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Pre-positioned Outbreak Research: The Joint Medical Emerging Diseases Intervention Clinical Capability Experience in Uganda

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The West Africa Ebola virus disease outbreak of 2014-2016 demonstrated that responses to viral hemorrhagic fever epidemics must go beyond emergency stopgap measures and should incorporate high-quality medical care and clinical research. Optimal patient management is essential to improving outcomes, and it must be implemented regardless of geographical location or patient socioeconomic status. Coupling clinical research with improved care has a significant added benefit: Improved data quality and management can guide the development of more effective supportive care algorithms and can support regulatory approvals of investigational medical countermeasures (MCMs), which can alter the cycle of emergency response to reemerging pathogens. However, executing clinical research during outbreaks of

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high-consequence pathogens is complicated and comes with ethical and research regulatory challenges. Aggressive care and excellent quality control must be balanced by the requirements of an appropriate infection prevention and control posture for healthcare workers and by overcoming the resource limitations inherent in many outbreak settings. The Joint Mobile Emerging Disease Intervention Clinical Capability was established in 2015 to develop a high-quality clinical trial capability in Uganda to support rigorous evaluation of MCMs targeting high-consequence pathogens like Ebola virus. This capability assembles clinicians, laboratorians, clinical researchers, logisticians, and regulatory professionals trained in infection prevention and control and in good clinical and good clinical laboratory practices. The resulting team is prepared to provide high-quality medical care and clinical research during high-consequence outbreaks.

Keywords: Medical countermeasures, Infectious diseases, Viral hemorrhagic fevers, Outbreak response, Uganda

Outbreaks of high-consequence pathogens, such as those causing viral hemorrhagic fever (VHF), pose clear public health threats.[1] They are also recognized as potential global biosecurity threats. Outbreaks of VHF often emerge in settings of social and economic vulnerability, where healthcare systems are unprepared for such events.[2-5] In the absence of advanced medical capabilities and VHF management training, healthcare systems can unintentionally amplify outbreaks. The loss or attrition of healthcare workers can then not only cripple the responses to VHF but concurrently increase morbidity and mortality from unrelated conditions. This was observed most strikingly in the 2014-2016 Ebola virus disease (EVD) epidemic in West Africa, which saw a sharp decline in access to primary maternal, newborn, and child health services and primary healthcare in general.[6-8] Local outbreaks have ripple effects on the local and international communities, which can threaten the integrity of social, economic, and political structures.[9,10]

To combat emerging and reemerging high-consequence pathogens, proactive, pre-positioned capacities should replace emergency stopgap responses. Potential outcomes of building local clinical and research capabilities include increasing understanding of human clinical syndromes, developing clinical and laboratory diagnostic algorithms to identify etiologic agents, improving understanding of disease transmission mechanisms, and conducting clinical research to develop promising medical countermeasures (MCMs).[11,12] Furthermore, the example of EVD has demonstrated that animal models of infection and retrospective data analysis from outbreaks may be insufficient to fully characterize the safety and efficacy of new treatments. The West African outbreak witnessed the failure of several investigational new drug (IND) candidates that had promising results in animal studies, and additional surprises were revealed by the recent PAmoja TuLinde Maisha (PALM) study in the Democratic Republic of Congo (DRC).[13-15] Accurately characterizing human disease is our best chance for optimizing standard of care and biocontainment procedures to treat patients in the immediate future, and it is our best opportunity to improve animal model validity and develop MCMs that will ultimately save lives.[16,17]

The importance of advancing tools to interrupt outbreaks is well encapsulated in the Global Health Security Agenda Action Packages.[18] However, achieving these aims is not trivial, and it requires pre-planning, the pre-positioning of assets, and the development of personnel and relationships.[12] Outbreaks often occur in resource-limited settings, where sufficient numbers of well-trained clinical and laboratory personnel are often lacking, basic maintenance of laboratory instruments is a challenge, and adherence to standards of good clinical practice and good clinical laboratory practice is almost unachievable without significant interventions. Clinicians lack resources to provide optimal care for severely ill patients, and the lack of infection prevention and control training, as well as education about VHF pathogens and their manifestations, limit the ability of the best-intentioned healthcare workers to provide care safely and effectively.[19-21] Logistical challenges, such as reliable electricity, waste management, communication, and cold chain support for supplies, require expertise and resources, all of which are dependent on funding and political will.

Recent cooperative initiatives, most notably the Coalition for Epidemic Preparedness Innovations (https://cepi.net), attempt to address some of the challenges to funding, particularly with respect to vaccine development. However, therapeutics and diagnostics remain a gap, and the advancement of MCMs targeting rare pathogens endemic to resource-limited regions has historically been de-prioritized by pharmaceutical companies because of the limited revenue potential associated with such products.[22,23] Challenges to supporting local hospital capacity for optimal clinical research in austere settings are even more complex: Costs are significant, and clinical research capacities are not self-sustaining in communities where hospital care is largely free and emergent. Long-term research partnerships are needed to engage, build, and sustain local clinical research capacity, ideally through research programs focused on locally relevant diseases.

In 2015, a multi-institute, multinational project, the Joint Mobile Emerging Disease Intervention Clinical Capability (JMEDICC), was launched in Uganda. The project is derived from a medical product acquisitions funding line; the fundamental goal is to establish a capability to conduct clinical trials of MCMs, specifically antiviral INDs, during outbreaks. However, on the path to establishing that capability, the team learned important lessons about the challenges that encumber clinical research on high-consequence pathogens in the field setting. JMEDICC is by no means the only team interested in implementing high-quality clinical research and medical care in outbreak settings. The efforts by the Institut National de Recherche Biomédicale, Médecins Sans Frontières (MSF), the World Health Organization (WHO), and the National Institute of Allergy and Infectious Diseases (NIAID), which are currently operating in the Democratic Republic of Congo (DRC), are truly heroic and will undoubtedly change the face of clinical research with high-consequence pathogens.[24] However, JMEDICC, to the best of our knowledge, is the only pre-positioned effort to sponsor and train a clinical research team at a location at risk for filovirus outbreaks, with the explicit intention of caring for patients under an IND clinical protocol.

