competency assessments to document technical skills and improve performance is standard practice in clinical laboratories (62, 167). To comply with regulatory requirements, clinical laboratories have established technical competencies for every procedure performed. Based on this history, it seems likely that regular assessment of biosafety competencies will improve the practice and safety of laboratory professionals in clinical, environmental, public health, academic, and research laboratories. However, there is little information available regarding the impact of competency assessments in clinical laboratories (171). In 2013, an informal survey was conducted by members of two clinical microbiology listservs. Ninety-eight laboratorians responded, 75 from clinical laboratories, 12 from public health laboratories, 5 from research laboratories and 3 from other laboratory environments. When asked if they were aware of these biosafety laboratory competency guidelines, 72% acknowledged being aware of the documents and 69% had reviewed the documents (personal communication 2020 from Mike Pentella). As discussed above, adoption of biosafety related competencies is a more difficult task because clinical laboratories often lack comprehensive guidance documents, experience, and training on how to create and incorporate the biosafety competencies (169).

To improve biosafety practices, CDC and APHL recommend incorporating biosafety competencies into the laboratory's quality management system (QMS) for both testing protocols and general laboratory safety practices, i.e., the proper use of PPE, working safely in a BSC, and waste management (169). In general, the tasks to incorporate biosafety competencies are to review the technical procedure and then perform biosafety risk assessment to gather all available information on hazards in the protocol and to determine the possible risks associated with exposure. Based on the biosafety risk assessment, mitigation strategies to reduce potential exposure and subsequent LAIs are implemented. The identified mitigation strategies lead to the selection of applicable competencies that staff members need to demonstrate to safely perform tasks. These additions would then form the essential aspects of the safety section of the protocol, which is used for training of staff and documentation of competencies. The APHL biosafety checklist may serve as a starting point for laboratories to assess the biosafety measures they have in place and determine competency and training needs (172).

CDC recommends laboratory leadership understand the connection between the biosafety risk assessment, the selection of mitigation measures, and biosafety competencies (169). Furthermore, management support for the incorporation of biosafety competencies into the laboratory's competency program is critical and leadership should convey the importance of these competencies so that staff understand they are not an additional burden, but essential to reducing exposures and LAIs. Clear instructions on how to implement biosafety competencies in the clinical laboratory are necessary, and a library of specific clinical laboratory biosafety competencies connected to common protocols, including examples of best practices for incorporation of biosafety competencies, would simplify this process. Once the biosafety competencies are established, it is incumbent upon clinical laboratory management to take corrective action

when staff do not achieve the level of competency needed to perform the work safely (169).

CDC and APHL's "Competency Guidelines for Public Health Laboratory Professionals" recommends regular, ongoing competency assessments to continually determine training needs for laboratory personnel in different positions, including trainees (i.e., trainees in laboratory medicine and pathology residents and fellows) as well as permanent staff, and identifies the areas in which staff need to be trained or retrained (170). Furthermore, it is important that the effectiveness and outcomes of the training efforts be evaluated to determine whether and how the competency gaps have been filled. Training evaluation can ensure that training programs address the competency gaps, are effective in improving safety practices and laboratory quality, as well as obtain feedback on the trainees' learning experience, satisfaction, and future training needs. Training evaluation is especially important for biosafety training efforts, to assess the strengths, weaknesses, and issues needing the attention of the trainers as well as the trainees (173).

Many organizations (e.g., CDC, ABSA, and APHL) and institutions provide biosafety training for laboratory professionals, but it is often challenging for training providers to systematically collect evaluation data beyond the learner satisfaction and immediate outcomes. Data on the use of training information in practice and/or for competency evaluation is lacking as to what extent laboratories conduct such monitoring and evaluation, and whether such evaluation is consistently performed across the laboratory community. Ideally, evaluation of training and competencies would benefit from access to data that document LAIs, exposures to infectious agents, accidents, and near misses occurring in clinical laboratories across the United States. This would facilitate addressing lessons learned, improving biosafety competencies for laboratory professionals, and better positioning clinical laboratories to prepare and respond to future outbreaks. One possible solution would be the development of a voluntary, nonpunitive surveillance and reporting system to track data from laboratory incidents, as recommended in the 2012 "Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories" (15). An example of a successful surveillance system is Canada's Laboratory Incident Notification Canada (LINC) system, mandated by the Public Health Agency of Canada (PHAC), which is responsible for monitoring, evaluating, and analyzing laboratory incident notifications (174). A purely voluntary system, however, comes with limitations, including institutional reticence, embarrassment, and fear of liability, and lack of academic credit or other incentives for publication of this type of data.

Finally, the development of a robust biosafety training and competency assessment program as described above will strengthen an organization's culture of safety. Organizational commitment, including resources, attention, and administrative support, would be crucial to promoting systematic assessments and developing effective biosafety programs (15).

**Exposure and exposure-response plans.** In the event that risk mitigation strategies fail, exposures may occur. Laboratories must have plans and competencies in place to manage such exposures (175). The initial elements of exposure response include assessment of who was exposed, where they were with respect to the exposure, how the exposure occurred and whether it is ongoing or has been contained. Once the exposure is identified and contained, medical follow-up of exposed and potentially infected laboratory workers, diagnostic testing, and postexposure prophylaxis and treatment of symptomatic persons is performed in collaboration with occupational health and, as needed, public health resources. The clinical laboratory follows their institution's Infection Prevention and Control department guidelines in these instances.

## ISSUES IN SPECIFIC AREAS OF THE CLINICAL LABORATORY

Clinical laboratory subspecialties have unique workflows, instrumentation, and exposure risk to pathogens. As a consequence, the laboratory personnel who work

exclusively in these areas often lack an understanding of all biosafety issues in areas of the clinical laboratory in which they do not specialize. As shared understanding of biosafety issues between subspecialties may facilitate teamwork and an overarching biosafety plan for the entire clinical laboratory, the following sections highlight specific biosafety issues that are unique to some laboratory subspecialties. Since each laboratory section has unique biosafety issues, regulatory attention might be paid to delineation of area-specific requirements, which currently exist only for specific areas such as mycobacteriology.

### Blood Bank

While blood banks and transfusion services play limited roles in establishing the diagnosis of emerging infectious agents, they provide essential aspects of supportive care for such illnesses. Blood components, factor concentrates, and immune globulin preparations can be highly relevant in treating complications of some infections, such as those caused by Ebola virus disease (176). Here, we will focus on challenges blood banks face during current practice in the setting of emerging infectious agents at their facility, with regard to: (i) transfusion compatibility testing, (ii) provision of blood components and blood derivatives, (iii) evaluation of possible transfusion-associated adverse events, and (iv) consideration of convalescent plasma therapies. In addition, there are evolving practices that are intended to protect the blood supply from emerging pathogens should an infected but asymptomatic individual happen to donate blood. This section will not discuss potential obstacles to allogeneic blood collection itself, particularly possible shortages of blood that could arise as a result of pandemic events. Discussions on strategies individual blood banks and transfusion services might consider to maintain adequate blood inventories in the face of short- to moderate-term impacts on their blood supply have been covered elsewhere (177, 178).

**Areas of biosafety risk concern. (i) Compatibility testing.** The basic compatibility testing offered by transfusion services includes ABO and Rh (D) typing of patient red blood cells (RBCs) and screening for alloantibodies in plasma or occasionally serum. Such testing most often is performed using an EDTA-anticoagulated whole blood specimen, with centrifugation and cell washing steps necessary for both typing and screening. Final analysis is most often carried out on automated analyzers or via manual "tube" methods. In addition, RBC units themselves can be tested for compatibility with intended recipients, using an aliquot of plasma from the patient and a portion of the RBC segment from the intended donor unit; this "crossmatch" step is also performed via either automated or manual tube methods.

A significant concern for compatibility testing in the face of a newly emerging or highly contagious infectious agent is the risk for disease exposure to laboratory staff from the generation of aerosols during processing, centrifugation, cell washing, or test performance (179). As such, one laboratory's approach to mitigate these risks during transfusion, when treating patients infected with Ebola virus, was to suspend basic compatibility testing and issue uncrossmatched blood products (108). Since contamination of automated equipment may also be a concern, reliance on manual tube methods (with tubes disposed of after testing) could be considered an alternative means. There have also been descriptions of the use of manual slide agglutination techniques for type and screen performance (180), as well as an increase in availability of POC assays for basic blood bank tests, such as ABO assessment (181, 182). It is critical to note that for U.S. based hospitals and laboratories, any blood bank compatibility testing must meet CLIA regulations (62, 108, 183).

**(ii) Provision of blood components and derivatives.** If the risk to laboratory personnel is deemed low, then it is possible that the performance of routine compatibility testing (as well as either standard or electronic crossmatching) can be carried out for all patients with a suspected infectious agent (179). Conversely, if the risk of pathogen transmission to laboratory personnel is deemed too great, then transfusion services and blood banks may be forced to rely on issuance of blood components without testing or compatibility assessment. In such cases, blood banks could operate as if they

were treating individuals in an emergent setting, not unlike that of trauma, with issuance of group O RBCs (ideally Rh [D]-negative to all patients, but certainly required for children and women of child-bearing age) (182). If a patient's alloantibody history is known to the blood bank, then appropriate antigen-negative RBCs should be selected for transfusion (179). Consideration could be given *a priori* to providing RBCs lacking the K and E antigens, since these are generally the two most common alloantibodies encountered and among the most immunogenic blood group antigens (184). Since only about 2 to 3% of the general population possesses RBC alloantibodies (184), the risks for a hemolytic reaction occurring in the setting of uncrossmatched RBC administration are quite low, particularly for patients with no history of transfusion or pregnancy. Nonetheless, use of uncrossmatched RBC units should be judicious and patients closely monitored for adverse events. Fortunately, the hazards for transfusion incompatibility are essentially only applicable to uncrossmatched RBC units, as patients of all ages and backgrounds can be safely transfused with group AB plasma and platelet products (182). Similarly, plasma derivatives, such as factor concentrates, albumin, and immune globulin preparations (e.g., Rh immune globulin), can be given without the need for basic compatibility testing.

**(iii) Evaluation of transfusion-associated adverse events.** The approach to a possible transfusion reaction typically involves: (i) stopping the transfusion, (ii) collection of a postreaction EDTA-treated specimen from the patient, and (iii) submission of the posttransfusion reaction specimen, as well as the remaining blood product, associated paperwork, and compatibility tags, to the blood bank for further evaluation (185–190). Once reaching the blood bank, testing on specimens may involve a visual inspection for hemolysis, repeat typing/antibody screening, repeat crossmatch, and inspection for any clerical errors, which can be deduced by examining the paperwork/compatibility tags associated with a given unit (191).

Transfusion-associated adverse events may be particularly problematic in the setting of an emerging pathogen because incomplete compatibility testing may have been performed prior to product issuance, the patient may have signs/symptoms mimicking those of a transfusion reaction (secondary to their underlying infection), and because the testing that can be done posttransfusion may be limited (192). If the risks to laboratory personnel are thought to be very low, then complete transfusion reaction evaluations as described above can be performed. However, if only limited testing can be completed, then the blood bank staff might attempt some work-arounds, including: visual inspection of plasma without additional compatibility testing (which remains a sensitive assessment for intravascular hemolysis), close clerical inspection of associated paperwork, and encouragement of appropriate testing that may help evaluate for some forms of reactions (e.g., urinalysis for hemolytic reactions and chest imaging for pulmonary reactions) (191). Although not ideal, such approaches constitute one reasonable investigation into a possible transfusion-associated adverse event.

**(iv) Consideration of convalescent plasma therapies.** There is some published data regarding the use of convalescent plasma to treat patients with emerging infectious agents; that is, plasma is collected from individuals who are recovering from a recent infection and that plasma (presumably with high-titer neutralizing antibodies) is then administered to others. Experiences with Ebola virus infection suggest that use of convalescent plasma may offer some benefits, particularly when no other viable treatment options are available (182). In addition, it can be challenging to establish efficacy and appropriate use of convalescent plasma therapy for a novel illness when other changes in management practice are occurring at the same time (193). Given that plasma is first and foremost a blood product, blood banks might find themselves in the position of being asked to collect and manufacture this component from convalescent individuals. As described in detail by Koepsell et al., such operations are not easy to establish in the midst of a response to an emerging infectious disease. If a convalescent plasma program is pursued, the facility must have experience, required licensing, and meet FDA and AABB standards (194, 195) in blood component manufacturing and to use

plasma collected from fully recovered individuals who have been tested for other transfusion-transmitted agents (182).

