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Diagnosis of ebola virus disease and protein antigen detection

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ABSTRACT

Ebola virus disease laboratory diagnosis is crucial to outbreak response efforts; However, it is still extremely difficult to develop risk-free and speedy testing strategies for this pathogen with a high biosafety level in environments with limited resources. Diagnostic techniques have shifted toward faster, more accurate molecular assays ever since the 1976 discovery of the Ebola virus through conventional viral culture methods and electron microscopy. Importantly, efforts to support decentralized diagnostic testing capacity that can be utilized at or close to the point of care for patients have increased alongside technological advancements. The unprecedented scope of the West Africa Ebola epidemic in 2014 and 2015 sparked a lot of innovation in this area. A number of new diagnostic platforms have made it into the field, and they have the potential to change how outbreaks are handled in the future and immediately improve surveillance efforts in West Africa. We discuss the development of Ebola virus disease diagnostic testing and initiatives to establish field diagnostic laboratories during previous outbreaks in this review. Then, we go over the difficulties in diagnosing the epidemics of 2014 and 2015 and go over a lot of new diagnostic tests that might help solve some of these problems in the future.

In 1976, there were two simultaneous outbreaks of acute viral hemorrhagic fever caused by the Ebola virus, with 284 cases in Nzara and 318 in Yambuku, Democratic Republic of the Congo. Up until 2013, there have been approximately 20 additional outbreaks involving nearly 2500 cases in the Democratic Republic of the Congo, Sudan, Gabon, Côte d'Ivoire, Uganda, and the Republic of the Congo since these initial cases.

Keywords: Ebola virus disease; Diagnostic techniques; laboratory diagnosis; testing; conventional viral culture; microscopy

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INTRODUCTION

The difficulties associated with diagnostic testing and the significance of rapid and accurate diagnosis of the Ebola virus disease (EVD) have been brought to light by the most recent outbreak in West Africa [1]. During the outbreaks of 2014 and 2015, diagnosis was primarily based on testing venepuncture blood samples from symptomatic individuals in a bio containment laboratory facility. This made it difficult to collect specimens, manage data, and often took a long time to get results [2]. As a direct consequence of this, there was a previously unheard-of uptick in the creation of brand-new EVD diagnostic techniques due to the demand for speedy and, in particular, point-of-care diagnostics. The evolution of laboratory-based methods for EVD diagnosis, their application for field-based testing during outbreaks, and recent advancements in diagnostic tools that are likely to benefit future clinical and surveillance efforts are all summarized in this review [3]. Clinicians will need a better understanding of each testing platform's analytic and practical advantages and disadvantages as new diagnostic technologies become available. In the end, a variety of factors, such as the health care setting (such as the infrastructure and availability of biosafety and infection control measures), training requirements, regional laboratory capacity, regulatory status, and cost, will all play a role in determining the most effective diagnostic strategy for a given setting [4].

The family of Filoviridae includes both the genus Marburg virus and the genus Ebola virus. The Bundibugyo, Zaire, Sudan, Côte d'Ivoire, and Reston Ebola viruses are among the five species of the virus [5]. The largest outbreaks in Africa have been caused by the first three, while the Reston Ebola virus has only been observed in animals in Asia and not in humans [6].

It is believed that fruit bats in the family Pteropodidae, including Hypsignathus monstrosus, Epomops franqueti, and Myonycteris torquata, are the Ebola viruses' natural hosts, with humans and other mammals acting as accidental hosts. Ebola virus has been linked to one of the main factors in the decline of African chimpanzee and gorilla populations in recent decades, and a variety of animal accidental hosts have been documented [7]. Ebola virus is spread to humans via blood and bodily fluids from an infected person or animal, either directly or indirectly through a contaminated environment. In addition, viral isolation in cell culture using Vero E6 African green monkey kidney cells is the traditional gold standard for confirming the presence of the Ebola virus [8]. Within one to five days of inoculation, propagated virus can be directly or indirectly observed using immunofluorescence microscopy. Although these methods are definitive for detecting the Ebola virus,

