Ebola Virus in the Democratic Republic of the Congo

Advances and Remaining Obstacles in Epidemic Control, Clinical Care, and Biomedical Research

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Zaire ebolavirus (EBOV) is an enveloped negative-sense single-stranded RNA virus of the *Filoviridae* family and is the etiologic agent of Ebola virus disease (EVD).¹ EBOV is transmitted through direct contact with infectious body fluids or tissues of an infected individual. Following an average 6-day asymptomatic incubation period, EVD manifests as high fever, myalgias, and progressive prostration. Within approximately 3 days of symptom onset, severe nausea, vomiting, and large-volume diarrhea ensue, and high-level viremia results in widespread infection of multiple cell types and tissues throughout the body.² Complex pathogenesis includes virally mediated hepatocellular and renal tubular necrosis and an exuberant host response contributing to disordered coagulation, increased vascular permeability, and multiorgan dysfunction or failure.

As of July 14, 2019, the EVD epidemic in the Democratic Republic of the Congo (DRC)

entered its 50th week with 2,501 cases and 1,668 deaths reported from 25 health zones in the North Kivu and Ituri provinces.³ On June 11, 2019, Uganda reported the first exported case of EVD from the DRC and on July 14, 2019, an EVD case was reported in Goma, a transportation hub in the DRC with nearly 2 million inhabitants. On July 17, 2019, given fears of regional and international spread, the World Health Organization declared this epidemic a Public Health Emergency of International Concern.

EBOV is the causative agent of the current DRC epidemic and the virus species responsible for the 2014 to 2016 West Africa epidemic that resulted in 28,616 cases and 11,310 deaths.⁴ EBOV was first identified in 1976 in the DRC,⁵ which has now experienced nine epidemics, with three occurring since 2017.⁶ In contrast to previous epidemics in the DRC, in which EBOV emerged in remote settings and resulted in an average of 133 cases per

ABBREVIATIONS: CFR = case fatality ratio; DRC = Democratic Republic of the Congo; EBOV = *Zaire ebolavirus*; ETU = Ebola Treatment Unit; EVD = Ebola virus disease; GP = glycoprotein; mAb = monoclonal antibody; RCT = randomized clinical trial; RT-qPCR = reverse transcription quantitative polymerase chain reaction; rVSV = recombinant vesicular stomatitis virus

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epidemic (range, 1-318 cases), the current epidemic has reached urban locales with > 2,500 cases occurring over > 1 year. The current article summarizes the use of an experimental vaccine to assist with control of the current epidemic, improvements in clinical care provided in Ebola Treatment Units (ETUs), and implementation of a randomized clinical trial (RCT) to assess efficacy of four potential therapies. Despite these advances, we also present data reflecting an uncontrolled epidemic with sustained high case-fatality and identify areas for improved epidemic control, patient care, and biomedical research during this and future epidemics.

An Effective Vaccine

A number of experimental vaccines have shown promise in preclinical and early-phase clinical studies,⁷ although the most advanced for clinical use is the recombinant vesicular stomatitis virus (rVSV)-EBOV glycoprotein (GP) vaccine. This replication competent recombinant vaccine uses VSV, a nonpathogenic virus to humans, to express EBOV surface GP. Phase I and II clinical trials indicate that rVSV-EBOV GP is safe and immunogenic. A phase III trial evaluating the effectiveness of rVSV-EBOV GP was conducted in Guinea and Sierra Leone during the 2014 to 2016 West Africa epidemic.⁸ Given that cases in West Africa were waning at the time, the trial was designed by using a ring vaccination strategy to provide the greatest opportunity to determine effectiveness in a short interval. In this trial, confirmed EVD cases were identified, and rings of contacts around cases and secondary rings around primary contacts were identified and vaccinated either immediately upon identification or following a 21-day interval. The trial provided a convincing result for vaccine effectiveness, with no EVD cases detected among the immediate vaccination group, after allowing 10 days for the vaccine to take effect; multiple EVD cases occurred in the delayed vaccination group.

Since August 2018, rVSV-EBOV GP, although not yet licensed for use, has been made available through compassionate use to protect health-care workers and assist with epidemic control.³ Based on World Health Organization weekly updates, an initial 3,220 vaccine doses became available, followed by a steady rise in availability and utilization; > 161,400 vaccinations have been administered thus far (Fig 1).