**(v) Emerging infections of interest to the blood bank community and mitigation strategies.** As discussed earlier, microorganisms can be problematic to a blood bank without an infected patient ever presenting to a facility for care, because asymptomatic individuals are capable of spreading pathogen(s) via blood donation. While extensive testing is performed on collected blood, it is not possible to test for every pathogen, and validated screening methodologies may not exist for recently recognized pathogens. As of 2018, emerging pathogens of significant interest to the transfusion community include viruses such as chikungunya, dengue, and Zika, as well as parasites such as *Babesia* species (192, 196). Each of these agents poses unique health risks to transfusion recipients and is a safety concern to the blood bank community.

Although testing for all emerging pathogens is not feasible, there are new tools available to help abrogate the spread of both known and emerging infectious agents. Over the past 10 to 15 years, some alternative options for preventing transfusion-transmitted diseases have arisen in the United States and abroad. These modifications to blood components, referred to as pathogen reduction technologies, come in a number of different forms, including solvent/detergent or methylene blue treatment (mainly targeting enveloped viruses) to use of psoralens or riboflavin nucleic acid intercalators (which incorporate into nucleic acids and, after exposure to UV light, render microorganisms as well as any contaminating white blood cells incapable of replication) (197). While the above technologies have only been approved in the United States for application to plasma (solvent/detergent treatment; psoralen) and platelet products (psoralen), current studies are under way seeking to expand pathogen reduction technologies to all potential blood components, including red blood cells and cryoprecipitate (197–201). Overall, these are promising tools to help the U.S. and global blood bank communities stem the tide of emerging transfusion-transmitted infections. Moreover, hospitals looking to minimize the probability of transmission of emerging infections to patients and the protection of laboratory professionals working in the blood bank could consider stocking products which have been subjected to some form of pathogen reduction.

### Core Laboratory

Most clinical laboratories have a "core lab" that performs routine testing, i.e., chemistry, hematology, and select high-throughput tests, often coupled with automation lines or other automated or semiautomated platforms. While the automation of core laboratory testing means they are less "hands-on," the contamination of an automated chemistry line with high-consequence pathogens (202) would interfere with the processing of hundreds or thousands of other clinical tests performed on the same instrument platforms. Some laboratory tests require manual processing, such as blood gas testing, manual dilutions, or centrifugation. Cumulatively, this means the hazards to laboratory workers come from a variety of sources and the biosafety risks to core laboratories may be significantly different from those encountered during direct patient care, manual testing, and microbiology testing. CDC and OSHA recommend core laboratory staff involved in handling specimens should have training in Standard Precautions at regular intervals to prevent lax practices (43, 70). The infrequent handling of sharps and microbiological cultures means the overall risks for LAIs by core laboratory staff are low. However, gaps remain in our understanding of the risks associated with handling highly infectious agents, and thus opportunities exist to reduce these risks.

The biosafety risks for core laboratory specimens can be classified into two categories: the first category contains risks from an infectious agent whose identity is unknown at the time of testing, and the second contains risks related to tests performed on patients who are suspected or known to have a highly infectious disease, such as Ebola. However, when communication breakdowns occur, or when patients at risk are not initially identified, the line between these categories blur.

For the first category, clinical laboratories are expected to adhere to Standard Precautions for routine testing and safe handling of blood-borne pathogens, regardless of the presence of most routine infectious agents (42). In the case of some viral hemorrhagic fevers (VHFs), routine processing of clinical specimens has been performed under BSL-2 conditions, including circumstances where the suspicion for a VHF was not known *a priori* (203–205). However, the number of such cases is small, and the level of risk associated with handling of high-consequence pathogens in modern core laboratories is poorly understood. Core laboratory staff may be less aware of the potential contamination of specimen(s), containers, and instrumentation than specially trained staff, e.g., those who work in BSL-3 facilities or even general microbiology staff, who perform sterile technique and get frequent indirect feedback on their handling techniques (i.e., a technologist's culture contamination rate). Routine core laboratory processing procedures may also fail to follow guidelines for safe handling of highly infectious agents, e.g., centrifugation without sealed rotors (87, 180). Together, these personnel and instrumentation issues can create biosafety gaps.

The second category, when a highly infectious agent is suspected or known, substantially increases the potential for pathogen exposure in clinical laboratories. This increase in risk was demonstrated during the 2014 to 2015 Ebola outbreak by the disparity between the way U.S. laboratories prepared to handle samples and patients with potential Ebola, and how those laboratories faced with actual patients actually handled EVD. One example of this disparity was the decision to perform testing on POC instruments in the patient's room or adjacent containment laboratories versus performing assays on core laboratory instrumentation (108, 180, 206, 207). A distinct advantage of POC instrumentation is the ease of containment without exposure risks to the core laboratory. However, not all clinical laboratories have the necessary POC equipment to support patients under evaluation for EVD, not all instrumentation is approved for critically ill patients, the volume of testing necessary to care for these patients can overwhelm POC instrumentation, POC tests have a limited test menu, the performance of POC can differ from standard core laboratory instrumentation, and the costs associated with maintenance, as well as quality control, of containment laboratories and POC instruments is not inconsequential (180, 206–208). Finally, the safety advantage of POC testing versus core laboratory testing is undocumented. Some hospital laboratories could therefore be faced with deciding between performing testing on core laboratory instruments that may carry undefined risks to staff, to decline or to significantly limit the test menu for critically ill patients, or to perform testing on unvalidated POC instruments. Each situation raises biosafety, ethical, and regulatory gaps, as well as dilemmas. For more information regarding test selection, please see section "Real Life Example of Biosafety Risk Management-Experience of a Community Hospital Laboratory During an Outbreak Situation."

**Areas of biosafety risk concern in the core laboratory.** Core laboratories present specific challenges in biosafety (87, 209). These include that core laboratory staff may have less awareness of biosafety issues than staff who work in frequently contaminated or high-risk areas, and that core laboratory procedures may not be adequate for containment of dangerous pathogens; the evidence base around these issues is very sparse. Similarly, the evidence base associated with specific mitigation measures, including but not limited to manual specimen handling in BSCs and substitution of near-patient testing for core laboratory testing, is limited. There is a critical role for manufacturers of clinical laboratory instrumentation in assessment and improvement of risk management, i.e., protecting instrument operators and maintenance personnel against infectious materials. While some organizations are developing guidance to address decontamination of laboratory equipment (e.g., CLSI is developing QMS27 Decontamination of Laboratory Equipment and Instrumentation), there remains an unmet need for guidance to laboratories on use of instrumentation, including high-throughput systems, for specimens from patients with emerging pathogens, and decontamination afterward.

For clinical laboratories without specific containment laboratories, several strategies that address both routine preparedness and scenarios where a specific agent is known or suspected have been demonstrated to mitigate risks in the core laboratory. CDC recommends the use of a risk assessment to assess risks and establish precautions and procedures to minimize exposure (15). For example, evaluation of the risks of manual manipulation of specimen tubes in a BSC versus the risks of using automated equipment. This can include scenarios where automated lines move uncapped tubes or use unsealed rotors, followed by an assessment of the error rate of automated versus manual specimen processing (87, 180). Additional evaluation of workflow modifications, such as performing all manual high-risk activities in a BSC or other form of containment, may be valuable. Workflow modifications do not necessarily need to be expensive or cumbersome. A simple modification to the procedure for handling a blood gas syringe to expel clots directly into a biohazard bag instead of onto gauze held by a gloved hand or exposed bench can reduce the risk associated with performing manual procedures in core (and other) laboratories. Manufacturers have an opportunity to work with clinical laboratories by providing detailed risk assessment documentation and cleaning procedures, recommending or providing splash shields and other containment options, particularly around high-risk areas such as decappers, and developing instruments that can sample from closed tubes (87).

### Microbiology Laboratory

In contrast to other areas within clinical laboratories, the microbiology laboratory is the one area where infectious organisms are deliberately amplified. Exposure risk begins with the handling of the outside of a specimen container and continues with the direct specimen setup that requires manually handling the specimen, inoculating medium, and preparing slides for staining—all activities with more manual manipulation than routine core laboratory testing (15). Microbiology specimens may pose different risks because of the diverse specimen types (15, 210), from blood and body fluids to tissues, feces, and swabs, received in a clinical microbiology laboratory. The risks encountered during general practice in the microbiology laboratory also vary. They include exposure during the examination of culture plates for microbial growth. During the reading process of bacterial and/or fungal isolates, there is an unclear risk of viral exposure from aerosols generated when opening plates or sampling liquid cultures, particularly if the viability of emerging/reemerging pathogens in culture medium is unknown. Further handling of cultures for identification by phenotypic/biochemical testing, mass spectrometry, and/or molecular extraction may increase risk. In particular, routine identification of bacteria and fungi by mass spectrometry can lead to exposures unless organisms are inactivated or instrument manufacturers incorporate biosafety features (211).

Most clinical microbiology laboratories have easy and routine access to BSCs. Some clinical microbiology laboratories are equipped with BSL-3 facilities, which may be routinely used for mycobacterial and fungal cultures (212). Clinical microbiology staff can receive specific training on infectious risks and have daily practice handling infectious specimens because of the requirement to follow aseptic technique. However, exposure and infections due to bacterial, fungal, and parasitic agents also continue to be a problem in clinical microbiology laboratories (24, 48).

**Areas of biosafety risk concern.** The Ebola outbreak identified previously unrecognized safety issues and gaps in safety procedures for clinical microbiology laboratories (213) and, despite CDC's guidance stating it was safe to test specimens from PUI for EVD in the clinical laboratory (119, 120, 214), many concerns were expressed by microbiologists. One concern was blood cultures, which are one of the major tests performed by laboratories and are critical for patient care (215). Not all blood culture instrument platforms were designed to use the CDC-recommended plastic bottles; therefore, many laboratories used glass bottles for blood cultures. If broken, glass bottles pose a risk for exposure to blood-borne pathogen(s). Laboratories were also concerned about potential exposure to aerosols when venting of the culture was required

prior to placement in the instrument. As it is rare for a laboratory to have more than one blood culture instrument platform, these challenges were hard to overcome. Alternative techniques, such as manually subculturing blood cultures, are imperfect in several regards. Manual subculturing is a slow and labor-intensive process and, if the specimens contain high concentrations of pathogens, there may be significant added risk. Additionally, subcultures from broth to solid medium will delay detection time for potentially significant agents of bacteremia. In addition to the difficulty in switching from an automated to a manual method, many clinical laboratories lack the procedures and trained personnel for manual culturing. One of the recommendations during the 2014 Ebola outbreak was to transport specimens from the bedside and decontaminate the exterior surface of the vial prior to placing the vial on the instrument (119). This practice, while not routine in most laboratories, might reduce risk from any bloodborne pathogen. Ebola also presented a problem for those laboratories that perform viral cultures. While the numbers of laboratories that perform viral cultures is decreasing (216, 217), these laboratories are at particular danger of replicating high-consequence pathogens if providers order tests without communicating possible hazards to the laboratory.

In addition to blood cultures, adherence to safety practices applies to other traditional microbiology specimens (upper and lower respiratory, urine, tissue, and body/joint fluids) and cultures. The objective is to avoid needless exposure to potentially dangerous pathogens by active manipulation of viable organisms when examining cultures. Some *Mycobacterium* spp. will grow on traditional blood agar plates and represent a potential biosafety hazard. Additional examples are *Brucella* spp., and *Francisella tularensis*. Because of their comparative rarity in many laboratories, identification is frequently delayed, resulting in risk of exposure to laboratory personnel. According to current American Society for Microbiology protocols (https://asm.org/Articles/Policy/Laboratory-Response-Network-LRN-Sentinel-Level-C), observing small Gram-negative rods in the initial Gram stain should automatically be followed with all manipulations being performed in a biological safety cabinet. The application of biosafety practices also applies to the management of specimens submitted for fungi, viruses, and parasites. There is currently no published data regarding hazards from respiratory or other viruses in standard bacterial, fungal, or mycobacterial cultures on solid media.

Many guidelines for testing specimens from PUI for EVD emphasized a need for triaging testing to maximize diagnostic yield, while limiting low-yield diagnostics less likely to impact clinical decision making. For example, tests were needed to rule out malaria for some patients (11) and while some nucleic acid-based assays for *Plasmodium* species exist, the standard thick smear remains a gold-standard diagnostic because of its increased sensitivity compared to thin smears and antigen-based rapid diagnostics. To maximize safety without compromising patient care, there is a need for highly sensitive malaria diagnostics that can be performed on inactivated specimens or within BSCs (218, 219). In contrast to tests critical to time-sensitive diagnoses, many laboratories have identified tests that can be deferred until an emerging pathogen is ruled out. For example, a rapid group A streptococcal antigen test may come with a risk of manual manipulation of direct specimens, but the patient does not need to be immediately treated to prevent the long-term sequela of the infection.

The 2014 Ebola outbreak highlighted that many clinical microbiology laboratories approached waste management by eliminating autoclaving of waste and, instead, relied on vendors to haul waste off site. Some RMW may require special permits and procedures, and vendors face their own downstream problems with potentially highly infectious waste (80, 220).

