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U.S. High-Level Isolation Unit Clinical Laboratory Capabilities Update

Jocelyn J. Herstein,[a] Peter C. Iwen,[b,c] Katelyn C. Jelden,[d] Paul D. Biddinger,[e,f] Shawn G. Gibbs,[g] Aurora B. Le,[g] Angela L. Hewlett,[h] John J. Lowe[a]

[a]Department of Environmental, Agricultural, and Occupational Health, University of Nebraska Medical Center, Omaha, Nebraska, USA

[b]Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

[c]Nebraska Public Health Laboratory, Omaha, Nebraska, USA

[d]College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

[e]Department of Emergency Medicine, Division of Emergency Preparedness, Massachusetts General Hospital, Boston, Massachusetts, USA

[f]Department of Emergency Medicine, Harvard Medical School, Boston, Massachusetts, USA

[g]Department of Environmental and Occupational Health, Indiana University School of Public Health, Bloomington, Indiana, USA

[h]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska, USA

ABSTRACT In late 2014, 56 hospitals in the United States were designated by state and federal public health authorities as specially designed high-level isolation units (HLIUs) equipped with advanced infrastructure, laboratory capabilities, and trained staff to care for patients with highly hazardous communicable diseases (HHCDs), such as Ebola virus disease. This survey describes the clinical laboratory support capabilities of U.S. HLIUs, including the specific test menus that HLIUs have identified to safely manage HHCD patients and the locations where such testing would be performed. In spring 2016, a survey was electronically distributed, as a fillable pdf file, to the 56 U.S. HLIUs. Site representatives completed the surveys, and data were coded and analyzed in an electronic spreadsheet, using descriptive statistics. Thirty-six HLIUs (64%) responded, and 33 completed the laboratory capabilities section. Thirty-one HLIUs (94%) had performed risk analyses for all laboratory procedures and equipment. Twenty-nine (88%) had decontamination procedures specified for all laboratory equipment used for patients with suspected or confirmed HHCDs. On-site laboratories in 27 HLIUs (81%) had the capacity to inventory and to securely store HHCD patient specimens. Ten HLIUs (31%) had at least one test they would conduct within the patient isolation room. The high-risk nature of HHCDs and the occupational exposures that may occur in clinical laboratories demand advanced preparation and risk assessment of work practices, laboratory equipment, and instrumentation by HLIU laboratories. Although risk analyses of clinical laboratory testing and equipment that HLIUs have conducted have likely focused on those for Ebola virus, HLIUs must be prepared to revise their current procedures for other HHCDs.

KEYWORDS biocontainment, diagnostic laboratory testing, Ebola virus disease, highly infectious disease

In late 2014, the Centers for Disease Control and Prevention (CDC) recommended that states stratify hospitals into one of three tiers, based on their ability to identify, to isolate, and to care for patients with confirmed or suspected Ebola virus disease (EVD) (1). The majority of U.S. hospitals providing emergency care were classified as frontline

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Address correspondence to Jocelyn J. Herstein, jocelyn.herstein@unmc.edu.

hospitals and, as such, were asked to identify patients with relevant EVD exposure history and EVD-compatible symptoms, to isolate those patients, and to inform the local health department. Ebola assessment hospitals were tasked with receiving, isolating, and providing supportive care for patients under investigation (PUIs) for up to 5 days, until laboratory results either confirmed or refuted the diagnosis. Upon confirmation of a diagnosis of EVD, states subsequently planned that patients would be transferred to an Ebola treatment center (ETC) capable of safely administering sustained medical care through the entire course of the illness.

Fifty-six hospitals in the United States were designated by the CDC as ETCs, having specially designed high-level isolation units (HLIUs) equipped with the advanced infrastructure, laboratory capabilities, and trained staff to minimize transmission risks while caring for patients with highly hazardous communicable diseases (HHCDs), such as EVD (2–7). HHCDs have been defined as easily transmissible, life-threatening diseases that pose a threat to both health care workers and the public (e.g., viral hemorrhagic fevers and severe acute respiratory syndrome [SARS]). Because of these infectious and pathogenic features, HHCDs warrant specific control measures, such as stringent infection control procedures and specialized personal protective equipment (2, 3). To expand upon the capabilities of this tiered network of ETCs, 10 hospitals were later designated by the Assistant Secretary for Preparedness and Response as regional Ebola and special pathogens treatment centers (RESPTCs) and were granted additional federal funding to enhance their isolation and care capabilities for HHCDs (8).