they typically only apply to research and public health laboratories and necessitate biosafety level 4 containment.
Since the first outbreak investigations of this virus in 1976, serologic assays for the detection of specific antiviral antibodies in patient serum have been used to demonstrate current or previous infection with Ebola virus [9]. Based on the viral antigen specificity of antibodies in convalescent-phase serum from individuals who had recovered from infections with these pathogens, an indirect fluorescent antibody detection test (IFAT) was used in 1977 to distinguish the newly discovered Marburg virus from the Ebola virus. Cell cultures infected with the Ebola virus are irradiated, fixed onto a slide, and incubated with sera from individuals who might have been exposed in this manner; A fluorescently labeled secondary antibody is then used to detect bound antibodies, and immunofluorescence microscopy is used to see them. Despite the fact that IFAT was instrumental in the establishment of clinical diagnoses during the first few Ebola outbreaks, it was deemed to have suboptimal sensitivity and specificity. Additionally, the requirement for BSL-4 biocontainment made this method unsuitable for large-scale diagnostic efforts.

DETECTION OF PROTEIN ANTIGEN

Since viral proteins typically accumulate to levels that are detectable within a few days of the onset of the disease, the detection of viral protein antigens circulating in the blood is a reliable method for diagnosing acute EVD in symptomatic patients. A pool of eight monoclonal mouse antibodies reactive against EBOV and SUDV and polyclonal antibodies from hyper immune rabbit serum (reactive against EBOV, SUDV, and RESTV) are utilized for antigen capture in an ELISA developed at USAMRIID in 1989 for the purpose of detecting Ebola virus antigens. In a field laboratory deployed by the CDC during the 2000 outbreak in Gulu, Uganda, this assay performed well for clinical diagnosis of acute EVD and was evaluated for clinical use for the first time during the outbreak in 1995 in Kikwit, Democratic Republic of the Congo. It was the fastest method of virus detection available at the time (less than 5 hours). This technique allows for the detection of viral antigen in the serum as early as the first day of symptoms, and by day three of illness, almost all EVD patients have detectable antigen. In fatal cases, antigen levels rise throughout the disease. During the first seven to ten days of illness, antigen levels in nonfatal infections are comparable to those in fatal infections, but they typically decline to undetectable levels by day 16 [10]. In subsequent outbreaks, the CDC's standard diagnostic testing suite included the antigen detection ELISA; however, the antibody reagents' limited availability may have restricted their application by other agencies. Some national reference laboratories have developed and use ELISA antigen detection tests that use monoclonal antibodies against the NP, VP40, or GP proteins that are generated from mice immunized with purified or recombinant Ebola virus proteins. However, these tests have not been used for clinical diagnosis because real-time reverse transcription-PCR (RT-PCR) methods have taken their place (more on this in the "Real-Time RT-PCR" section below). During the most recent outbreak, lateral flow immunoassays (LFIs) emerged as potent instruments for quick, point-of-care antibody-mediated antigen capture.

CONCLUSION

The most common method for diagnosing EVD is real-time RT-PCR, which is a precise and fast method. The World Health Organization (WHO) and the Food and Drug Administration (FDA) have approved a number of standard real-time RT-PCR tests for use in emergency situations. Four of these tests are available as kits in the market. Determination by standard ongoing RT-PCR in a flare-up setting requires field labs with significant foundation, activity and support of mind boggling hardware, and mastery in atomic methods. Even though these resources were eventually put to use during the epidemics of 2014 and 2015, it will be difficult to integrate them into sustainable regional laboratory capacities for ongoing surveillance and response to future outbreaks. Additionally, the need to collect and transport blood from venipunctures will continue to pose additional logistical and safety concerns. The development of practical improvements to pre- and post-analytic processes and the training of local laboratory technicians in molecular diagnostic techniques, biosafety practices, and quality control are two ways in which international partners and national health ministries can strengthen laboratory capacity in Ebola-endemic regions.
Moving forward, novel diagnostic platforms like automated NAATs and rapid antigen detection tests that can be utilized in decentralized health care settings with minimal laboratory infrastructure are likely to play a significant role. In order to determine how these novel tests should be used, additional field data are required. RDTs, if thoughtfully incorporated into testing algorithms, may have an immediate impact as point-of-care tests in high-risk populations, according to existing evidence.

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