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FILOVIRUS SYMPOSIUM SUPPLEMENT

Perspectives on Advancing Countermeasures for Filovirus Disease: Report from a Multi-Sector Meeting

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Although there are now approved treatments and vaccines for Ebola virus disease (EVD), the case fatality of EVD remains unacceptably high even when treated with the newly approved therapeutics; furthermore, these countermeasures are not expected to be effective against disease caused by other filoviruses. A meeting of subject matter experts from public health, research, and countermeasure development agencies and manufacturers was held during the 10th International Filovirus Symposium to discuss strategies to address these gaps, including how newer countermeasures could be advanced for field readiness. Several investigational therapeutics, vaccine candidates, and combination strategies were presented. In all, a common theme emerged: the greatest challenge to completing development was the implementation of well-designed clinical trials of safety and efficacy during filovirus disease outbreaks. These outbreaks are usually of short duration, providing but a brief opportunity for trials to be launched, and have too few cases to allow for full enrollment during a single outbreak, so clinical trials will necessarily need to span multiple outbreaks which may occur in a number of at-risk countries. Preparing for this will require agreed-upon common protocols for trials intended to bridge multiple outbreaks across all at-risk countries. A multi-national research consortium including, and led by, at-risk countries would be an ideal mechanism to negotiate agreement on protocol design and coordinate preparation. Discussion participants recommended a follow-up meeting be held in Africa with national public health and research agencies from at-risk countries to establish such a consortium.

Key words: Filoviridae, Therapeutics, Vaccines, Disease Outbreaks, Clinical Trial, Africa

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Main text

With the FDA approval of monoclonal antibody therapies and vaccines to treat and prevent Ebola virus disease (EVD), countermeasures are now available against Ebola virus (EBOV). However, although EBOV causes most cases of filovirus disease (FVD), it is responsible for only about half of FVD outbreaks[i,ii]. No countermeasures have yet been shown to be effective in humans against any other causative agents of FVD, including Sudan virus (SUDV), Bundibugyo virus (BDBV), Marburg virus (MARV), Ravn virus (RAVV), and Taï Forest virus (TAFV). Despite having antibody therapies effective at improving EVD survival, there is dire need for improvements in patient outcomes as the mortality rates due to EBOV infection remain unacceptably high, even with treatment[iii]. Furthermore, the therapeutic interventions that might reduce clinical sequelae of EVD and persistent EBOV infection leading to renewed human-to-human transmission and reignition of outbreaks is yet to be established [iv,v].

Several products are in different stages of development for preventing and treating the full range of disease caused by filoviruses, yet advancement of the development process towards regulatory approval is demanding and has many obstacles. Optimization and validation of manufacturing processes, evaluation of safety and toxicity in preclinical studies, and identification of optimal dose regimens in animal models that can be extrapolated to humans are critical aspects of the development process that require considerable time and resources to complete. Developers are supporting activities to establish acceptable animal models of infection to enable use of the FDA's Animal Rule for approval in parallel to maintaining readiness to be included in potential outbreak clinical trials, such as those that supported licensure of the approved EBOV vaccines and therapeutics. For some countermeasures, such trials will be a necessary step towards licensure and execution of trials has been challenging.

Although the countermeasure development progress has advanced steadily during inter-outbreak periods, attempts to implement clinical trials during recent outbreaks have not been successful. The challenges to execute high-quality registrational studies which demonstrate clinical efficacy and safety of a vaccine or a therapeutic sufficient for licensure are significant[vi]. To date, only the two largest EVD epidemics, in West Africa (2014-2016) and the Democratic Republic of the Congo (2018-2020) represented public health emergencies of sufficient magnitude and duration to bring about licensure of EVD countermeasures. The fact that EBOV has been shown to infect the respiratory tract, a future FVD outbreak may have the potential to cause a larger epidemic.