Analysis of previous institutional actions in response to HHCD events in the United States has revealed delayed critical laboratory analyses for patients suspected of having disease (2). Because of this history, the CDC included specific recommendations for performance of laboratory testing in its list of augmented areas necessary for EVD care (1). To qualify for designation as an ETC, HLIUs were required to possess the capability of safely processing laboratory specimens on site, utilizing appropriate laboratory procedures and protocols, dedicated space, possible point-of-care testing, appropriate equipment, staffing, and reagents, advanced training, and specialized specimen transport (1). HLIUs were required to utilize highly trained and skilled laboratory personnel and to perform risk analyses of the range of laboratory tests that they might perform, to offer optimal patient support while minimizing occupational risks to laboratory workers.

Although the CDC and the U.S. HLIUs that treated EVD patients have released best-practice recommendations for clinical laboratory support (9–14), inconsistencies in guidelines and practices remain (15, 16). A 2015 survey of HLIUs conducted by our group found that 91% of HLIUs had biosafety level 3 (BSL-3) laboratory support in their clinical laboratory and/or public health laboratory (PHL) and 87% planned to provide some type of laboratory support (e.g., point-of-care testing) within the isolated patient's room (4). However, the extent of laboratory support available in the hospital laboratory (as opposed to the PHL) and within the patient's room remained unknown. This study aimed to describe clinical laboratory support capabilities of U.S. HLIUs, including identification of the specific test menus that HLIUs have identified to safely manage HHCD patients and the locations where such testing would be performed.

MATERIALS AND METHODS

In early 2016, a follow-up survey to the 2015 HLIU survey was emailed to each of the original 56 designated U.S. HLIUs, including the 10 RESPTCs. If the HLIU had completed the 2015 survey, then the listed point of contact was used; for the remaining HLIUs, the survey was sent to the same contact as used for the 2015 study. When possible, known personnel from the remaining HLIU units were identified and contacted using publicly accessible email addresses. Nonrespondents were additionally solicited for responses, by email, twice after the original deadline had passed.

The follow-up survey was administered to expand on findings from the 2015 survey (4–6) and included questions relating to personal protective equipment, staffing models and personnel management, operational capabilities, sustainability concerns, infection control protocols, and laboratory capabilities. The clinical laboratory capabilities section, the results of which are detailed here, assessed diagnostic testing and laboratory tools available to HLIU patients and the location of testing for each instrument, as well as decontamination protocols for laboratory equipment, the results of risk analyses for procedures and equipment, and protocols for the transport of specimens.

TABLE 1 Reported tools available for diagnostic testing for patients with HHCDs and tool locations closest to the patient care room in 32 U.S. HLIUs

Tool	No. (%) available					
	For HLIU	Within patient care room	Within isolation unit	Within facility	Outside facility[a]	Other
Incubator for bacterial culture[b]	30 (94)	0 (0)	8 (27)	19 (63)	2 (7)	1[c] (3)
Biological safety cabinet	31 (97)	0 (0)	17 (55)	14 (45)	0 (0)	0 (0)
PCR assay	28 (88)	0 (0)	9[d] (32)	11[d] (39)	8[e] (29)	0 (0)
EIA reader[f]	19 (59)	1 (5)	4 (21)	11 (58)	2 (11)	1[c] (5)
Microscope	23 (72)	0 (0)	6 (26)	17 (74)	0 (0)	0 (0)

