Perspective Piece

Ebola Virus Disease: Rapid Diagnosis and Timely Case Reporting are Critical to the Early Response for Outbreak Control

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Abstract. Ebola virus disease (EVD) is a life-threatening zoonosis caused by infection with the Ebola virus. Since the first reported EVD outbreak in the Democratic Republic of the Congo, several small outbreaks have been reported in central Africa with about 2,400 cases occurring between 1976 and 2013. The 2013–2015 EVD outbreak in west Africa is the first documented outbreak in this region and the largest ever with over 27,000 cases and more than 11,000 deaths. Although EVD transmission rates have recently decreased in west Africa, this crisis continues to threaten global health and security, particularly since infected travelers could spread EVD to other resource-limited areas of the world. Because vaccines and drugs are not yet licensed for EVD, outbreak control is dependent on the use of non-pharmaceutical interventions (e.g., infection control practices, isolation of EVD cases, contact tracing with follow-up and quarantine, sanitary burial, health education). However, delays in diagnosing and reporting EVD cases in less accessible rural areas continue to hamper control efforts. New advances in rapid diagnostics for identifying presumptive EVD cases and in mobile-based technologies for communicating critical health-related information should facilitate deployment of an early response to prevent the amplification of sporadic EVD cases into large-scale outbreaks.

We live in a globally interconnected world where the rapidity of modern travel allows us, and the microbes that infect us, to be virtually anywhere within only hours. In earlier times, weeks or months were often needed to traverse the barriers that were imposed by geography and distance. The lengthiness of travel afforded some protection against the introduction of virulent pathogens to new locales because many who were infected either recovered or succumbed before reaching their final destination. This is no longer the case. Several tropical viral diseases (e.g., dengue, Middle East respiratory syndrome, chikungunya, and Ebola virus disease [EVD]) have expanded their geographical range due in part to transit of infected humans.¹ Of these diseases, EVD has received the lion's share of international attention. This is because of the 2013–2015 EVD outbreak in west Africa where over 27,000 cases with more than 11,000 deaths have been reported.² Although EVD transmission rates have decreased and Liberia was recently declared free of EVD transmission by the World Health Organization (WHO), this crisis continues to threaten global health and security.

EVD is caused by infection with a single-stranded, negative-sense RNA virus of the genus *Ebolavirus*.³ *Zaire ebolavirus* (EBOV) was first identified in humans in an outbreak that occurred in 1976 near the Ebola River in the Democratic Republic of the Congo (DRC, formerly Zaire).⁴ Three additional African species, *Sudan*, *Tai Forest*, and *Bundibugyo ebolavirus*, also cause disease in humans, but the case fatality rates due to infection with these viruses are not as high as that due to EBOV, which can reach 90%. Although the natural reservoir of Ebola virus has not been definitively determined, serological and molecular data indicate that this virus is present in some species of African frugivorous and insectivorous

bats.^{5–7} Zoonotic transmission of Ebola virus may occur in humans who are exposed during hunting and butchering of infected bats.^{5,8} Increases in human population, coupled with changes in land use, enhance the risk of contact with reservoirs of Ebola virus.⁸ Pigott and others⁶ mapped the zoonotic niche of EVD in central and west Africa and reported that 22 million humans inhabit at-risk areas. It is possible that EVD could spread more readily in these areas because of increasing population growth and mobility.

Human-to-human transmission of EVD occurs primarily via direct contact with bodily fluids of an infected human after fever has developed or with the body of a human who has recently died of EVD.³ The incubation period usually lasts about 1 week, but can be 3 weeks or possibly longer. Thus, humans who are incubating disease, but not yet symptomatic, can travel a considerable distance before they begin to shed the virus as demonstrated by the introduction of EVD via ground travel (e.g., Guinea to Liberia, Sierra Leone, and Senegal) and via air travel (e.g., Guinea to the United States; Liberia to Nigeria, the United States, and the United Kingdom; Sierra Leone to Italy).^{2,9,10}

Although the current EVD outbreak has waned, infections are still occurring in some hot spots in west Africa. Because of the international connectivity of west Africa, there is concern that EVD could spread to other densely populated, resource-limited areas of the world that are ill-prepared to control this disease for which there is as yet no licensed vaccine or proven curative therapy.^{10–13} Halting EVD transmission is critical to prevent further spread of EVD within and beyond west Africa. The use of multifaceted non-pharmaceutical interventions (e.g., infection control practices, EVD treatment units for case isolation, contact tracing with follow-up and quarantine, sanitary burial, health education) has decreased EVD transmission in many areas of west Africa. Nevertheless, delays in diagnosing and reporting new EVD cases in less accessible rural areas continue to hamper control efforts.¹⁴

If control interventions had been deployed early on, the EVD outbreak in west Africa may have been contained in a relatively short time similar to some EVD outbreaks that