### Anatomic Pathology: the Practice of Surgical Pathology, Cytology, and Hospital Autopsy

The practice of surgical pathology, cytology, and autopsy may have regular manual contact with large volume/mass specimens with high titers of unknown and/or known pathogens, raising concerns of percutaneous, droplet, and aerosol exposures. Here, we

will focus on surgical pathology and autopsy risks, a subset of which are shared by cytology.

**Risks associated with surgical pathology and autopsy.** In surgical pathology, the risks begin in the operating room and procedural suite, where blood and body fluids can contaminate paper requisition forms and the outside surfaces of specimen containers (15, 221). Pathologists and other clinical staff, accustomed to handling tissues and fluids, may be desensitized to the presence of potentially infectious materials on requisitions and specimen containers, which may subsequently be handled without PPE. Furthermore, nonclinical administrative support staff may be less familiar with infectious risks and safe handling practices. Potential risks increase substantially in the gross room during manual specimen handling and dissection, where the physical nature of the specimen, particularly bone fragments and foreign objects, as well as surgical instruments, such as scissors and scalpels, pose percutaneous injury risks (15). Another risk is the cryostat which is a refrigerated unit that contains a microtome with a razor-sharp blade. It is used to cut frozen sections on fresh, unfixed tissue in order to render a rapid preliminary diagnosis to guide the physician performing surgery. The sharp blade can result in cuts to the hands and fingers during placement of the tissue prior to sectioning, when repositioning the blade, or during cleaning and disinfecting the unit. In addition, when frozen tissue is cut using the cryostat, there is an exposure risk to the operator's skin, mouth, nose, and eyes from aerosolization of frozen tissue fragments which accumulate in the tray beneath the microtome as the tissue is cut. These fragments are small, extremely thin, and easily moved by air currents around the instrument or by the operator's breath as they cut the tissue (171, 215). While respiratory protection and face shields may mitigate this risk, they are not always worn (174, 222).

The autopsy suite is similar to the surgical operating room, as the pathologist and support staff routinely work with sharp instruments, such as scalpels, scissors, surgical needles, as well as bone saws, and exposure to large amounts of blood and body fluids is a regular occurrence. Each deceased patient has the potential to harbor unsuspected infectious disease(s) and, therefore, all autopsies are performed using Standard Precautions (221). PPE is the first line of defense and includes full body coverage: scrub suits covered by long sleeved surgical gowns with plastic aprons, arm and leg covers, head covers, shoe covers, double gloves, respiratory and eye protection. High-risk autopsies are defined as those conducted on patients who have transmissible agents and infectious diseases that could be transferred to the autopsy staff and result in chronic disease or death. Examples include tuberculosis, AIDS, Creutzfeldt-Jakob disease (Prion disease), Hantavirus pulmonary syndrome, *Neisseria meningitidis*, HBV, and HCV. While Standard Precautions were designed to protect health care staff from blood-borne diseases, special precautions need to be followed when some diseases are suspected, such as Creutzfeldt-Jakob or other prion diseases (223). Communication among individuals (prosectors) who perform the autopsy is particularly important when multiple people are involved in a case, or for personnel accustomed to performing individual dissections in surgical pathology. Waters et al. recommend that, in these cases, only one person should perform the autopsy at a time to reduce the risk of a sharps injury between prosectors (224). However, when Ebola became a concern, the recommendation was not to do an autopsy at all (221) unless considered absolutely necessary after consulting with CDC (163).

Many factors may contribute to suboptimal conditions under which some autopsies are performed. For example, the design of older facilities may not provide adequate space to meet current recommendations for donning and doffing in separate areas. Air handling recommendations include downdraft ventilation and negative pressure airflow (12 air changes an hour), which may not be present in such facilities (225). The recommendation for separate storage areas and morgue also may present challenges (221, 224). Another issue is that the declining rate of autopsies may result in pathologists with less experience which, in turn, could result in an

increase of occupational injuries (224). The pathology community should remain alert for known and emerging infectious diseases that may require a specialized approach. This is demonstrated by the historical reports of Ebola virus transmission at autopsy (226–228), which clearly indicates the risk that highly infectious pathogens pose. Furthermore, the 2014 to 2015 Ebola outbreak raised additional infectious and logistical considerations with how to handle expired patients with highly infectious pathogens (222), particularly when the postmortem handling of patients, independent of autopsy, have been historically associated with exposure and transmission of Ebola. Additional information regarding the risks associated with autopsy and surgical pathology are available elsewhere (226).

For both surgical pathology and autopsy pathology, some infectious risks remain following routine formalin fixation and processing (229). This is a cause for concern, as postfixation specimens may be processed without PPE. Concerns have also been raised in nonclinical embalming (229). Notably, prions are not destroyed by routine fixation and must undergo additional decontamination procedures (14). This can pose a significant risk if the presence of prions is not previously known. Reports of viable pathogens from formalin-fixed tissue have also been described, including organisms thought to be environmentally stable such as *Coxiella burnetii* (230) and *Mycobacterium* spp. (231, 232), as well as even more commonly encountered bacterial pathogens (232). Incomplete fixation due to large or lipophilic (fatty) specimens or minimization of fixation time for efficiency and turn-around-time may further increase the risk of incomplete killing of infectious agents in fixed tissue.

**Mitigation and future research.** Although studies often lack the granularity to identify risks exclusive to pathology, it has been demonstrated that laboratory staff and pathologists are likely among the higher-risk groups of HCW (33, 233). A national survey in Switzerland with 163 respondents identified cutting injuries in 52.8%, needle injuries in 19.1% of pathologists, and 22.7% of all respondents who had experienced an injury within the last year (234). Fortunately, only one case of HBV transmission was attributed to occupational exposure by the respondents in this study. In addition, aerosolization of tissue fragments, blood, and body fluids also remains a concern, as aerosolization of *M. tuberculosis*-infected tissues and body fluids is a known risk among pathologists and support staff working with surgical and autopsy specimens (222). Risks due to aerosolization of hazardous materials when using cryostats are being addressed through the use of PPE, design modifications (e.g., negative airflow and downdraft airflow), etc. However, additional research and discussion with manufacturers of cryostat instrumentation, as well as engineering solutions, in order to ensure the safety of operators as well as other personnel in close proximity to the cryostat are needed. Autopsies have unique biosafety risks which may be more complicated to address than those of the clinical sections of the laboratory. However, it is without question that autopsies have a role in public health by providing valuable information for hospital quality assurance and risk management programs, clarifying cause of death, revealing unknown disease states, contributing to the surviving family medical history, and providing physician knowledge as well as education (100). One of the many examples where an autopsy revealed an unsuspected public health crisis was the 2012 fungal meningitis outbreak. The index case was found to have an invasive fungal infection of his brain at the hospital autopsy, which was traced back to a contaminated steroid medication, delivered via injection. The ensuing hospital and public health investigation eventually identified over 753 people who were infected and 64 deaths (235).

Here, we have described risks and identified gaps, as well as areas for improvement, in the practice of anatomic pathology. Beginning with requisition forms and specimen transport containers, to processing fixed specimens, there is an opportunity for additional studies and risk mitigation strategies to evaluate and reduce associated biosafety risks. Increased power and granularity of data on LAIs would lead to a better understanding and reduced risks to personnel in pathology and

| RISK ASSESSMENT | | | | | |
|---|---|---|---|---|---|
| Yes | No | Not Applicable | | RESOURCES | COMMENTS |
| ☐ | ☐ | ☐ | Is there a written policy and/or a standard operating procedure (SOP) for performing risk assessments? | Biological Risk Assessment Guidelines can be found on pages 7-12 of CDC's Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories | |
| ☐ | ☐ | ☐ | Do risk assessments consider both agent hazards and laboratory procedure hazards? | An example Risk Assessment form can be found on CDC's Biosafety Website. | It is recommended that at a minimum risk assessments include:<br>• an assessment of risks associated with specimen source and likely organisms<br>• method of transmission, route of exposure, infectivity and infectious dose<br>• test requested from submitter<br>• epidemiological information such as symptoms, travel history, and occupation<br>• risk factors and experience of individual performing the assay<br>• when assays require inactivating BSL-3/4 agents and bringing them out to a BSL-2 for testing |
| ☐ | ☐ | ☐ | Has the person performing the risk assessment received training and are they experienced in risk assessments? | | Examples of trainings include the American Society of Clinical Pathology's "Using Risk Analysis to Assess Biosafety" and the American Biological Safety Association's "ABSA Advanced Biosafety Training Series Module 1" |
| ☐ | ☐ | ☐ | Is a risk assessment performed when:<br>• new assays are introduced?<br>• new methods are introduced?<br>• equipment is moved?<br>• new equipment is introduced?<br>• the potential for aerosolization is introduced<br>• the potential for needlesticks is introduced?<br>• a laboratory is physically moved?<br>• a new pathogen is detected?<br>• staffing changes? | | |
| ☐ | ☐ | ☐ | Are risk assessments conducted annually for assays performed in the laboratory? | | |

**FIG 3** Sample checklist to document risk assessment from APHL (171). An example checklist to document risk assessment from APHL. CDC's Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories is available at https://www.cdc.gov/mmwr/pdf/other/su6101.pdf and the Biosafety Website is available at https://www.cdc.gov/safelabs/resources-tools.html. The ABSA Advanced Biosafety Training Series, including the module containing the checklist, can be accessed at https://absa.org/abts/. (Reproduced from reference 171. © Association of Public Health Laboratories. Reprinted with permission; all rights reserved.)

other disciplines that also encounter similar risks but have differing workflows. Given the potential high risks associated with anatomic pathology specialties, additional evidence-based and ethical guidelines could identify which pathology procedures are necessary and do not compromise patient care when an emerging infectious disease is detected, versus procedures which may be triaged and performed at a later date. Lastly, Regional Autopsy Centers have been suggested to address the issue of hospitals that perform few autopsies per year and may not have the skilled autopsy staff or autopsy facilities that meet national and regional safety standards. These centers would be staffed with appropriately trained personnel and housed in well-designed facilities. It is thought this would facilitate adherence to safety guidelines and standards, as well as provide other benefits, including education and research (236).

## BIORISK MANAGEMENT

### Risk Assessment in Clinical Laboratories

Every organization seeks to protect their workers, the community, and the environment against hazards. Clinical laboratories working with hazards such as infectious agents or toxins carry an additional biosafety risk of exposure and disease. Risk assessments are iterative processes that help institutions to understand, then mitigate, and thereby manage their risks—not just protect against hazards (237). Many industries require risk assessments; CDC and WHO biosafety guidelines also recommend the use