An Uncontrolled Epidemic

Based on publicly available data through the World Health Organization,³ during the summer of 2018, the

number of weekly confirmed EVD cases in the DRC peaked at 45, and subsequently declined, suggesting that early interventions might effectively control this epidemic (Fig 1). However, by October to mid-March 2019, a total of 11 to 50 new confirmed cases per week were reported and since late March to July 2019, a total of 56 to 121 confirmed cases per week have been reported. These data indicate that despite international public health initiatives and a widening vaccination campaign, the EBOV epidemic in the DRC remains uncontrolled. Regional insecurity with frequent acts or threats of violence toward health-care workers or ETUs have disrupted case findings and delayed isolation of cases, contact tracing, the opportunity to provide safe and dignified burials, and the ring vaccination required for epidemic control.^{3,9} Despite extensive use of the vaccine, delays in implementation of outbreak control measures have allowed for a continued rise in new confirmed cases each week.

These observations are consistent with predictions of a mathematical model developed by Wells et al,¹⁰ which suggests that a one- or two-week delay in ring vaccination reduces effectiveness to prevent new cases by 50% and 80%, respectively. This model predicts what public health experts know, which is that epidemic control is dependent on timely interventions. Translating this knowledge into practice, however, requires overcoming violence, mistrust, and misinformation in the community, and imperfect coordination and communication among multiple national and international actors managing a complex and dynamic epidemic response.^{9,11}

Improved Diagnostics and Clinical Care

Early and accurate diagnosis of EVD is essential for rapid isolation of cases and implementation of medical care. Historically, EBOV diagnostics were not readily available within or near ETUs, often contributing to nosocomial transmission and delays in care. During the 2014 to 2016 West Africa epidemic, reverse transcription quantitative polymerase chain reaction (RT-qPCR)-based assays became widely available for EVD diagnosis at or near ETUs, and this practice remains in place during the current epidemic in the DRC. Although RT-qPCR-based assays remain the gold standard for EBOV diagnosis, they require technical expertise and specialized equipment. The longer an individual under evaluation for EBOV infection remains in an ETU awaiting blood test results, the more likely that nosocomial transmission will occur. There remains

Figure 1 – Number of confirmed Ebola virus disease cases, cumulative number of Ebola vaccines administered, and cumulative case fatality ratio in the Democratic Republic of Congo, August 5, 2018, to July 14, 2019.

a need for rapid, simple, and accurate diagnostics for use at the point of care to guide triage and infection control during EBOV epidemics.¹²

Although antigen-based diagnostic assays have attempted to fill this niche, none has achieved the combined sensitivity and specificity of RT-qPCR, thus limiting their application.¹³ A test with suboptimal sensitivity may provide a false-negative result, leading to discharge of patients with EVD into the community, and a test with suboptimal specificity may provide a false-positive result, risking admission of uninfected patients; both outcomes are undesirable. At present no test is capable of detecting EBOV infection during the average 6-day incubation period when RT-qPCR assays are consistently negative due to absent or undetectable viral RNA in blood. Identification of a reliable host or viral signature of infection during the incubation period would allow significant lead-time in isolation of cases and initiation of care.¹⁴

Historically, limited medical care was available to patients infected with EBOV in remote settings where the focus was on isolation of cases to facilitate epidemic control rather than on treatment of the sick. This paradigm began to shift during the 2014 to 2016 West Africa epidemic, during which basic supportive care (including oral and later IV hydration, antimicrobial therapy, antipyretics, and analgesics) was more routinely available. In addition, clinical expertise gained during the 2014 to 2016 epidemic

provided new insight into disease pathophysiology, informing care algorithms.^{1,15,16}

During the present epidemic in the DRC, novel approaches to the care environment in ETUs¹⁷ have allowed for more frequent clinical monitoring and nursing care and closer fluid and electrolyte management guided by point-of-care clinical diagnostics. However, severe EVD can manifest with multiorgan failure, including renal and respiratory failure, which current ETUs are neither staffed nor equipped to manage. If EVD mortality is to be truly minimized, then future care would include support for respiratory and renal failure.