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occurred previously in central Africa.^{15,16} Unfortunately, the lack of surveillance for EVD in west Africa, a region that was largely unfamiliar with this disease, and the lack of adequate public health capacity, impeded an early response and allowed the establishment of multiple foci of EVD in Guinea. However, there is hope that new advances in rapid diagnostics and mobile-based communication technology will expedite the deployment of resources to control EVD outbreaks.^{1,17,18} Rapid diagnosis of EVD is critical because the early symptoms of EVD (i.e., high fever, malaise, fatigue, body aches) can be confused with those of some other endemic infectious diseases (e.g., malaria, influenza, typhoid, dengue, yellow fever, Lassa fever).^{19,20} The WHO recently approved the ReEBOV Antigen Rapid Test, developed by Tulane University researchers (New Orleans, LA) in partnership with Corgenix Inc. (Broomfield, CO), for procurement in EVD-affected countries.²¹ This lateral flow immunochromatographic assay can provide results within 15–25 minutes and is based on the qualitative detection of EBOV VP40 antigen in serum, plasma, or finger-stick whole blood.²² Although less accurate (92% sensitivity; 85% specificity) than “gold standard” nucleic acid amplification tests (NAATs), the ReEBOV Antigen Rapid Test is less expensive, easier to perform, and does not require electricity. With appropriate infection control precautions, the ReEBOV Antigen Rapid Test can be used by trained personnel as a screening tool in rural health clinic settings for presumptive detection of EBOV in patients whose signs and symptoms, in conjunction with epidemiological risk factors, are consistent with EVD. Rapid diagnosis of presumptive EVD cases allows for 1) isolation of symptomatic individuals while they await confirmatory NAAT to prevent health-care-associated EVD; 2) quarantine and monitoring of contacts to prevent spread of EVD to the community; 3) early administration of supportive treatments (i.e., rehydration, electrolytes, antibiotics, antimalarials) to improve patient outcome; and 4) timely engagement of affected communities to reduce fear and to encourage cooperation with control interventions. However, because of the lower specificity of the ReEBOV Antigen Rapid Test, further refinements will be necessary to improve its positive predictive value when EVD case numbers are low to reduce exposure of patients with false positive test results to patients with EVD. The U.K.’s Defense Science and Technology Laboratory (DSTL) has developed a rapid diagnostic test (RDT) that is similar in principle to the ReEBOV Antigen Rapid Test, but is based on detection of an undisclosed Ebola virus antigen.²³ The DSTL EVD RDT can produce a semiquantitative result by scoring the test (T) line on color intensity (2–10). Although the DSTL EVD RDT appears to have high sensitivity (100%) with a specificity of (~92–97%) compared with NAAT (i.e., when the control and T line (CT) score is above 2, 4, or 6), further studies are needed before this test can be approved for screening purposes. Other RDTs for EVD are in various stages of development. For example, researchers at the Massachusetts Institute of Technology (Cambridge, MA) and Harvard Medical School (Boston, MA) engineered a multiplexed pathogen detection platform that uses multicolored silver nanoparticles conjugated to monoclonal antibodies directed against EBOV, dengue virus, or yellow fever virus to detect the presence of these agents in human serum.²⁴ Further development of this experimental device, with inclusion of monoclonal antibodies directed against malaria, a common endemic infection, may

result in a rapid screening test that could aid differential diagnosis of febrile patients who are suspected to have EVD.

Once presumptive EVD cases have been identified, they must be promptly reported to public health authorities to quickly mobilize resources for outbreak control. Advances in mobile-based communication technology are enabling faster, cheaper, and more reliable reporting of EVD cases with expanded geographic coverage. One of several promising examples is mHero (mobile Health Worker Electronic Response and Outreach), a new, two-way, mobile communication platform.²⁵ IntraHealth International (Chapel Hill, NC), in partnership with the United Nations Children’s Fund and Liberia’s Ministry of Health and Social Welfare (MOHSW), has deployed mHero to help frontline health workers (HWs) respond to EVD outbreaks. mHero enables Liberia’s MOHSW to instantly send critical information to thousands of HWs’ mobile phones and HWs to send time-sensitive information to the MOHSW. This powerful tool allows for reporting and tracking of new EVD cases, communicating laboratory test results, sharing reference and training materials, testing and improving HWs’ knowledge, and coordinating with rural health clinics. IntraHealth is introducing mHero in Guinea and discussions are underway to roll out mHero to other countries in west Africa.

In addition to expediting EVD case reporting, advances in mobile-based communication technology could help to track the spread of EVD. Accurate, near real-time information on population mobility in west Africa, one of the most highly connected and densely populated regions of Africa, could show where people have gone after leaving an area of EVD transmission, thus suggesting where new cases might appear. This information is valuable because it enables public health authorities to rapidly focus intervention efforts to interrupt EVD transmission. Only a decade ago, obtaining detailed and comprehensive data for this region would have been impossible. Today, call data records (CDRs) that contain mobility data are stored on cell phone carrier servers. Although CDRs have yet to be released for Guinea, Liberia, and Sierra Leone, the west African countries most affected by the EVD outbreak, mobility pattern models have been generated for Côte d’Ivoire and Senegal to demonstrate the feasibility of this approach, which has been previously used to track the spread of malaria in Kenya and cholera in Haiti.²⁶

Thus far, more than 24 outbreaks of EVD have occurred in Africa since the first documented outbreak in the DRC in 1976. The 2013–2015 EVD outbreak in west Africa is a stark reminder that an emerging infectious disease can exact a terrible toll on human life, severely affect health-care systems, devastate fragile economies, and destabilize governments. Because Ebola virus has an animal reservoir, it cannot be eradicated. Zoonotic introduction of Ebola virus into the African population will continue to occur and must be detected and tackled early on at the source to prevent amplification of sporadic EVD cases into large-scale outbreaks that are driven by human to human transmission.^{7,27} Improved rapid diagnostics and mobile-based communication technology are critical to enable a swift response to EVD and must be included in the EVD preparedness response. Finally, the current EVD outbreak has highlighted the urgent need to rebuild the greatly weakened public health infrastructure of EVD-affected west Africa. This will require a long-term international commitment of significant financial and technical resources. Nonetheless, investments along these lines will surely pay off many times

over for global health by strengthening west Africa's capacity to mount an early response to control outbreaks of EVD and other emerging infectious diseases.

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