**Risk Assessment Template: Centrifuge Use**

| Description of Risk | Hazard | | | | Analyze/Evaluate Risk | | | |
|---|---|---|---|---|---|---|---|---|
| | Source | Current Controls | Event | Category | Consequences | Agents | Exposure | Probability |
| *Door Release Lock Fails:* Centrifuge has an inbuilt control so it cannot spin if door is not properly locked. If locking fails, user is at high risk of injury from spinning rotor. | Mechanical | When built in control fails, notify safety officer immediatly and do not use centrifuge. Wait for the rotor to stop spinning completely, before opening lid. | Injury can result from spinning rotor at a very high speed when lid is opened. | Being hit by a moving object. | **Substantial:** Centrifuge speeds can reach up to or greater than 20,000rpm | N/A | **Frequent:** Daily use of centrifuges types. | **Practically Impossible:** Built in safety mechanism in centrifuges. Injury unlikely if control measures are followed. |
| *Exposure to Biological Fluids:* All personnel in the lab use centrifuges. | Microbiological | All personnel are trained in use of centrifuges. Use of PPE. Personnel required to consult MSDS and perform risk assessments for any chemicals being used in lab. Clean up spills immediately according to MSDS instruction. Balance tubes carefully (by weight for larger centrifuges [tubes over 10mL], by eye for microfuge {0.5-2.0mL tubes}). Inspect equipment prior to use. External maintenance as required. Place cups on buckets or rotor prior to centrifuging hazardous substances to prevent leakage during use. Imbalance function detection built in on some centrifuges to cause the centrifuge to stop if unbalanced. | Containers may break due to faulty equipment, tubes being unbalanced, tubes being damaged or not sealed correctly. This can result in gross spillage of hazardous biological fluids or the generation of hazardous aerosols. | Contact with, or exposure to biological factors. | Substantial: Worst case scenario - e.g. spinning samples, spills or aerosols created through incorrect usage may (at worst) cause transmission of pathogens. | Bloodborne Pathogens Hep B, Hep C, HIV easily inactivated by laboratory hospital approved disinfectants. Infectious dose unknown. Hep B stable in dried blood (up to 7 days at RT). Hep C is viable for at least 16 hours (up to 4 days at RT). HIV is vialbe for 1-3 days after drying (longer if frozen). From whole blood, serum, plasma, CSF, urine. Vaccine available for Hep B. | **Unusual:** Less harmful materials (such as cultured cells) is centrifuged on almost a daily basis. | **Conceivable:** It is unlikely to happen if lids are placed on buckets and if correct tubes are used, but not impossible. |
| Exposure to Hazardous Chemicals: All personnel in the lab uses centrifuges | Chemical | All personnel are trained in use of centrifuges. Use of PPE. Personnel required to consult MSDS and perform risk assessments for any chemicals being used in lab. Clean up spills immediately according to MSDS instruction. Balance tubes carefully (by weight for larger centrifuges [tubes over 10mL], by eye for microfuge {0.5-2.0mL tubes}). Inspect equipment prior to use. External maintenance as required. Place cups on buckets or rotor prior to centrifuging hazardous substances to prevent leakage during use. Imbalance function detection inbuilt on some centrifuges to cause the centrifuge to stop if unbalanced. | Containers may break due to faulty equipment, tubes being unbalanced, tubes being damaged or not sealed correctly. | Single contact with chemical or substance. | Substantial: Depending on chemicals involved, persons could incur injury to skin. | N/A | **Rare:** Personnel use centrifuge on a weekly basis with solutions that contain various components. | **Conceivable:** Conceivable that exposure may occur but unlikely with control features in place. |
| *Injury in Quick-Spin Centrifuges:* Use of microcentrifuge on daily basis to quickly spin down 0.2mL, 0.5mL, 1.5mL tubes. | Mechanical | The lid is secured before the quick spin is commenced. The lid is not openeed till the centrifuge stopped completely, and then the tubes are removed. Also the centrifute is placed in the center of the bench, and not close to the edge to avoid it falling off the bench during the spin. | The fingers may get hit if attempt to remove the tubes while the centrifuge is still in spin mode. These centrifuges are light weight and at such high speed could move and fal off the bench if it was placed near the endge and could cause injury to part of body (i.e. foot). | Being hit by a moving object. | Substantial: Could get hit by a flying object or fingers hit when rotor is still spining. | N/A | **Frequent:** Quick-spin microcentrifuges are used on a daily basis | **Conceivable:** Unlikely if used properly. |
| *Risk of Electrocution:* When equipment fails, electrical hazards can cause damage. | Electrical | Circuit breakers, induction and training in use of the equipment. Power supply to the centrifuge should be regularily checked. Relevant equipment is tagged and tested. Equipment is tested by engineering for technical compliance annually. As long as equipment is maintained in good operating condition, the risk of electrocution is larely negated. | Exposure to live current. Movement of equipment can cause damage to leads, exposing user to electrical hazard. | Contact with electricity. | Very Serious: Person could get an electric shock causing disability or fatality. | N/A | **Rare:** Rare exposure to live electricity, especially with regular testing and tagging in place. | **Practically Impossible:** All power points in lab are grounded. Equipment is tested by engineering for technical compliance annually. |
| *Rotor Failure or Detachment During Use:* Imbalance and mishooked buckets can cause rotor failure. Corrosion and stress can also cause rotor failure. Rotors damaged due to dropping etc. can cause rotor to fail. | Mechanical | All personel are trained in use of centrifuge. Balance tubes carefully by weighing tubes on a balance. Tubes to be balanced across from each other in rotor. Check all buckets are hooked correctly and can swing freely before starting centrifuge. Visually inspect rotor for signs of damage before use. External maintenance as required. | Very poor balance of tubes may cause the rotor to fail during operation, possibly generating flying debris. Rotors are dropped while changing-causing injury to personnel or compromiseing rotor integrity. | Being hit by moving object. | Substantial: Depends on degree of rotor damage and speed and size of centrifuge, top speed would be 4000 rpm in the lab. | N/A | **Frequent:** All personnel in the laboratory use a centrifuge on almost daily basis. | **Conceivable:** A person may forget to balance their tubes or not notice a fault in the centrifuge itself. |

| | | | |
|---|---|---|---|
| **Department** | | **Manager** | |
| **Section** | | **Supervisor** | |
| **Assessor** | | **Date** | |

**Laboratory Director(s) Signature**

**FIG 4** Sample equipment-specific risk assessment (277). An example of an equipment-specific risk assessment from Yale-New Haven Health System Department of Laboratory Medicine. (Reproduced from reference 277 with permission of Yale-New Haven Health System.)

of risk assessments (14, 210). However, compared to a more traditional research-focused laboratory setting, assessing the biosafety risks within a clinical laboratory presents distinct challenges. Clinical laboratory staff often receive limited specimen information and rarely know the infectious agents(s) or other hazards (e.g., chemical or radiological) present in the specimen(s) received. Furthermore, clinical laboratories receive a variety of different types of tissue and fluid specimens from numerous patients on a daily basis that may contain multiple hazardous agents within a single clinical specimen. These unknown hazards potentially increase the risk of exposure to staff in a clinical laboratory setting.

Risk assessment, along with risk mitigation and performance evaluation, are components of a biorisk management system (237). Risk assessments enable organizations to effectively identify biohazards and assess and prioritize risks in order to implement mitigation controls that reduce the risks associated with hazardous biological materials. The overall performance of the system is continually evaluated based on implemented controls, which reinforces continuous improvement. This cyclic process of assessment, mitigation, and performance evaluation allows biorisk management systems to respond to ever-changing biosafety and biosecurity needs. Biorisk management systems are analogous to a QMS or individualized quality control plans (IQCP) that clinical laboratories use to produce and sustain quality test results (183). The difference is that the intent of biorisk management system(s) is to reduce the risk of exposure to biological agents and toxins for staff, the surrounding community, and the environment. Although OSHA requires clinical laboratories to have laboratory safety plans (43, 238), not every organization utilizes biorisk management systems or has incorporated biosafety into their QMS.

As a means to identify sources of exposure, a risk assessment needs to be conducted for each activity within the specimen management chain (15, 207, 239). Most assessment methodologies start with the nature of the infectious agent. However, as clinical laboratories do not normally know the presence, let alone the identity, of the infectious agent(s) in specimens, this uncertainty contributes to gaps in assessing risks. A number of U.S. clinical laboratories that conducted risk assessments during the Ebola outbreak encountered gaps in knowledge, understanding, and/or experience to conduct biosafety risk assessments (13, 240). Often they proceeded directly to implementing mitigation controls, without assessing the risks of the procedures performed in the laboratories (241, 242). The implementation of direct mitigation strategies that block the routes of exposure (i.e., portals of entry) into the body (e.g., eyes, nose, mouth, and nonintact skin) reduces the risk of transmission but may not fully consider the nature of the infectious agent.

Additional information that can allude to the identity of the infectious agent may include the geographic origin of the specimen, the patient's travel history, and recent outbreaks in the area/region. However, this information rarely is relayed to the clinical laboratory at the time a specimen is received. Other considerations include: the type of specimen submitted and test(s) ordered, organisms encountered in the population, and the knowledge of chronic or previous medical diagnoses. Clinical laboratories may encourage physicians to notify the laboratory when they suspect patients may have an infectious disease that could pose specific risks to laboratory staff.

CDC recommends risk assessments be site specific and representative of the activities performed (15). Guidance and templates for performing and documenting risk assessments are available from APHL and WHO (243). Fig. 3 and 4 serve as examples of Risk Assessment Forms.

### Evaluation

Institutions adopt safety management systems in order to transition their approach to biosafety/biosecurity from a single hazard representing a single risk that is mitigated through use of a biosafety level, to a systemic organization-level approach where the responsibilities and roles of each individual are defined. Risk assessments of each risk category within an institution serve as a foundation for biorisk management systems and are used to develop specific mitigation measures. One key aspect of these management systems is that performance needs to be constantly monitored to evaluate

and improve mitigation measures. This continual, iterative evaluation facilitates proactive risk-based decisions regarding the unique operations of each institution. As biorisk management systems consider every aspect of an institution's operations, and in any case are evolving and unevenly implemented, a comprehensive discussion regarding their effectiveness during the Ebola outbreak is beyond the scope of this review. However, there are components critical to biorisk management systems that span all laboratory specialties, where gaps were identified. These gaps highlight the absence of performance evaluation data to ascertain the effectiveness of the implemented controls. This demonstrates that without executing all three elements (assessment, mitigation, and performance evaluation) of the biorisk management process, the overall effectiveness of laboratory biosafety measures is impaired (237).

Mature quality improvement programs "complete the cycle" with schema such as "plan, do, check, act," where quality surveillance or monitoring leads to changes in policy. The effects of these policy changes are in turn evaluated to prove they have had the desired effect. Clinical laboratory safety systems at this time are rarely developed to the point of being fully cyclic; safety interventions are essentially preventative, often for rare events, and laboratories have not yet evolved systems for monitoring and evaluating safety interventions analogous to those for quality improvement (237). This constitutes a "gap" in the science of clinical laboratory safety. Ultimately, laboratories will likely evaluate safety interventions in ways analogous to infection prevention interventions in the health care system, i.e., by monitoring adherence to policies for PPE use, monitoring the effectiveness of administrative controls enforcing safe procedures, assessing the effectiveness of responses in outbreak drills and situations, and larger-scale efforts industry-wide to improve the safety of laboratory equipment and processes.

### Real-Life Example of Biosafety Risk Management—Experience of a Community Hospital Laboratory during an Outbreak Situation

During the 2014 Ebola outbreak, the first U.S. patient who was infected with Ebola virus while working in Africa initially presented to the Texas Health Presbyterian Hospital Dallas (Texas Health Dallas) Emergency Department, and then was eventually admitted into this hospital after his conditions worsened (244, 245). During the subsequent care of this patient, two nurses became infected with Ebola but made full recoveries (244, 245). This section focuses on how the clinical laboratory in this community hospital, without access to biocontainment units, successfully assisted in directing the care of these three patients by using risk assessment to guide the development of safe laboratory procedures, provided testing services needed for patient care while keeping laboratory personnel safe, and used the lessons learned to inform continual improvement in preparedness for emerging infectious diseases.

**Background.** Prior to the 2014 Ebola outbreak Texas Health Dallas clinical laboratory employed a basic SOP that addressed disaster readiness (e.g., plane crashes, tornadoes, chemical exposures) and infectious disease (e.g., select agents). For example, the general SOP for when infectious disease agents of concern were encountered included moving the associated microbiology testing to the mycobacteria work area (which was under negative pressure airflow), using PPE that was used for mycobacteria work, and performing testing on POC instruments or manually under negative airflow in a BSC. While these SOPs met laboratory accreditation guidelines at the time, they were not disease-specific and did not address risk assessment in writing.

**Risk assessment for updating biosafety standard operating procedure.** In response to admitting the first patient diagnosed with Ebola, the Laboratory Biosafety SOP planning and laboratory test services had to address several issues. These included assessing the scope of testing to be provided with effective communication of the testing menu, as well as the collection and transport of highly infectious specimens. It was necessary to produce processes and procedures for laboratory receipt and processing, including packaging and shipping of specimens. Plans were constrained by the instrumentation available for analytic processing, including staffing, PPE, and supplies, and

**Medical ICU Laboratory Test Menu and Guidelines for Patients with Ebola**

**The Laboratory will perform the following testing for Medical ICU patients with Ebola.**

- CBC without manual differential
- Blood Parasite (includes Thin Smear and Rapid Malarial Antigen)
- Comprehensive Metabolic Panel (as below)
  - Sodium
  - Potassium
  - Chloride
  - $CO_2$
  - Glucose
  - BUN
  - Creatinine
  - Total Protein
  - Albumin
  - Bilirubin (total)
  - AST
  - ALT
  - Calcium
  - Alkaline Phosphatase
- Beta HCG
- Bilirubin (direct)
- CK/CKMB
- Troponin
- GGT
- HIV
- LDH
- Magnesium
- Phosphorus
- Vancomycin

**Guidelines for Test Orders, Specimen Collection, Handling and Transport for Ebola patients**

1. One routine test run for analytes listed above will be performed each day at approximately 8:00 am. Blood draw should be collected prior to calling lab for transport.
2. Call the Core Laboratory and ask to speak to a laboratory supervisor.
3. Request that lab personnel be dispatched for transport of the specimen(s) directly from the cold zone in the ICU to the clinical lab.
4. If the ordering physician requires tests other than those listed or needs testing performed other than the daily morning run, the physician should contact the laboratory medical director prior to placing the order and/or obtaining the specimen.

**FIG 5** Example intensive care unit test menu used at Texas Health Dallas. This example test menu was used by Texas Health Dallas during the 2014 Ebola event. (Courtesy of Texas Health Dallas, reproduced with permission.)

by the need to plan for decontamination of instruments and environment, including management of laboratory accidents, management of specimen waste from instruments, including wastewater, and blood and body fluid specimen disposal and specimen storage. Finally, it was necessary to address the preparedness of staff, including training to perform testing with High Level PPE (HLPPE) and BSL-2/-3 precautions.