[a]Including the jurisdictional PHL (excluding the CDC laboratory for confirmation diagnosis).
[b]Including the availability of a standalone incubator for bacterial culture; although this did not include automated blood culture systems, many facilities preferred to incubate blood culture bottles in a standalone incubator for visual observation, with Gram staining and culture performed when necessary.
[c]The health system's core laboratory.
[d]PCR testing within the isolation unit or facility generally included access to BioFire instrumentation (BioFire, Salt Lake City, UT), including the FDA emergency use authorization-approved FilmArray Biothreat Etest to test for the presumptive presence of Ebola Zaire virus, as well as FDA-approved FilmArray assays including panels for blood culture identification (BCID) and gastrointestinal tract and respiratory tract pathogens.
[e]Jurisdictional PHLs utilized real-time PCR assays developed by the CDC and validated in-house to test for pathogens such as Ebola Zaire virus, novel Middle Eastern respiratory syndrome (MERS) coronavirus, and influenza A/H7 virus.
[f]Including enzyme immunoassay (EIA) readers for the direct detection of agents such as influenza viruses, group A *Streptococcus*, HIV, and malaria.

The location of tools available for diagnostic testing and the test location closest to the patient's room were defined as within the patient care room, within the isolation unit, within the facility, or outside the facility (excluding the CDC laboratory for confirmation diagnosis). A patient care room was defined as the location within the isolation unit where the patient was contained for care. The isolation unit was defined as a controlled-access patient care area functionally separated from other hospital wards and independently operated.

Surveys were completed by site representatives and were collected via Adobe Pro. Data were coded and analyzed in an electronic spreadsheet, using descriptive statistics. The survey was reviewed by the University of Nebraska Medical Center institutional review board and determined to be exempt from review.

RESULTS

Thirty-six hospitals (64%) responded to the survey, and 33 completed the clinical laboratory capabilities section. Thirty-one (94%) of the 33 HLIUs with data on laboratory capabilities stated that they had performed risk analyses for all laboratory procedures and equipment. Twenty-nine (88%) had decontamination procedures specified for all laboratory equipment used for patients with suspected or confirmed HHCD, while the four units without procedures planned to dispose of equipment after HHCD use. The equipment considered "disposable" included the Piccolo chemistry analyzer (Abbott Laboratories, Abbott Park, IL), the i-Stat system for blood analysis (Abbott Laboratories), glucometers, the pocH-100*i* hematology analyzer (Sysmex, Lincolnshire, IL), the FilmArray PCR system (BioFire Diagnostics, Salt Lake City, UT), and the Clinitek urine dipstick reader (Siemens Medical Solutions USA, Malvern, PA).

On-site laboratories in 27 HLIUs (81%) had the capacity to inventory and to securely store HHCD patient specimens for additional testing as needed. For off-site testing, government officials (i.e., local or state health department officials) were trained to transport specimens that might contain a high-consequence pathogen to off-site laboratories for 18 HLIUs (55%), while 12 (36%) would use commercial courier services and 3 (9%) would utilize hospital staff. Thirty-two HLIUs (97%) had procedures for recording the chain of custody, to document specimen handling throughout transport.

HLIUs reported an average distance to the jurisdictional PHL of 46.67 miles (median, 20 miles; range, <1 to 290 miles). Turnaround times (TATs) for initial tests at the PHLs had a median of 6 h (range, 3 to 36 h). Available laboratory tools and their locations are indicated in Tables 1 and 2. A total of 10 HLIUs (31%) that reported laboratory testing menus had at least one test they would conduct within the patient care room.

DISCUSSION

These results supplement findings from our 2015 HLIU survey on HHCD laboratory support by specifying the tests available at the various laboratory locations (4). Results indicate that HLIUs in the United States are prepared to provide a range of laboratory

TABLE 2 Reported tests available for HHCD patient clinical care and test locations closest to the patient care room in 32 U.S. HLIUs