The 10th International Filovirus Symposium provided an opportunity to convene a meeting of subject matter experts to discuss countermeasure opportunities, gaps, and potential development paths. On September 22, 2022, representatives of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health; the Biomedical Advanced Research and Development Authority (BARDA), part of the Administration for Strategic Preparedness and Response; the Centers for Disease Control and Prevention (CDC); the Public Health Agency of Canada; the University of Texas Medical Branch-Galveston National Laboratory (UTMB-GNL);

Médecins Sans Frontières (MSF); Mapp Biopharmaceutical; Gilead Sciences, and the Democratic Republic of the Congo's National Institute for Biomedical Research met to discuss how current investigational countermeasures could be advanced to licensure and made available to improve outcomes in future FVD outbreaks.

The meeting's participants were asked to consider vaccines and antibody therapies for FVDs not caused by EBOV, the combination of remdesivir and antibody therapy as treatment for FVD, and an investigational oral antiviral analog of remdesivir.

Mapp Biopharmaceutical presented MBP134, a cocktail of two monoclonal antibodies effective in nonhuman primates against multiple ebolavirus species, for which safety has been demonstrated in a phase I trial (personal communication MappBio). Nonhuman primate (NHP) studies suggest the drug's efficacy in protection against EBOV, SUDV, and BDBV challenges[vii]. MBP-091 is a single monoclonal antibody, also developed by Mapp Biopharmaceutical, that demonstrates efficacy in protection against MARV challenge in the rhesus macaque model[viii] and safety established in a phase I trial (personal communication MappBio). These two products could allow for the treatment of all diseases caused by filoviruses, but, as of September 2022, neither was available in sufficient quantities to allow for phase III trials. Since then, Mapp has worked diligently to prepare for patient access and potential clinical efficacy studies while continuing to pursue approval under the FDA's Animal Rule; funding for development of both antibody products is from the US government through BARDA.

BARDA presented several vaccine candidates for protection against FVD for which they support preclinical and clinical development. Vaccines analogous to the currently approved rVSV-EBOV (ERVEBO) vaccine produced by Merck are being developed by The International AIDS Vaccine Initiative and Public Health Vaccines for protection against MARV and SUDV [ixx][xi]. While limited cross protection is observed with heterologous filovirus immunogens, preclinical studies indicate that rVSV-MARV and rVSV-SUDV may offer similar protection against homologous challenges observed with ERVEBO[9,xii,xiii]. Also in development from the Sabin Vaccine Institute are vaccines against MARV and SUDV using a chimpanzee adenovirus platform and a trivalent rVSV vaccine against EBOV, SUDV, and MARV [xiv][xv]. Vaccines based on the rVSV platform improve survival in NHPs when given shortly after exposure [xvi]. Whether they have this effect in humans is currently uncertain and will be difficult to determine. In any case, protective immunity is rapidly induced (e.g., following ring vaccination) with the clinical efficacy study of ERVEBO showing no EVD cases after 6 days post-vaccination[xvii]. Vaccine researchers estimate that at least ten thousand doses of vaccine are needed to support a clinical trial like the one that demonstrated the efficacy of Merck's ERVEBO vaccine. None of these candidate vaccines were available in such quantities as of September 2022, but efforts were made to expedite manufacturing during the outbreaks to get to at least 10,000 doses of vaccine that could be used in clinical trials [manuscript submitted and under review].

A collaborative effort between UTMB-GNL, MappBio, and Gilead demonstrated the combination of MBP431 (an extended half-life version of MBP134) and remdesivir provided protection that was superior to either treatment alone against SUDV challenge in the rhesus macaque model when delivered at a very advanced stage of disease[xviii]. In an analogous study, the combination of MR186 (an anti-Marburg virus glycoprotein antibody) and remdesivir was similarly superior to either treatment alone against advanced MARV disease[xix]. As care of FVD patients is frequently complicated by late arrival of the patient for definitive care, these studies suggest that the combination therapy of a monoclonal antibody or antibodies and a direct-acting antiviral might further improve patient survival, even in late stages of illness, as compared to either monotherapy alone. Neither of these studies were designed to assess human safety; however, the NHP data did not suggest immediate safety concerns for similar clinical use. Nonetheless, clinical safety should be assessed in the future. The meeting participants agreed an important next step would be to conduct a similar study of the therapeutic window afforded by the combination of remdesivir and one of the currently approved antibody treatments against an EBOV challenge in NHPs.