**Determination of laboratory test menu in response to Ebola cases. (i) Step 1: identify the risk level of the pathogen(s).** With consideration of the risks of transmission to the laboratory and clinical staff responsible for collecting patient specimens, several risk factors were initially assessed to determine the test menu for Ebola patients (Fig. 5). These risk factors included: (i) whether transmission of disease is airborne, droplet, or contact; (ii) which body fluids or tissues are infectious and what dose of pathogen results in disease; (iii) whether prophylaxis, vaccine, or treatments for the disease are

| Disease | CareConnect Order | Specimen Requirements | Shipping Category | How will results be communicated? | Positive or Critical Results Requiring a Phone Call |
|---|---|---|---|---|---|
| **Measles** | Rubeola Antibody IgM Isolation Panel | Serum, gold top | B | Results documented in CareConnect, no phone call | Entity to Caregiver and Infection Prevention |
| | Rubeola Antibody IgG | Serum, gold top | B | Results documented in CareConnect, no phone call | |
| | Miscellaneous Referral | Throat Swab, UTM 3mL | B | Results documented in CareConnect, no phone call | Entity to Caregiver and Infection Prevention |
| **Mumps** | Mumps Antibody IgM Isolation Panel | Serum, gold top | B | Results documented in CareConnect, no phone call | Entity to Caregiver and Infection Prevention |
| | Mumps Antibody IgG | Serum, gold top | B | Results documented in CareConnect, no phone call | |
| | Miscellaneous Referral | Buccal Swab, UTM 3mL | B | Results documented in CareConnect, no phone call | Entity to Caregiver and Infection Prevention |
| **Pertussis** | Bordetella pertussis by PCR | NP Swab, UTM | B to THD | *Results documented in CareConnect* | THD to Entity (Entity to Caregiver/IP) |
| **VHF** | Malaria Smears | Whole Blood (lavender) | B to HUB (other than Istat) | *Results documented in CareConnect* | HUB to Entity (Entity to Caregiver) |
| | CBC with auto-diff | Whole Blood (lavender) | | *Results documented in CareConnect* | HUB to Entity (Entity to Caregiver) |
| | Bedside Whole Blood Panel | Green Top | | *Results documented in CareConnect* | |
| | Group A Rapid Strep Screen | Throat Swab | | *Results documented in CareConnect* | HUB to Entity (Entity to Caregiver) |
| | Urinalysis Screen, no microscopic | Urine (yellow top) | | *Results documented in CareConnect* | |
| **MERS** | Rapid Flu Panel (aka Influenza) | NP Swab, UTM 1 ml | n/a performed at submitting entity | *Results documented in CareConnect* | Entity to Caregiver |
| | Pneumococcal Antigen, Urine or CSF | Urine (yellow top) | | *Results documented in CareConnect* | Entity to Caregiver |
| | Respiratory Viral Plus PCR, Isolation Panel | NP Swab, UTM 1 ml | B to THD | *Results documented in CareConnect* | THD to Entity (Entity to Caregiver) |
| **Avian influenza** | Rapid Flu Panel (aka Influenza) | NP Swab, UTM 1 ml | n/a performed at submitting entity | *Results documented in CareConnect* | Entity to Caregiver |
| | Group A Rapid Strep Screen | Throat Swab | | *Results documented in CareConnect* | Entity to Caregiver |
| | Respiratory Viral Plus PCR, Isolation Panel | NP Swab, UTM 1 ml | B to THD | *Results documented in CareConnect* | THD to Entity (Entity to Caregiver) |
| **Zika** | Zika IgM | Serum, gold top | B | *Results documented in CareConnect* | Entity to Caregiver |
| | Zika PCR, blood | Serum, gold top | B | *Results documented in CareConnect* | Entity to Caregiver |
| | Zika PCR, urine | Urine (yellow top) | B | *Results documented in CareConnect* | Entity to Caregiver |
| **Chikungunya** | Miscellaneous Referral | Serum, gold top | B | *Results documented in CareConnect* | Entity to Caregiver |
| | Miscellaneous Referral | serum, gold top OR plasma, lavender | B | *Results documented in CareConnect* | Entity to Caregiver |
| **Dengue** | Dengue Fever Ab IgG & IgM | Serum, gold top | B | *Results documented in CareConnect* | Entity to Caregiver |
| | Miscellaneous Referral | serum, gold top OR plasma, lavender | B | *Results documented in CareConnect* | Entity to Caregiver |

**FIG 6** Emerging infectious agent referral testing menu used by Texas Health Dallas during the Ebola event. UTM, universal transport medium; NP, nasopharyngeal; CBC, complete blood count; ARUP, ARUP laboratories; THD, Texas Department of Health; HUB, centralized microbiology HUB laboratory. (Courtesy of Texas Health Dallas, reproduced with permission.)

available; and (iv) what degree of risk is considered acceptable to the institution or to the individual(s).

This assessment was also used to generate a hospital-specific pathogen table of the most important transmissible human infectious diseases that may be encountered, thereby providing a quick reference for laboratory-related infection control information (Fig. 6) (246).

**(ii) Step 2: determine the scope of testing and responsibilities.** The restriction of the laboratory test menu for the Ebola patients was supervised by the medical director of the laboratory with the input and collaboration of clinicians, who provided direct care for these patients, to ensure testing essential for the diagnosis and acute treatment of the patients was available. The limited test menu included basic chemistry analytes, blood count, blood gas, routine coagulation testing, and limited infectious disease testing that could be performed as POC bedside testing.

The disease-relevant test menu was then vetted by administrative and laboratory technical managers to ascertain the acceptable risk of performing these test(s), taking into consideration the physical laboratory environment and staff competency. Communication of the available test menu, as well as the types and numbers of specimens needed for testing, was made easily accessible to staff in the patient care room(s) or departmental areas during the outbreak (Fig. 5 and 7). During the 2014 Ebola event, any deviation from the published test menu was vetted by both the clinician caring for the patient and the medical director of the laboratory. Routine add-on test orders for specimens stored in the

## Emergency Department Laboratory Testing Menu and Guidelines for Patients with Suspected Ebola

The Laboratory will provide the following tests for Emergency Department patients with suspected Ebola Virus.

### Symptomatic Patients with exposure to the Ebola virus patient with no travel history to Africa

- CMP (Comprehensive Metabolic Panel)- 4.5 ml light green
- CBC with automated differential only- 3 ml lavender
- 2 additional 6 ml EDTA lavender tubes for viral testing at the CDC and TDH

### Symptomatic patients with a recent travel history to Africa

- CMP (Comprehensive Metabolic Panel)- 4.5 ml light green
- CBC with automated differential- 3 ml lavender
- Blood Parasite: Thin Prep Stain and Rapid Malaria Antigen – 3 ml lavender
- 2 additional 6 ml EDTA lavender tubes for viral testing at the CDC and TDH

### Guidelines for Test Orders, Specimen Collection, Handling and Transport- DO NOT TUBE THE SPECIMEN OR DELIVER TO THE LAB LIAISON

1. Specimens should not be collected in triage before the physician has placed orders.
2. Collect only the tubes necessary to do the testing listed above.
3. Call the Core Laboratory and ask to speak to a laboratory supervisor.
4. Confirm with the Lab Supervisor that Infection Prevention has been notified.
5. Request that lab personnel be dispatched to transport the specimen directly from Pod 3 to the lab. The lab personnel will meet the Pod 3 nurse at the double doors without compromising the nurse's PPE or entering the isolation area. **The specimen should not be delivered to the ED Lab Liaison Area, transported through the tube system, or transported from to the laboratory by non-lab personnel.**

**FIG 7** Example emergency department test menu from Texas Health Dallas. (Courtesy of Texas Health Dallas, reproduced with permission.) TDH, Texas Department of Health.

laboratory, while a typical process in community hospitals, was determined not acceptable because of the risk of transmission of disease.

The laboratory testing risk assessment also included utilization of communication mechanisms to review and update processes as the clinical situation changed to ensure patient-centered care. Guidance was provided to the medical staff on making laboratory test ordering decisions based on carefully weighing the clinical value of the test result to patient care, with the risk of exposing laboratory staff to a high-consequence pathogen and possible contamination of the core laboratory environment. All communication regarding testing had to be evaluated first by the medical laboratory director in collaboration with clinicians and then with the support of the administrative laboratory director.

During the 2014 Ebola outbreak, Texas Health Dallas Hospital also observed that, in addition to the routine critical care analytes listed above, it was necessary to test for blood group and type, as plasma from convalescent patients could be used as a source

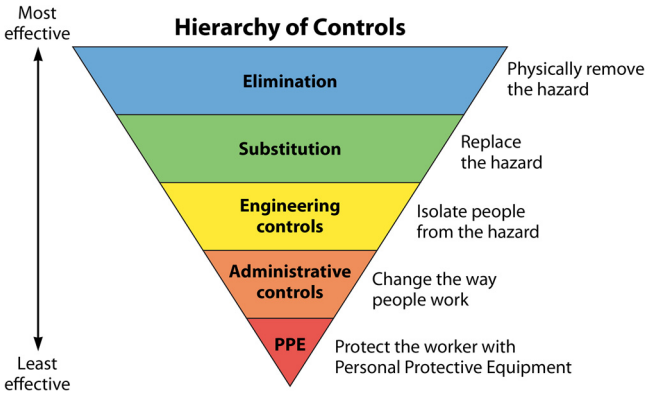


**FIG 8** The hierarchy of controls as described by CDC (www.cdc.gov/niosh/topics/hierarchy/default.html).

of immunotherapy for acutely ill Ebola patients. Slide agglutination testing was performed in a Class II BSC within a negative air pressure room by blood bank staff in HLPPE. Renal failure in an Ebola patient being treated with antibiotics (vancomycin) initiated a request for therapeutic drug levels to determine possible toxic levels of the antimicrobial as the proximate cause of the renal insufficiency. Since vancomycin was available on the chemistry robotic line, the risk assessment was deemed similar to the other analytes being performed on the line, and the test was performed. These examples of unexpected test requests, which were medically reasonable or necessary for treatment, reinforced the need for iterative planning and reconsideration of both the original test menu and the biosafety plan during the outbreak (180).

**(iii) Step 3: define the strategies for risk mitigation.** Several infection control strategies were considered and instituted at Texas Health Dallas (Fig. 8). The test menu was limited to the minimum analyses that were essential for acute treatment or differential diagnosis of the disease process in order to mitigate laboratory transmission risk while providing results for PUI or until the patient was diagnosed and transferred to a higher level of care (Fig. 5 and 7). Substitution controls were used, such as using a closed system of testing in the laboratory or performing bedside testing in the patient's room using POC instrumentation when possible. Performing testing in the patient's room, instead of in the core laboratory, mitigated the risk to laboratory professionals and many others by limiting risk of exposure, phlebotomy contact, and the transport of infectious specimens within the hospital (Fig. 8).

Other controls, such as controlling the timing of the testing and limiting the number of laboratory staff exposed during testing, were important to decreasing the risk of transmission. Frequent drills and training which addressed PPE, its proper use, and donning and doffing were essential to the safety of the laboratory staff.

**Biosafety controls. (i) Engineering controls to mitigate risk in the core laboratory.** Texas Health Dallas Hospital utilized an isolated (or partitioned) laboratory work space, rotor covers for the centrifuge, multiple BSCs, a negative air pressure room with anteroom, an autoclave, a closed-system chemistry robotic track with decapper, and limited transport of infectious specimens to mitigate risk of transmission during the Dallas Ebola event. Limiting the number of specimens, as well as the proper packaging of the specimens (247) during transport, were also vital to achieving infection control (Fig. 8).

During the Ebola event, routine daily testing (diagnostic monitoring) in the core laboratory was limited to specific times of the day and was carefully choreographed by laboratory staff in collaboration with ICU nursing colleagues. Every batch of testing was conducted in a cordoned area by two laboratory staff who wore HLPPE and who employed the buddy system; one staff served as an observer to critique proper aseptic technique and ensure utilization of biosafety protocols while the other functioned as

the test-performing analyst. Testing was performed at a designated time each day of service, after the routine patient specimens had been run, and was coordinated with the nursing service by verbal communication. Excess movement of staff within the laboratory was restricted during the testing period. Dedicated analyzers were used each time for testing to reduce the instrumentation that required decontamination.

To support acute care needs in the ICU, more frequent diagnostic testing was performed in the patient's room by the direct patient care staff. Critical analytes such as electrolytes, glucose, creatinine, and hematocrit/hemoglobin were performed on a dedicated wireless POC instrument.