Test	No. (%) available					
	For HLIU	Within patient care room	Within isolation unit	Within facility	Outside facility[a]	Other
Complete blood count with automated differential	29[b] (91)	0 (0)	16 (55)	11 (38)	0 (0)	0 (0)
Basic metabolic panel	29 (91)	4 (13)	17 (59)	8 (28)	0 (0)	0 (0)
Magnesium level	21 (66)	0 (0)	14 (67)	7 (33)	0 (0)	0 (0)
Comprehensive metabolic panel	25 (78)	0 (0)	15 (60)	10 (40)	0 (0)	0 (0)
Ionized calcium level	24 (75)	4 (17)	12 (50)	7 (29)	0 (0)	1[c] (4)
Standard calcium level	25 (78)	0 (0)	16 (64)	9 (36)	0 (0)	0 (0)
Phosphorous level	21[b] (66)	0 (0)	10 (48)	9 (43)	0 (0)	0 (0)
Cortisol level	8 (25)	0 (0)	0 (0)	7 (88)	0	1[c] (12)
Troponin level	12 (38)	0 (0)	3 (25)	8 (67)	0 (0)	1[d] (8)
Blood gas concentrations	28 (88)	4 (14)	14 (50)	10 (36)	0 (0)	0 (0)
Lactate level	23 (72)	3 (13)	12 (52)	8 (35)	0 (0)	0 (0)
Prothrombin time	25 (78)	3 (12)	13 (52)	9 (36)	0 (0)	0 (0)
Partial thromboplastin time	16 (50)	0 (0)	8 (50)	8 (50)	0 (0)	0 (0)
Platelet count	28 (88)	0 (0)	15 (54)	13 (46)	0 (0)	0 (0)
Blood typing	16 (50)	0 (0)	6 (38)	9 (56)	0 (0)	1[e] (6)
Blood culture[f]	28 (88)	0 (0)	9 (32)	17 (61)	1 (4)	1[c] (4)
Urine culture[f]	14 (44)	0 (0)	2 (14)	10 (71)	1 (7)	1[c] (7)
Other body fluid culture[f]	15 (47)	0 (0)	3 (20)	10 (67)	1 (7)	1[c] (7)
Molecular assay	17[b] (53)	0 (0)	2 (12)	8 (47)	4 (24)	1[c] (6)
Manual differential[g]	15 (47)	0 (0)	3 (20)	12 (80)	0 (0)	0 (0)
Lipase level	13 (41)	0 (0)	3 (23)	10 (77)	0 (0)	0 (0)
Amylase level	16[h] (50)	0 (0)	6 (38)	9 (56)	0 (0)	0 (0)
Total creatine kinase level	11 (34)	0 (0)	4 (36)	7 (64)	0 (0)	0 (0)
Malaria smear[g]	28[h] (88)	0 (0)	9 (32)	18 (64)	0 (0)	0 (0)
HIV screen	17 (53)	0 (0)	6 (35)	10 (59)	1 (6)	0 (0)
Urinalysis	24 (75)	4 (17)	12 (50)	8 (33)	0 (0)	0 (0)
Pregnancy test	23 (72)	3 (13)	11 (48)	9 (39)	0 (0)	0 (0)
Cerebrospinal fluid analysis[i]	7 (22)	0 (0)	0 (0)	7 (100)	0 (0)	0 (0)

[a]For example, a PHL or reference laboratory.
[b]Two HLIUs did not report where the test was located.
[c]The health system's core laboratory.
[d]Not planned but could be obtained from the i-Stat system if needed.
[e]Not planned, but slide interpretation was available.
[f]Microbiological assays, including inoculation of culture medium followed by incubation and pathogen identification if necessary.
[g]Including staining and microscopic identification.
[h]One HLIU did not report where the test was located.
[i]Including microbiological analysis (culture and Gram staining), cell counting, and protein/glucose analysis.

tests for patients with HHCDs, both within the unit and in the facility's clinical laboratory. Most HLIUs have conducted risk analyses and developed specimen transport procedures.

Laboratory support is critical for optimal patient care; however, the risk to laboratory workers in handling HHCD specimens should be assessed prior to ordering such tests (15). The Nebraska Biocontainment Unit and the Emory University Serious Communicable Disease Unit, two U.S. HLIUs that cared for repatriated EVD patients in the autumn of 2014, have described their risk evaluation of laboratory processes and instruments generating aerosols and microdroplets and have detailed the equipment and testing offered in their laboratories (11–14). The units differed in testing locations, as Emory University confined all laboratory testing within the HLIU except for specimens sent to the CDC, while the Nebraska Biocontainment Unit performed testing at multiple locations within the HLIU, hospital, and campus. Both approaches proved to be safe and successful in managing the laboratory support for patients with EVD. The two units, along with guidance issued by the CDC, have also described procedures for specimen transport both within the hospital and outside the institution (10, 11, 13).