Obeldesivir (GS-5245) is an investigational nucleoside prodrug that is metabolized in cells and tissues to the same active GS-441524 triphosphate metabolite as remdesivir and thus exerts the identical antiviral mechanism of action[xx]. Unlike remdesivir, obeldesivir is administered orally. It demonstrated efficacy in an NHP model of SARS-CoV-2 infection, successfully completed a phase 1 pharmacokinetics and safety trial in healthy humans and is currently in two phase 3 trials for outpatient treatment of COVID-19 in high-risk and standard-risk participants[18,xxi,xxii,xxiii]. Gilead Sciences is currently testing obeldesivir in several NHP models of filovirus infection. In vivo efficacy demonstrated in these models would open a significant opportunity to test obeldesivir in future FVD outbreaks and/or to continue the development under the FDA Animal Rule. Availability of an oral agent for FVD, such as obeldesivir, will allow for an easy oral postexposure prophylaxis of healthcare workers and other direct contacts of FVD patients, which holds great potential for improving the active control of future FVD outbreaks, particularly in cases when another efficacious prophylaxis is not available or practical.

On the day of the meeting in La Jolla, California, Uganda declared an outbreak of Sudan virus disease (SVD). In the following months, there were attempts to make use of some of the countermeasures discussed in the La Jolla meeting, both in the Uganda SVD outbreak and the subsequent Marburg virus disease outbreaks that occurred in Equatorial Guinea and Tanzania in early 2023. In partnership with the Ugandan Ministry of Health (MoH), several SVD patients were treated with MBP134 or remdesivir under compassionate use, and the MBP134/remdesivir combination therapy was introduced into the design of a clinical trial proposed by WHO for Uganda, but no trial design was agreed upon prior to outbreak end[xxiv,xxv]. Several MARV vaccines and MBP091 were considered by WHO for use in Equatorial Guinea and Tanzania but were not deployed during these outbreaks[xxvi,xxvii].

Well-designed clinical trials are complex undertakings and require time to prepare if they are expected to generate robust and interpretable data. As FVD outbreaks occur without warning and usually run their course within a few months, implementing trials in time to enroll patients during the outbreak is difficult. The two outbreaks in which clinical trials have been successfully conducted were two of the longest in history, each extending over approximately two years.

The environment in which FVD outbreaks occur also can be an impediment. Epizootic spillover typically occurs in remote underserved parts of equatorial Africa with limited resources and infrastructure to support research, posing logistical problems and occasionally adding the difficulty of working in a region experiencing armed conflict. Cultural differences and local beliefs are often at odds with disease control measures, creating an environment of mistrust into which research is not easily introduced[xxviii]. These obstacles are not insurmountable, but overcoming them requires labor, resources, and time, none of which are in abundance during FVD outbreaks, and so being well prepared improves the chances of success.