**(ii) Administrative controls and PPE to mitigate transmission risk.** During the Ebola outbreak, Texas Health Dallas developed a set of administrative controls and other rules to mitigate transmission risk for the safety of both the patients and the laboratory professionals (Fig. 8). Personnel who performed the testing were experienced laboratory scientists who were knowledgeable with the HLPPE donning and doffing procedure, and who were familiar with the instrumentation utilized. In the case of Class II BSC use, administrative controls were in place to ensure that unsafe work practices did not subvert other control systems, such as engineering control(s). Staff performing tasks in the BSC were observed by senior medical laboratory scientists with BSC experience in order to mitigate risky behaviors while working with Ebola-contaminated specimens.

Laboratory testing was performed using a minimum number of staff to reduce potential exposure. The restricted test menu minimized total testing time, which decreased the likelihood of physical or mental fatigue, as well as excessive situational anxiety while working with highly infectious specimens. Rotating testing personnel was also necessary to give staff a break from highly stressful tasks. It was important that the staff who performed analyses were comfortable working in HLPPE, remained intensively focused on tasks, and understood the testing SOP, including procedures for spills or splashes in case of a laboratory accident. Contingency planning for the continuation of routine testing for all other hospitalized patients in case of a laboratory accident was considered.

Risk assessment was also conducted on available instrumentation and the addition of closed systems for testing, including but not limited to rotor caps in centrifuges to prevent aerosolization, robotic lines with closed decappers, and waste bins that contained bleach for immediate decontamination of discarded consumables. In the absence of a robotic decapper, the procedure was performed with gauze placement over the blood tube cap to avoid splash, with tube manipulation carried out within the BSC by laboratory staff attired in HLPPE, as needed.

At the time of the 2014 Ebola event, highly infectious pathogen instrument decontamination and particle dispersion had not been specifically evaluated by every instrument vendor, and assurances regarding the efficacy of routine instrument decontamination or the risk of instrument methodology resulting in pathogen dispersion were lacking in vendor-supplied documentation. Therefore, instrument malfunction, tube breakage or spillage, decontamination, as well as waste disposal, were also considered in the individual instrument risk assessment and documented in the biosafety preparedness SOP to complement the information provided in the vendor documentation.

**Lessons learned.** These hard-won practical experiences showed that high-consequence pathogen specimen testing could be performed in a community hospital core laboratory without resulting in LAIs. With proper risk assessment and mitigation procedures, a community hospital laboratory could safely test the specimens of patients who might have an emerging infectious disease without a biocontainment unit while protecting the health of patients, clinical staff, laboratory staff, and the community. For a clinical laboratory that did not have access to high-consequence biocontainment facilities, having strategies and processes in place to optimize biosafety and infection control was critical for providing timely and medically necessary diagnostic testing services that were essential to the initial care of the patients. Even the most carefully

developed SOP could contain biosafety gaps unless the risk assessment encompassed the total testing process, including observation of the staff performing specific tasks in appropriate PPE in the physical environment where the work was accomplished. In addition, laboratory expertise was critical for the order-test-report decision tree and needed to be included on all primary communications to identify tests that could be safely performed for PUIs for emerging infectious diseases.

**Post-Ebola laboratory preparedness plans.** The lessons learned during the 2014 outbreak have informed the current Texas Health Dallas laboratory preparedness plan, which continues to be reviewed and improved as needed. The backbone of the plan is the risk assessment process that occurs for each of the tasks that the laboratory is responsible for.

Laboratory SOPs for emerging infectious diseases are standardized across the Texas Health Resources system. They include instructions on specimen collection, packaging and transport of specimens to the laboratory, testing procedures, and waste disposal. All automated tests are performed on closed air instruments only, whereas manual tests are performed in the BSC in a negative air pressure environment by staff who have completed training on appropriate BSC use (247). These strategies facilitate biosafety management and training both for laboratory personnel and for hospital staff. The SOPs are updated as new infectious disease agents become a concern.

The test menu is standardized with the tests for VHF available as an order set in the Computerized Provider Order Entry (CPOE). Testing of PUIs is standardized and limited to the two reference laboratories in the system. The pathogen table (Fig. 6) is appended to the emerging disease plan for the laboratory to provide current, easily accessible information for clinicians as well as laboratory professionals. Development of additional pathogen table(s) is based on up-to-date risk group information (my.absa.org/Riskgroups and www.cdc.gov/safelabs/resources-tools) and safe practice guidelines (42, 248). These have been added to the list of accessible electronic medical record references for clinicians, especially emergency department (ED) practitioners.

Emerging disease preparedness and response committees that include laboratory participation exist at the Texas Health System level, as well as at each of the 14 hospitals and acute health care centers in the system, and each meet on a regular basis. Each patient who is seen within the hospital system is evaluated to rule out an emerging infectious disease. If the patient meets the PUI criteria, then a post patient care event debriefing is performed to look for gaps in the processes and procedures used in the care of the patient. Frequent communication also occurs between the laboratory, the ED, and the state public health laboratory. The laboratory is notified when there is a PUI so they can prepare for testing, prepare to don HLPPE or appropriate PPE for the suspected pathogen, and call in additional staff if needed.

PPE is standardized across the Texas Health system and training is performed by laboratory employees. Use of HLPPE for specific laboratory needs is determined by a risk assessment, donning and doffing scripts are followed, and the buddy system is employed. Laboratory teams also help with risk assessment and biosafety SOPs for smaller hospitals in the system.

The laboratory SOPs have been designed to allow changes to the procedures during an actual response to best address the diagnosis and patient care needs, and biosafety considerations for laboratory personnel, clinical staff, the patients, and the community.

**Example of staff management and risk communication issues during the Ebola outbreak.** Laboratory preparedness for an outbreak or crisis includes planning for management of staffing and communication with employees. Effective communication can dispel the fear and anxiety that will inevitably occur during an outbreak or epidemic. This section discusses how fear expressed during the treatment of patients with Ebola in 2014 had a profound impact on the operations of the clinical laboratory in Texas Health Dallas, and shows that risk communication is one of the most important tools for managing fear (249, 250).

**(i) Staffing challenges in the outbreak.** Ensuring adequate staffing is a difficult undertaking during routine situations, but during an outbreak may be a nearly

insurmountable challenge for leadership. While the nature of the infectious agent causing the outbreak varies, leadership will likely encounter issues with staff's fear of disease transmission, staff absences because of illness, and staff resignations or call-in absences, resulting in a reduction of the staffing pool. The "worried well" syndrome also occurs and may result in somatic symptoms and staff absence (251, 252).

Many of these issues were realized during the Ebola outbreak at Texas Health Dallas Hospital, as staff were fearful of transmission of a disease that had no specific treatment available and had been portrayed in film and science fiction as causing death in a horrific manner (253–256). Laboratory staff experienced fear for their lives as well as the lives of others they came into contact with. In addition, some laboratory staff and their family members perceived stigmatization in their communities and schools. This type of social stigmatization was not expected in the laboratory's SOP prior to the Ebola outbreak and was an unsettling surprise as the Texas Health Dallas Hospital staff started caring for Ebola patients (257). Unforeseen issues were also caused by many instituted safeguards, including increased staff fatigue due to minimizing the number of staff who performed testing procedures to decrease possible exposures, as well as cancellation of trips and vacations as a result of the 21 days of post last-exposure quarantine (251).

To combat these issues, the Texas Health Dallas leadership set boundaries on staff work hours, sent postshift personnel home, and emphasized teamwork. Leadership also provided guidance and emotional support for those who were anxious and established work teams to foster trust and camaraderie to help address fear and anxiety. For example, a specimen transport team, a shipping/packaging team, and testing teams for each department gave control to the staff and provided a positive work culture and a means of emotional support.

**(ii) Staff risk communication.** The motto of the Texas Health Dallas laboratory during this event was "Keep calm and put your Tyvek on." While Tyvek suits were used only in direct patient-facing roles in this case, the spirit of this slogan was culturally important in the laboratory as well. In addition to providing ongoing guidance for staff management and communication support, the laboratory medical director and administrative leadership provided updates to laboratory staff on a daily basis about the hospital and laboratory response to the Ebola outbreak. Laboratory staff meetings were held daily and as needed to evaluate existing procedures and develop improvements for safe handling of Ebola patient specimens. The laboratory leadership was also onsite and available at all times (24/7) to staff for questions and concerns. The ongoing open communications and staff support were essential to building a team approach to management of the crisis and helped ensure the safety and productivity of the hospital and laboratory staff.

## LESSONS LEARNED FROM THE EBOLA OUTBREAK RESPONSE BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION

### Findings of the Ebola Readiness Assessments by CDC Rapid Ebola Preparedness Teams

During the 2014 Ebola outbreak, CDC assembled multidisciplinary Rapid Ebola Preparedness (REP) teams to assist state public health departments in evaluating their hospitals' capacity and preparedness to receive, identify, and treat critically ill patients with EVD (258–260). CDC teams visited 81 facilities in 21 states as well as the District of Columbia, and helped 55 qualify as Ebola Treatment Centers (ETC) (245). During these site visits, biosafety concerns were identified throughout the hospital from patient arrival to patient departure, clearly revealing issues clinical laboratories faced in the middle of an unprecedented situation (261, 262). One of the primary gaps identified was the lack of consistent guidance available to clinical laboratories on performing comprehensive risk assessments during outbreaks of emerging and/or reemerging infectious diseases (262, 263). This gap resulted in many unanswered questions and misunderstanding, i.e., confusion on which guidance to follow as well as discordance between

PPE and infection control guidance for HCP and laboratory staff, that hindered the ability of the clinical laboratory community to assess and mitigate risk with confidence.

**Biosafety gaps observed during site visits.** All health care systems have infection prevention personnel who develop and implement strategies to minimize nosocomial infections (74, 264). Despite these extensive infection control strategies, there were systemic biosafety gaps identified in prospective ETC regarding patients, HCW, laboratory personnel, support staff, the hospital environment, and external parties such as emergency management services (EMS) or vehicles for hire (259, 265). The following gaps identified in the clinical laboratory total testing process from preanalytic to analytic to postanalytic phase are based on published reports together with the observations of REP team members (262, 266) (personal communication 2020 Elizabeth Weirich and Luis Lowe).

**(i) Preanalytical.** (*a*) *Specimen collection and transport.* Specimen collection could occur in multiple locations, from the ED to dedicated patient care area(s). Depending on the location, specimens had to be transported to the diagnostic testing area. In some cases, there were gaps in how to safely pack specimens to prevent leakage and potential exposure, and how to decontaminate any potential contamination during specimen transport. One gap identified repeatedly during the 2014 Ebola outbreak was related to packaging and shipping of specimens for off-site testing. There was a shortage of United Nations-certified packaging supplies, as well as staff trained and certified to ship Category A infectious substances as specified in the International Air Transport Association requirements (152). For more information, please see the section on transport of specimens in "Biosafety Gaps in the Clinical Laboratory Testing Process."

(*b*) *Specimen receipt and processing.* Transfer from the specimen receiving area to the appropriate section of the clinical laboratory, (e.g., blood bank, core laboratory, microbiology, etc.) was accomplished in various ways. It was noted by CDC teams that pneumatic tube systems were not used for high-risk specimens from potential Ebola patients. Many routine clinical laboratory processing procedures (e.g., removing sealed caps, opening tubes, centrifuging specimens, manipulating needles, pipetting liquids, making smears, vortexing, aliquoting, grinding, or plating) can generate infectious aerosols or droplets, and may create a risk of inhalation or direct mucous membrane contact for staff. Therefore, institutions attempted to identify the risks associated with the specific procedures and evaluate each piece of equipment that would be used to process patient specimens. However, sometimes hazards, such as equipment generating droplets and/or aerosols containing potentially infectious materials, were overlooked. In addition, in some areas of the clinical laboratory such as the core laboratory, where the identification of the causative agent is not part of testing, the risk of potential exposure was not always realized or understood, and therefore there was a gap in assessing the risk of handling patient specimens.

**(ii) Analytical.** Many clinical laboratories conduct high-throughput diagnostic testing using highly automated instruments and technologies. There are also clinical laboratories that primarily conduct manual testing, or a combination of both. Diagnostic testing of patient specimens varies greatly among different institutions, including how tests are ordered, who orders them, where they are conducted, who performs the testing, and how they were conducted. For example, testing locations can include the ED, the patient's room (POC testing), dedicated space adjacent to the patient area, biocontainment units, general and core laboratories, microbiology laboratories, BSL-3 laboratories, public health laboratories, and LRN or reference laboratories off site. Throughout the various testing environments, the gaps consistently observed by the REP teams included discrepancies in biosafety guidance for handling and testing patient specimens, and challenges to communication among clinicians, infection prevention/control practitioners, and laboratory professionals. PPE issues included identification of the appropriate PPE to conduct laboratory testing, guidance on safe and consistent PPE donning and doffing procedures, frequent changing of SOPs for

donning and doffing PPE, which required frequent training and monitoring of staff technical competencies, provision of sufficient storage space for PPE near the location where it was needed, provision of sufficient space for doffing contaminated PPE to avoid cross-contamination between clean and dirty areas or objects, and proper handling of contaminated PPE and waste (e.g., storage, transport, and disposal). In addition, there was need for guidance and SOPs for environmental surface cleaning and decontamination of diagnostic testing equipment.