All responding U.S. HLIUs reported the ability to provide laboratory support within the hospital, if not closer to the patient care room (i.e., within the isolation unit or in the patient care room itself). Although the survey did not specifically ask which instruments or assays were used to perform the various tests, point-of-care assays, compact

TABLE 3 Analyzers used by various HLIUs for testing of specimens that might contain a high-consequence pathogen

Manufacturer	Device[a]	Clinical area	Analyzer type[b]	Test type(s)[c]
Beckman Coulter	DxC880i	Chemistry	Core	Electrolytes
Abbott Laboratories	i-Stat	Chemistry	POC	Electrolytes and blood gases
Siemens	Clinitek	Chemistry	POC	Urinalysis and pregnancy test
Abaxis	Piccolo Xpress	Chemistry	Compact	Electrolytes and blood gases
Alere	epoc blood analysis	Chemistry	POC	Electrolytes and blood gases
SynDx Medical	SenDx 100	Chemistry	POC	Electrolytes and blood gases
Instrumentation Laboratory	Gem Premier 4000	Chemistry	Compact	Electrolytes and blood gases
Ciba Corning	Corning 865	Chemistry	Compact	Blood gases
Siemens	Dimension RxL	Chemistry	Core	Electrolytes
ITC	Hemochron Signature	Coagulation	POC	Coagulation analysis
Sysmex	pocH-100*i*	Hematology	Compact	CBC with differential
Sysmex	XN 9000	Hematology	Core	CBC with differential

[a]List of analyzer types (not all inclusive) that have been known to be validated and used by HLIUs for the safe testing of specimens that might contain a high-consequence pathogen.
[b]Including analyzer types that are point-of-care (POC) testing devices that could be used for testing in the patient care room, compact analyzers with a small footprint for utilization within a biosafety cabinet, or large automated analyzers with closed-tube testing capabilities that could be used in a core testing facility.
[c]CBC, complete blood count.

analyzers, and core analyzers that have been reported to be used for the care of EVD patients are indicated in Table 3 (9, 11, 13). Our previous study, conducted in 2015, found that 87% of surveyed HLIUs initially planned to provide some type of laboratory support within the patient care room. Results from this follow-up study, however, indicate that only 31% of HLIUs now plan to conduct the specified tests or to use the listed tools within the patient care room (Tables 1 and 2). While some HLIUs might have elected to minimize testing capabilities within the unit, it is important to note that this list may not be exhaustive regarding the laboratory support HLIUs plan to provide for HHCD patients within the patient care room. Moreover, the contacts completing the survey might not have been laboratorians and might have chosen not to specify the testing locations if they were unsure.

All specimens collected from persons suspected or confirmed to have EVD require specialized packaging as category A infectious substances and must comply with federally regulated transport procedures if they are transported outside the facility (17). Specimens that test positive for Ebola virus using a PCR assay are considered presumptive positive and must be transported to the CDC for further evaluation and confirmation, and only personnel trained and certified to package and to transport category A substances are allowed to package and to ship Ebola virus-infected specimens (10, 11). All but three HLIUs have identified category A shippers, with one-third identifying a certified courier service. During the EVD outbreak in 2014 to 2016, however, few certified couriers accepted category A risk group 4 pathogens for transport. Moreover, the costs of transporting samples during the EVD outbreak were exorbitant, and the TAT for testing is not acceptable for optimal patient care. The extent of these services if an HHCD outbreak occurs within the United States remains to be seen (11).

Although a majority of HLIUs had procedures for decontaminating laboratory equipment used for HHCD patients, the four units that planned to dispose of devices after use must identify "disposable equipment" specific to each HHCD, as reported equipment is applicable only to EVD. Planning to dispose of equipment represents a great potential cost to those facilities. However, those that plan to decontaminate laboratory equipment may face challenges in acquiring the necessary services and maintenance for their diagnostic devices. During the EVD outbreak in 2014 to 2016, contrary to CDC recommendations that laboratory equipment used for testing of Ebola virus samples could be disinfected and reused safely, many manufacturers reported that they would restrict maintenance services for laboratory equipment that had been used for patients with EVD, citing exposure risks for their technicians, while other manufacturers advised that devices be incinerated after use for EVD patients (9, 18). Refusal to service and to maintain diagnostic devices may lead laboratories to seek other options, as they are unable to afford the costs of disposing of equipment after use

for each HHCD patient. Moreover, the same equipment is used, disinfected, and reused after testing specimens from patients with other HHCDs, including extensively drug-resistant tuberculosis (XDR-TB), and diseases that have elicited the same heightened public fears in the past (e.g., HIV).