Although the discussion in La Jolla was structured around the countermeasures described here, preparing to meet the challenge of implementing clinical trials during an outbreak was a common theme. For clinical trials to even be considered feasible, there needs to be sufficient GMP material and formulated investigational drug product needs to be available beforehand to support these trials. Moreover, well controlled nonclinical studies demonstrating efficacy, and phase 1 trials establishing safety, pharmacokinetics, and, where relevant, immunogenicity also should be complete. If these steps can be accomplished, considerable time and effort will be required to reach agreement on which vaccines or treatments to study, to achieve consensus on the study design and other details of the protocol, especially as it relates to acceptance by regulatory agencies towards the goal of licensure, to obtain ethical approval and importation permits for investigational products, to ship these products to the outbreak location, identify local principal investigators (PI's), and to set up the trial infrastructure. If a trial is launched, the window to enroll patients is rather short given previous outbreak kinetics, so all preparative work that can be completed ahead of time should be. All this pre-trial preparation would be a major undertaking if were needed in only one country. However, as the location of the next outbreak is not known, these preparations must be made in each country where an outbreak is likely to begin. As of early 2023, eighteen African countries experienced FVD outbreaks, and these have many neighboring countries that could be considered at risk[1,2]. Given the number of at-risk countries, preparedness for only just the highest risk countries will be no small matter.

Further complicating matters, the number of patients needed for enrollment in randomized clinical trials of FVD therapeutics to realistically support regulatory approval of tested products is often significantly larger than the size of most outbreaks. The PALM trial conducted in Eastern DRC in 2018-2020, which demonstrated the safety and efficacy of two subsequently approved antibody treatments, enrolled 681 patients in four study arms[3]. Of the 52 naturally occurring FVD outbreaks since 1967, only 13 resulted in more than 100 recorded cases of the disease, and only the two largest had enough patients for a trial like PALM to complete

enrollment during the outbreak[1,2]. Very large outbreaks, like the EVD epidemics in West Africa in 2014-2016 or in DRC in 2018-2020, can provide an opportunity to gather sufficient data within the outbreak to complete a clinical trial, but these are exceptional events, and outbreaks of comparable size caused by filoviruses other than EBOV have not occurred. Each FVD outbreak is a rare and unpredictable event, and by itself is usually a limited opportunity to advance our understanding of the effectiveness of treatments and vaccines. To make the most of these opportunities, clinical trials should be ready to be launched as soon as the outbreak is detected and designed in a way that allows conducting the trial over the course of multiple outbreaks until fully enrolled.

The location of the next FVD outbreak cannot be predicted, placing many African countries at risk. Given this, and as multiple outbreaks may be required to complete one clinical trial, a single international protocol is needed. To have this, all at-risk countries need to agree on trial protocol details. In fact, a set of shared protocols is necessary to study treatment of the infected, post-exposure prophylaxis for the exposed, vaccination of the unexposed, and mitigation of the risk of late transmission from survivors, with some details of each protocol varying according to the particular filovirus involved. Negotiation of multi-country platform trials and oversight of trial preparations in each interested country is a significant undertaking and will require robust intergovernmental collaborations and partnerships across multiple sectors in the form of a consortium able to work across the diverse geographies, languages, and cultures in Africa. In addition, contingency plans and study protocol extensions should be available in case an FVD outbreak further extends globally.

The participants in La Jolla recognized the absence of representatives from African nations at the meeting, with the exception of the DRC, was a significant limitation. It is absolutely critical for the success of the proposed strategies and countermeasures that there is leadership in their development and expertise from relevant at-risk countries. Therefore, meeting participants concluded the next urgent step in advancing filovirus countermeasures is to organize a follow-up meeting in Africa with public health representatives from countries at-risk of FVD outbreaks who are interested in implementing these measures in their countries as a part of preparation for future outbreak response. The objective of such a meeting would be to establish a consortium capable of developing strategies designed to stop or prevent future outbreaks and spread and negotiating a common set of shared protocols and organizing trial preparations in at-risk countries ahead of FVD outbreaks. Beyond the development and prepositioning of clinical trial protocols, advancing research on filovirus countermeasures will also require efforts to improve healthcare infrastructure, surveillance systems, education, and community engagement. Once these pre-trial preparations have been made, clinical trials can be rapidly implemented during future outbreaks, and the evidence base generated to complete the development of the most promising vaccines and treatments and make these globally available for use against all forms of FVD.

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Footnote Page

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