(*a*) *Point-of-care testing.* During the Ebola outbreak, POC tests, such as blood chemistries, were sometimes performed by individuals with insufficient biosafety training to identify and understand the risks of exposure associated with diagnostic testing on unfamiliar instrumentation.

In some cases, POC testing could not be performed because the instrument did not meet the intended use, as approved by the FDA (160). If intended use excluded testing critically ill patients, this was considered off-label use and laboratories had to establish performance specifications and validate instrument performance before using these POC instruments for patient specimens (183).

(*b*) *Laboratory testing.* The use of laboratory equipment, including instruments for analytical testing and equipment designed to protect personnel, may also present safety risks. Specific areas of potential contamination and lack of engineering controls observed on automated analyzers included open specimen tubes/containers being transported along a conveyor belt for analyte testing before being recapped and stored, exposed areas of the conveyor belt not enclosed by Plexiglas shields or other containment, open decapper discharge chutes, lack of sealed centrifuge rotors or centrifuge safety cups, and nonenclosed disposal containers for liquid waste. Other biosafety gaps that were primarily associated with the analytic phase of diagnostic testing included conflicting information regarding the safety of laboratory equipment, lack of dedicated space for conducting diagnostic testing, differing physical layout of the testing area (i.e., open laboratory space versus separate procedure rooms), insufficient knowledge of safe work practices while working in a BSC (such as compromising airflow by overloading the BSC or by blocking air intake grille), and lack of direct observation of staff who perform tasks in full PPE.

**(iii) Postanalytical.** Some biosafety gaps identified during the postanalytical phase revealed insufficient risk assessments in several domains. These include specimen storage, where there is potential for exposure if frozen specimens were thawed, if there was a breach in the storage container, or if inappropriate storage containers were used. Laboratories frequently failed to fully assess the risks of using cryogenic liquids (e.g., liquid nitrogen) and to ensure secure storage for specimens that contained select agents.

Waste management at the facility, community, intrastate, and interstate levels, including storage, transport, and final disposal, was a problem. Laboratories struggled with handling the unanticipated quantities of contaminated waste generated, handling contaminated liquid waste from laboratory instruments and equipment, engaging local EPA and wastewater management facilities, determining how waste would be transported and the transportation route, and ensuring compliance with requirements for biohazard bags, waste containers, and permits. In addition, there were gaps in management of the deceased, including storage, transport, autopsy, and final departure, and in final cleaning and decontamination of patient areas.

**Other significant biosafety gaps observed by the REP teams.** Additional gaps not clearly classifiable included underestimating the impact on staff who work during outbreaks, i.e., the physical and emotional tolls associated with a crisis that could result in impaired judgement and lapses in safety procedures. In addition, there was lack of planning for emotional and mental-health support for staff experiencing excessive situational anxiety, stress, fear, fatigue, and social stigmatization. There were also inadequate systems to account for staff coming in contact with patients and provisions for personal health status monitoring. There were variations among staff in their perceptions and tolerance for risk and, in some cases, the implementation of impractical

**TABLE 7** Stakeholders, values, and concerns relevant to clinical laboratory (13)

| Stakeholder | Values | Concerns |
|---|---|---|
| Patients | Prompt, effective care for their illness | Will my illness be diagnosed and treated as rapidly and effectively as possible? Will the possibility that I'm infectious make providers reluctant to care for me? |
| Front-line providers | Care for their patients; Personal safety | Will I be able to get effective diagnostic support for clinical care? Will I know rapidly if a patient is infectious? Will I know rapidly if a patient is NOT infectious? Should I treat these patients? |
| Health care system administrators | Efficient, effective care for all patients served by system; Financial stability of the system | Will procedures for handling potentially infectious patients impact care of others? Will handling infectious patients impact the system efficiency, throughput, or access? Should we accept these patients or send them to the facility down the road? |
| Front-line laboratory workers | Patient care; Personal safety | How will handling potentially infectious specimens impact my workflow? How infectious are these specimens? How effective are engineering and administrative controls, and PPE against this novel and mysterious pathogen? Should I agree to handle these specimens? |
| Laboratory management | Patient care; Staff safety; Laboratory operations | How do we maintain services while handling potentially contaminated specimens? Should we implement diagnostics for the emerging threat? If so, how? Should we accept specimens from potentially infectious patients? If so, for what testing? What controls should we impose on such specimens? How will handling potentially or actually infectious specimens impact laboratory operations? Can we handle the increased complexity and workload? What is the risk of environmental contamination of the laboratory, and what impact would it have? |
| Public health authorities | Public health | Will diagnoses of emerging pathogens be available in a timely manner? Will laboratories effectively contain pathogens, or will they become new sources of infection?Will the work be in compliance with applicable regulations regarding dangerous pathogens?" |
| The public at large | Personal safety; Public health | Is my neighbor, the clinical or public health laboratory worker, safe to be around? How do we know if people are infected? How do we know if it is spreading? |

mitigation controls (i.e., mitigation disproportionate to the risk, such as wearing four pairs of gloves for diagnostic testing).

There were several gaps related to PPE. These included the unanticipated burden to staff who worked in HLPPE (267). Staff who wore HLPPE became claustrophobic, fatigued, light-headed, anxious, dehydrated, and overheated. This impacted concentration, sensory perception, visibility, communication, hearing, mobility, balance, and manual dexterity. These factors reduced the amount of time HCW could work in HLPPE. Additionally, there was a lack of emergency response procedures in case of a breach in PPE or a health issue with staff who wore PPE. Unexpected quantities of PPE were needed and used. Shortages of vendor-specific PPE resulted in staff wearing incompatible, ill fitting, or unfamiliar (without prior training) PPE.

## ETHICAL ISSUES RAISED BY EBOLA OUTBREAK: CLINICAL AND PUBLIC HEALTH LABORATORIES

The 2014 Ebola outbreak raised significant concerns among public health and health care professionals about the tenuous balance between the duty to provide quality care to patients and the duty to minimize risks to both health care professionals and the community at large (268, 269). The transfer of Ebola-infected HCW from the outbreak zone to U.S. hospitals raised public awareness and fear of spread of the disease. In addition, viral transmission to two attending nurses (270) who were caring for a patient with Ebola in a U.S. hospital (271, 272) further amplified concerns about the

**TABLE 8** Information sources for laboratory decision-making

| Source | Strengths | Weaknesses |
|---|---|---|
| World health authorities | Authoritative; Have substantial resources and procedures to develop and disseminate guidance; Have big-picture view of outbreak and up-to-the-minute surveillance data; Have global expertise to draw upon. | Global view may translate poorly to specific circumstances; one size rarely fits all, particularly across national borders; Can be slow-moving; Potentially subject to political constraints; Likely to be subject to severe resource overstretch in a global outbreak situation. |
| National public health authorities | Authoritative; Have substantial resources and procedures to develop and disseminate guidance; Have big-picture view of outbreak and up-to-the-minute surveillance data; Have expertise (internal and external) to draw upon. | Can be slow moving; Potentially subject to political constraints; Unlikely to address locally unique issues; Likely to be subject to severe resource overstretch in a major outbreak. |
| State and local public health authorities | Good lines of communication with both national authorities and local health care entities; Good awareness of local situation, constraints, capabilities. | Resources typically limited; Potential for political constraints; Public health laboratories may not have deep understanding of clinical laboratory operations. |
| Professional societies | High level of expertise; Relative lack of political constraints; Can develop resources and guidance relatively rapidly. | Narrow focus in a specialty area; Dependence on small no. of experts; Do not possess regulatory authority. |
| Peer-reviewed scientific literature | Authoritative; Relatively insensitive to political or other biases; Widely available. | Slow to appear; Typically very narrowly focused on technical questions, at least initially. |
| Unreviewed literature on preprint servers/ websites | Rapidly available; Usually provide sufficient data for assessment of strengths and weaknesses of the research. | Typically very narrowly focused on technical questions, at least initially; Lacks the refinement of peer-reviewed material; Initial studies frequently difficult to assess; unique observations often fail to be replicated. |
| Informal channels of communication; listservs, social media | Rapidly, sometimes immediately available; Peer-to-peer communication allows interactive development of best practices. | Anecdotal; Not formally peer-reviewed; "Echo-chamber" effect can limit diverse viewpoints. |

spread of infectious diseases among health care and laboratory staff caring for potentially infected patients. While the number of cases in the United States was low, the outbreak of EVD raised ethical challenges that affected diverse health care settings, including clinical and public health laboratories (Table 7).

While different codes of ethics may have various areas of emphasis, in general, health care professionals are expected to commit to providing quality care to patients while protecting themselves and others from unidentified and known risks (13). During the Ebola outbreak in the United States, clinical laboratories received specimens from patients who were at risk for the disease and from a few patients suffering from EVD. The laboratory staff at risk of exposure to the disease had significant concerns for their own safety. They faced distinct dilemmas because their primary "duty to care" meant not only considering the welfare of the patient, but also ensuring that each patient received the highest quality of care by maintaining operations for health care systems and patient populations (13). Table 7 summarizes many conflicts that could exist when responding to the emergence of a new infectious illness, couple with existing demands, across the priorities of protecting individual laboratory professionals, providing care, and protecting the public.

Uncertainty regarding the level and nature of associated risks characterizes early stages of an emerging disease, and laboratories struggle in reconciling and absorbing information from many sources, from global and national health authorities to professional organizations, the scientific literature, peers, and the general media. As described in a publication on the Ebola response, the large amount of misinformation in the media generated anxiety in educated health care staff and had consequences beyond the immediate workplace that

had to be anticipated and thoughtfully addressed (Table 8) (13). For example, family members of a physician caring for a patient with Ebola could experience fear because of the physician's contact with the patient, daycare facilities could be concerned about the physician's child having the virus, and other hospitals might not want an HCW who had cared for Ebola patients to work at their facility (257, 269). During that outbreak, thousands of people in West Africa contracted the life-threatening disease, but there were no specific therapies to prevent or treat the disease. Incomplete data on the disease process, severity, and routes of transmission, especially early in the course of the outbreak, led to fear, uncertainty, and doubt (273, 274). These limitations may have influenced the laboratories' ability to conduct risk assessments, implement mitigation strategies, and balance risks to staff and patients.

The 2014 Ebola outbreak raised questions for U.S. clinical laboratories about how to handle specimens from patients and suspected cases, as well as whether standard laboratory safety practices could effectively mitigate the risks to staff who performed routine testing services. One serious consequence of these uncertainties and concerns about possible exposure to Ebola was that several major clinical reference laboratories in the United Sates refused to accept specimens suspected to contain Ebola virus (12). Although existing guidelines recommended sending such specimens to CDC and the LRN reference laboratories for confirmatory testing, concerns and uncertainties remained in the clinical laboratory community (11). Initially, guidance focused mainly on specialized testing for Ebola virus itself; guidance on routine testing of persons at risk for disease was not widely accepted in the clinical laboratory community. Inconsistencies in recommendations from different sources further contributed to confusion among laboratory professionals about the degree and nature of the risks (13).

Outbreaks of Ebola and other infectious diseases have demonstrated that these public health threats often cannot be contained within national boundaries, and can affect the health, economy, and safety of people globally (Table 7). Therefore, there are additional, unique considerations for clinical and public health authorities during international outbreaks (275).

First, when a disease outbreak takes place in a rural, or resource-limited site, providing needed laboratory services while ensuring laboratory and health care staff safety may be challenging due to the lack of recommended facilities, PPE, adequately validated screening and/or diagnostic tests, and trained staff. Consequently, it may be more difficult for health care systems and laboratories to handle specimen collection, transport, testing, and contamination events.

Second, the storage and sharing of patient and/or other specimens from outbreaks may be necessary for conducting validation, quality assessment, and research. However, different ethical standards and practices add operational complexity to the challenges for laboratory and health care workers. While challenging, ethical preparedness is a necessary part of laboratory preparedness for disease outbreaks.

## SUMMARIZING REMARKS

### Biosafety Gaps in Clinical Laboratories—Outbreaks Highlighted the Existing Risks

Clinical laboratories perform billions of tests in the United States every year (276) and any failure or gaps in safety practices at any step of the total testing process could have a significant impact on the laboratory personnel, health care workers, patient care, and public health. From regulatory oversight to instrument design to workforce training, this review highlights not only the biosafety-related gaps and concerns that affected clinical laboratory testing during the 2014 Ebola outbreak, but also those that persist in day-to-day clinical laboratory work, in the ongoing COVID-19 pandemic, and which may affect laboratory services during future infectious disease outbreaks.