TATs for testing performed at PHLs ranged from 3 to 36 h. PHLs have only a very limited menu of confirmatory tests (e.g., EVD, Middle East respiratory syndrome [MERS], and avian influenza), and any other testing would need to be performed at the CDC, further extending the TAT. Extended TATs could result in a patient being in isolation longer than necessary and, as a result, utilizing limited resources (e.g., facilities, personnel, and equipment) that would then be unavailable to other patients in need of HLIU care. Minimizing processing times is of paramount importance in the care of EVD patients, who require extensive fluid and electrolyte management, as well as dialysis in some cases. The Nebraska Biocontainment Unit reported that TATs for certain routine laboratory tests were initially longer than expected, and it made significant efforts to decrease TATs during the care of their EVD patients (11).

There is wide variation in the laboratory management guidelines for EVD patients that were released by international and domestic public health agencies and private organizations during and in the aftermath of the outbreak in 2014 to 2016 (15). These inconsistencies may generate confusion among HLIU laboratorians regarding the tests and instruments that should be provided for HHCD patients, waste disposal, and occupational safety procedures to minimize exposure risks. Therefore, consistent guidelines among international and national organizations are needed to delineate HLIU laboratory standards and capabilities.

Although this report describes the current capabilities of U.S. HLIUs pertaining to laboratory testing, it does not address the laboratory needs of assessment hospitals or frontline facilities. Guidelines focused on HHCD treatment facilities are not necessarily adequate for assessment hospitals, as such facilities have been asked to offer their own laboratory testing capabilities for an extensive differential diagnosis list, including malaria and influenza (9). The ability of assessment hospitals to perform basic laboratory testing is critical, as assessment centers are more likely to receive a PUI who is eventually not found to have the disease than an HLIU that receives a patient with confirmed disease. Frontline facilities also may end up performing laboratory testing on a patient who is in critical condition; thus, they require protocols for safely handling specimens that may contain a high-consequence pathogen. Future guidance for such hospitals is required so that, when necessary, they may safely test specimens while waiting for results from the jurisdictional PHL for confirmation of the diagnosis.

There were limitations to this study. Survey questions were not validated prior to distribution, and results were self-reported by HLIU site representatives. The survey was distributed to one HLIU contact; in most cases, this was not laboratory personnel. Although respondents were encouraged to split the survey and forward the sections to the appropriate person for each survey section, it is possible that not all responses regarding laboratory capabilities were completed by a laboratorian; therefore, answers may not be accurate. Additionally, the response rate decreased from the 2015 survey to this follow-up survey (from 85% to 64%). Since the designation of these units by the CDC in 2014, at least three have opted to discontinue high-level isolation operations (7), and the lower response rate may indicate that others have also chosen to no longer maintain high-level isolation capabilities. Similarly, respondents might have more advanced capabilities and thus might have been more willing to complete the survey. Therefore, results may not be entirely indicative of all CDC-designated HLIUs. Lastly, we acknowledge that numerous hospitals across the United States have invested in strengthening their laboratory capabilities to identify, to support, and to manage PUIs until confirmed HHCD diagnosis but were not included in our survey of CDC-designated HLIUs.

Due to the high-risk nature of HHCDs and potential occupational exposures that can occur in clinical laboratories, advanced preparation and risk assessment of work practices, personal protective equipment requirements, laboratory equipment, and instru-

mentation by HLIU laboratories are critical for providing a safe working environment and adapting to evolving HHCD situations. Although risk analyses that HLIUs have conducted on clinical laboratory testing and equipment have likely focused on those for Ebola virus, HLIUs must be prepared to revise their current procedures for other HHCDs and unknown emerging infectious diseases.

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