Persistently High Case-Fatality

Historically, as evidenced by the 1976 epidemic, EVD case fatality ratios (CFRs) have been as high as 88% (95% CI, 87.8-88.3), largely among patients who received minimal or no medical care.¹⁸ During the 2014 to 2016 West Africa epidemic, rehydration, nutrition, and other basic care were provided with an associated decrease in CFR to 39.5% (95% CI, 39.5-39.5).⁴ Among 27 patients provided advanced supportive care in Europe and the United States, the CFR was 18% (95% CI, 4-33).¹⁵ These data support the conclusion that supportive care in the face of life-threatening EBOV infection improves survival. In August 2018, at the onset of the current epidemic in the DRC, the CFR peaked at 79% (95% CI,

77-92) (Fig 1). The cumulative CFR subsequently declined to a low of 57% (95% CI, 57-62) in November 2018 but has since steadily increased through July 2019 to 67% (95% CI, 67-69). Why, in the face of improved clinical care available in ETUs and availability of experiment therapeutics (as discussed later), has the CFR remained persistently elevated?

Based on publicly available data, during January to July 2019, the number of weekly new deaths reported by the DRC Ministry of Health fluctuated from approximately 16 to 94 (Fig 2), with the predominance of deaths occurring among patients who never sought nor reached care in an ETU.¹⁹ Remarkably, during periods in January, February, and May 2019, $\geq 70\%$ of deaths occurred outside of ETUs, reflecting ongoing challenges with early case identification, isolation, and care. If overall CFR is to be reduced during this outbreak, then patients must reach and receive care in ETUs with adequately trained and equipped staff.

Research on Targeted Therapies

The efficacy of ZMapp (the result of a collaboration between Mapp Biopharmaceutical, Inc. and LeafBio [San Diego, CA], Defyrus Inc. [Toronto, ON, Canada], and the U.S. government and the Public Health Agency of Canada), a cocktail of three monoclonal antibodies (mAbs) targeting EBOV GP,²⁰ was evaluated in a phase III RCT during the 2014 to 2016 West Africa epidemic.²¹

Death occurred in eight of 36 (22%) patients who received standard of care plus ZMapp compared with 13 of 35 (37%) patients who received standard of care alone. A definitive determination of ZMapp efficacy was not possible, however, due to waning cases at the epidemic's end. ZMapp is now being compared vs two additional GP-targeting mAb-based therapies (mAb114 and REGN-EB3) and vs a viral polymerase inhibitor (Remdesivir; Gilead Sciences) in a multi-arm RCT.^{22,23} This trial represents a significant step forward in implementing essential biomedical research during complex and lethal epidemics and holds promise for identifying efficacious therapies for improved survival in EVD. As suggested by the first ZMapp RCT, however, targeted therapies, without concurrent intensive supportive care, allowing time for organ recovery and viral clearance, may not significantly reduce mortality below the 22% observed in the ZMapp arm of the first RCT.

Discussion

The current EVD epidemic in the DRC remains uncontrolled with a high CFR despite advances in vaccine availability and use, improved clinical care within ETUs, and implementation of an RCT evaluating targeted therapies. Limitations in epidemic control and a high CFR reveal the necessity of early case finding, effective isolation, contact tracing, safe and dignified burials, and advanced medical care. Late administration

Figure 2 – The number of deaths from Ebola virus disease and the percentage of those deaths occurring outside of an ETU in the Democratic Republic of the Congo, January 6, 2019, to July 15, 2019. ETU = Ebola Treatment Unit.

of an effective vaccine or therapy will not prevent EBOV infection or reverse existing organ injury, respectively. Overcoming obstacles of violence, mistrust, and disinformation are essential to all basic yet fundamental public health interventions required to end this epidemic.

Improved care and survival within ETUs coupled with open and transparent community engagement are central to establishing and maintaining trust within communities.⁹ Although standard public health interventions will remain the backbone of this and future EBOV epidemic responses, ongoing advances in vaccines, diagnostics, clinical care, and targeted therapies will provide new tools to aid epidemic control and reduce mortality. These tools can only be achieved through biomedical research seeking to elucidate and mitigate complex viral-host interactions that contribute to organ dysfunction and failure. Areas that require further investigation that might benefit from targeted therapies include mechanisms of large-volume watery diarrhea, early indirect lymphocyte death, vascular leakage, disseminated intravascular coagulation, and viral persistence in immunoprotected sites. The combination of basic and translation research, state-of-the-art clinical care, and tried-and-true public health interventions implemented through robust community engagement hold promise for more effective responses during this and future epidemics.

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