This review highlights the following gaps in the practice of clinical laboratory biosafety.

**Gaps common across the clinical laboratory.**

1. The laboratory might lack direct control over how specimens are collected and transported to the laboratory. The risk of exposure to personnel and the

environment to hazardous materials (such as infectious agents, toxins, and chemicals) exists across the total testing process, but especially in the preanalytic phase. Achieving standardized procedures for specimen collection and transport might be difficult without inclusion of laboratory personnel in the hospital-wide biosafety plan.

2. While laboratory equipment and instrumentation used to test patient specimens have the potential to generate percutaneous, droplet, and aerosol risks, our knowledge of instrument contamination during routine use, or during use with highly pathogenic microbes, is limited, and these risks may be under appreciated.
3. There is a lack of knowledge of and planning for decontamination of laboratory instruments. Clinical laboratories lack training and certification in environmental sampling needed to verify instrument decontamination.
4. There are discrepancies between the current designation of Category A infectious substances and the actual wide range of waste materials generated during clinical laboratory testing.
5. The discrepancies identified above (number iv) impact the management and packaging for transportation of laboratory waste. The biosafety concerns were evident during the Ebola outbreak, as laboratories that did not have autoclaving equipment or the ability to incinerate waste on site had to rely on vendors to transport waste off site.
6. There is inadequate guidance or training for clinical laboratory professionals in use of PPE.
7. The availability of PPE in clinical laboratories is often insufficient, and knowledge of how to apply different types of PPE for different situations is generally lacking.
8. The need for high-risk PPE and stepwise procedures for donning and doffing PPE to mitigate exposure to highly infectious agent(s) was not fully recognized until the Ebola outbreak. There remains confusion between the differences in using PPE for direct patient care and the processes for PPE use in a clinical laboratory and testing environment.
9. While many organizations and institutions provide biosafety training for laboratory professionals, it is often challenging for training providers to systematically collect evaluation data beyond the learner satisfaction and immediate outcomes.
10. Data are lacking on to what extent laboratories conduct monitoring and evaluation, and whether such evaluation is consistently performed across the laboratory community.

**Gaps unique to specific areas of the clinical laboratory.**

1. While blood banks and transfusion services play limited roles in establishing the diagnosis of emerging infectious agents, they provide essential aspects of supportive care for such illnesses and unique biosafety concerns exist.
2. Hazards in the core laboratories are significantly different than those in other areas of the laboratory. From high-throughput instruments to blood gas testing and specimen dilutions, biosafety risks exist from a variety of manual and automated processes.
3. Gaps in clinical microbiology laboratories' safety procedures highlighted during the 2014 Ebola incident included use of blood culture instrument platforms, difficulty in switching from an automated to a manual testing method, and the viability of pathogens during and after preparation of malaria smears and Gram stains, leading to unwillingness in making and reading slides necessary to issue the laboratory report.
4. The practice of surgical pathology, cytology, and autopsy may involve regular manual contact with large volume/mass specimens with high titers of unknown and/or known pathogens, raising concerns of percutaneous, droplet, and

aerosol exposures. Laboratory staff and pathologists are likely among the HCW with a relatively high risk of LAIs.

**Biorisk management.**

1. Since clinical laboratories often do not know the presence or the identity of the infectious agent(s) in specimens, this uncertainty contributes to gaps in risk assessment and management, especially when suspect patients may have an infectious disease that could pose specific risks to laboratory staff but the risk-related patient information is not transmitted to the clinical laboratories.
2. Current laboratory safety interventions often focus on rare events and preventive efforts, whereas systems for monitoring and evaluating safety interventions analogous to those for quality improvement are usually absent.
3. The lack of performance evaluation data to ascertain the effectiveness of the implemented controls also highlights the absence of a full biorisk management cycle (assessment, mitigation, and performance evaluation) in individual clinical laboratories and in the clinical laboratory community in general.
4. Studies have shown that data on LAIs remain incomplete because of the lack of an official surveillance mechanism and there is concern regarding punitive action by management or an oversight agency if exposures or infections are reported (15, 49).
5. Lack of evidence-based research and publications focused on biosafety; studies documenting safe practices in the day-to-day operations of diagnostic laboratories are missing.
6. National regulations specific for clinical laboratory safety, as well as biosafety, are limited, and overall there is a lack of uniformly implemented and routinely monitored systems in place for laboratory biosafety nationwide. Challenges and difficulties exist in applying current laboratory oversight and biosafety guidance to clinical laboratories:
7. CLIA regulations provide only general requirements for laboratory safety. The extent to which safety requirements are addressed ultimately depends on the clinical laboratory or individual surveyor's expertise.
8. Laboratories that only conduct waived testing are not subject to routine regulatory oversight, including CLIA requirements for laboratory safety.
9. Only a few of the deemed status accrediting organizations have specific accreditation requirements that address laboratory biosafety. However, they are not uniform across all accreditation programs, and the requirements generally lack details and measures on how to build a biosafety program. Furthermore, there are few established templates and models for such programs, and a lack of resources within laboratories to develop and implement such systems.
10. Existing biosafety guidelines and guidance documents do not adequately reflect clinical laboratory practices, especially during emerging infectious disease outbreaks.
11. Biosafety guidelines inadequately address specific risks associated with specialty areas of the laboratory.

**Specific lessons learned from the Ebola outbreak of 2014.**

1. There were safety gaps identified in the clinical laboratory total testing process from preanalytic to analytic to postanalytic phases.
2. Laboratories needed help developing testing menus for PUI for EVD that emphasized the need to maximize diagnostic yield while limiting low-yield diagnostics that were less likely to impact clinical decision making.
3. The Ebola outbreak raised questions for U.S. clinical laboratories about how to handle specimens from patients and suspected cases, as well as whether standard laboratory safety practices could effectively mitigate the risks to staff who performed routine testing services. These ethical challenges included how to balance the duty to provide laboratory services for routine patient care and suspected patients, and laboratory personnel protection.

4. Inconsistencies in recommendations from different sources further contributed to confusion among laboratory professionals about the degree and nature of the risks.
5. Ethical issues related to clinical laboratory practice remain poorly understood, and ethical codes and frameworks for laboratory practice are lacking.

## The Path Forward

New risk-based guidance needs to recognize that clinical laboratories are unique environments that use unique instruments and procedures. We identified several challenges in applying current guidance, as well as the lack of guidelines and guidance that adequately address current clinical laboratory practices. The following are among the opportunities to address the gaps and challenges described in this review.

**Enhanced national oversight for clinical biosafety.** More effective implementation of the current regulatory requirements can be a critical step forward to enhance the national oversight system for clinical laboratory biosafety, as well as other safety areas. Incorporation of additional risk management standards into accreditation programs could both augment the current regulatory system and guide clinical laboratories in improving safety practices. In addition, improvement in biosafety training and competencies for laboratory professionals and inspectors is essential to aid compliance with regulatory requirements, accreditation standards, and safe work practices consistently nationwide.

**Instrument design.** Instrument design often fails to adequately address the safety of the operator and the environment during use, as well as decontamination procedures for POC and laboratory instruments after their use. This could be addressed by additional research on contamination mechanisms and patterns in various types of instrumentation, the hazards associated with such contamination, and ways of mitigating them. Examples include: blood bank automated systems, centrifuges (sealed rotors) or other ways to prevent aerosols, core laboratory automated analyzers, microbiology automated systems like blood culture instruments and antibiotic susceptibility platforms, and survival of emerging pathogens in both anatomic and clinical pathology laboratory specimens. It should be noted that CLSI has convened a committee to develop new guidance, QMS27 Decontamination of Laboratory Equipment and Instrumentation, to address some of these issues.

**Training.** The community needs more freely available guidelines and resources to educate and train laboratory professionals in safer work practices, and implementation of biorisk management programs. For example, a framework for conducting risk assessments is needed because most laboratories have to build these from scratch, which is a labor intensive and complex undertaking. CDC trainings on BSC and centrifuges (available at www.cdc.gov/safelabs/trainings.html) are a good start, but more training development is needed.

**Laboratory workflow.** There is a need for additional guidance that encourages laboratory professionals to be involved in the development of hospital biosafety plans and emergency operations. Laboratories have specialized workflows for patient specimens that differ from clinical workflows designed for patients. Examples include:

1. Laboratory workflow.
2. Specimen collection and transport, which also involves patient care, hospital staff, and hospital visitors.
3. Specimen processing issues, including contamination of specimen requisitions, outside of specimen containers, and handling of sharps. How can both safety and specimen integrity be optimized?
4. POC laboratory test instruments used outside the laboratory, often by nonlaboratory personnel, who may lack training in quality control, decontamination, and other areas.
5. Psychosocial support for laboratory staff who handle dangerous pathogens on how to interact with other staff, family, and their community.

**Surveillance system.** A comprehensive surveillance system is needed to document laboratory exposures and acquired infections to provide an evidence-based database for

identifying types and numbers of exposures, and to assess the effectiveness of biosafety interventions in decreasing exposures/infections. This system could be modeled on the Canadian surveillance system, which has been in place since 2016 (49, 174).

**Research.** Clinical laboratories would benefit from additional biosafety research in the following areas:

1. PPE.
2. Engineering controls.
3. Facility design.
4. Workflow and process design for safety.
5. Adequacy of inactivation of pathogens in tissue and fluids after fixation in formalin and other fixatives. This would be beneficial in autopsy, surgical and pathology, hematology, and microbiology.
6. Additional work is needed on the strengths and weaknesses of POC versus laboratory testing during outbreaks. Research should address POC issues such as low volume, limited menus, test performance, high costs for maintenance, quality control, decontamination, and safety of the user.

**Guidance on Category A waste.** There may be a need to revisit the Category A infectious substance list with regard to waste handling (145). Revised guidance could help clarify the discrepancies in which clinical laboratory-generated waste should be designated Category A and appropriate packaging that would allow for the efficient off-site treatment using available treatment technologies.

**(i) Waste management.** For many clinical laboratories, on-site autoclaves and/or incinerators are not available. As a result, they depend on vendors to discard the large amount of waste that is often generated. Yet, during the Ebola outbreak, vendors refused to take waste that was possibly contaminated with Ebola virus.

**Specimen storage.** Clinical laboratories need the capacity to store, bank, and archive specimens for future research and therapeutic use (e.g., convalescent plasma treatments for Ebola). However, many clinical laboratories lack the physical space for secure specimen storage, lack adequate storage units (including back-up systems), and lack appropriate electronic inventory systems.

Clinical laboratories are unique environments, and their essential role in health care makes maintenance and continual improvement of biosafety in clinical laboratories a critical necessity. Risk assessments on the level of the individual laboratory for continuous improvement of safety practices, on the level of manufacturers to incorporate safety into laboratory instrument design, and systemically by the laboratory community are essential tools to move forward. In order to be prepared for future outbreaks, laboratory biosafety preparedness needs to be an essential component of building surge capacity. We hope this review of issues, needs, and aspirations in clinical laboratory biosafety will contribute to progress in this area. Furthermore, we discussed the relationship between biosafety gaps, assessing, managing, and mitigating risks, laboratory safety, and test quality. Although various organizations have started work on these issues, no single entity can resolve all these gaps. Instead, comprehensive solutions will require the combined effort of laboratory professionals and the organizations that support them. In addition to ensuring laboratory quality, clinical laboratories have a responsibility to manage the risks to workers, health care facilities, our communities, and the environment. However, we must not overly focus on solving the issues of previous outbreaks but prioritize the creation of dynamic systems to improve laboratory biosafety and build the capacity to better combat the next emerging infectious agent.

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**Judith G. Giri**, Ph.D., completed doctoral studies in Microbiology at Rutgers University, and fellowships in molecular developmental biology and immunology at Columbia and Pennsylvania State universities. In 2004, she joined the faculty of the Medical College of Georgia as Associate Professor in the Department of Pathology and established and served as Director of the statewide cancer biorepository and institutional tumor and bone marrow bank. In 2012, she joined the CDC Division of Laboratory Systems to help oversee the CDC's central biorepository. At present, she is a specimen management consultant supporting global health programs, developing specimen resources for infectious disease research (CHAMPS Program, Emory University), and for clinical specimens for diagnostics development and evaluation (Colorado School of Public Health). Since 2004 she has been concentrating on education and training and development and implementation of policies, standard procedures, and best practices, for specimen and biorepository safety and quality management.

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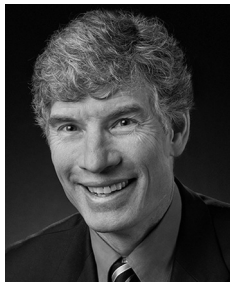

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