This article outlines the significant challenges related to conducting ethical, equitable clinical research and providing good clinical quality of care in the context of high-consequence pathogen outbreaks. We argue that to address many of these challenges, there are no shortcuts to long-term investment and training, and that by engaging proactively in readiness efforts, the challenges associated with "building the ship while sailing" can be mitigated.[25]

JMEDICC Overview

JMEDICC is a collaborative effort among entities in the United States and research organizations in Uganda, including the Henry M. Jackson Foundation for the Advancement of Military Medicine, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the Naval Medical Research Center, the Makerere University Walter Reed Project (MUWRP), the Makerere University Infectious Diseases Institute (IDI), and the National Emerging Infectious Diseases Laboratories at Boston University. The project is also supported by outside consultants, independent experts with a range of field VHF epidemic experience, and contract organizations that assist with logistics and regulatory affairs.

Funding for JMEDICC is provided by the US Department of Defense (DoD) Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical, a component of the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense. The US DoD has a long history of supporting the development of MCMs targeting rare pathogens, including filoviruses. Drawing on lessons learned from the 2014-2016 West African Ebola outbreak, DoD established JMEDICC as risk mitigation for future filovirus MCM development, forecasting that a pre-positioned team with the capability to conduct clinical research would provide human clinical data on the safety and efficacy of MCMs to supplement regulatory submissions under the animal rule.

In 2016, JMEDICC undertook a stakeholder identification and relationship-building effort. This effort included socializing the JMEDICC concept with the Fort Portal Regional Referral Hospital (FPRRH) in Fort Portal, Uganda; the Ugandan Ministry of Health; the WHO in Uganda; MSF; Ugandan national referral laboratories, including the Central Public Health Laboratory and the Uganda Virus Research Institute (UVRI); the Ugandan National Drug Authority (NDA); the interagency health team at the US Embassy in Kampala; and the US Centers for Disease Control and Prevention (US CDC). Concurrently, the team learned about the Ugandan national outbreak response structure and received input on the optimal integration of the project into local processes.

Since 2016, the project has assembled a full-time multidisciplinary team with clinical, laboratory, logistics, pharmacy, and regulatory expertise. The team consists of 34 Ugandan personnel based in Fort Portal and additional support in Kampala, Uganda. At Fort Portal, JMEDICC renovated a research ward with the capability for patient isolation and care. JMEDICC has coordinated multiple capability exercises, including a multinational demonstration in July 2017 and a joint sample handling and diagnostic exercise with Ugandan authorities in 2018. In Fort Portal, the team exercises clinical research skills by executing an observational sepsis study on a day-to-day basis while supplementing their schedules with ongoing infection prevention and control, advanced clinical care, biocontainment, and biosecurity training. The observational sepsis study serves as a training platform for clinical research and clinical management of severely ill patients; it is also a research platform for testing and evaluation of novel technologies and generates meaningful data on the pathogens causing severe disease in the area.

Personnel

A critical and valuable lesson learned from the JMEDICC experience is that personnel are the most precious resource of the team. Identifying personnel with the baseline expertise in clinical, laboratory, regulatory, and logistical requirements was an essential starting point. Table 1 shows a snapshot of the current full-time JMEDICC staff in Fort Portal, as well as part-time support from leadership in Kampala. The project advanced existing skill sets to include expertise in VHF-appropriate infection prevention and control as well as the data quality management and documentation required to execute US Food and Drug Administration (FDA)–compliant clinical trials. The training

Table 1

Role	Number of Full-Time Personnel in Fort Portal	Part-Time Personnel Based in Kampala	Comment
Study Coordinator	1	2	
Medical Officers	2	7	Kampala personnel includes trained surge personnel
QA/QC Officers, Data Management, and Regulatory Support	1	5	
Research Nurse	4	0	
Study Nurse	4	0	
Nurse-Hygienist	6	0	
Laboratory Technologists	6	0	
Laboratory QA/QC	1	6	
Laboratory Lead	1	1	
Community Outreach Officer	1	1	
Logistics and Finance Personnel	2	5	
Technology Support Personnel	0	4	
Sanitary Officer/Hygienists	3	0	
Driver	1	1	
Pharmacists and/or Pharmacy Technicians	1	2	Kampala personnel anticipated to surge to Fort Portal as needed

was conducted in collaboration with numerous outside subject matter experts and internal team members who dedicated their time to raising the team's capability. Notably, this training also increased the value of the staff among their peers; while this is undoubtedly a benefit to the host nation, it did also create a new project challenge of personnel retention.

At entry into JMEDICC, all staff complete the WHO Ebola Virus Disease Case Management Training, followed by intensive weekly training on infection prevention and control.[26] Tasks of increasing complexity are performed in drills for a minimum of 2 exercises per month for all staff. Continuous improvement is implemented using the "plan-do-study-act" quality improvement framework, and scheduled competency assessments are performed using standardized checklists.[26] By using long-term training, the program has been able to introduce complexity to the instruction, which includes specific case management (ie, presentation of simulated patients to hospital triage) and emergency-based management (ie, situations such as when a healthcare worker is exposed or becomes unconscious: "HCW down").

Past outbreaks have revealed the evolving complexities of VHF management as more nonhealth professionals become involved in case management and consequently have elevated risk of infection. To address this finding, logisticians, electricians, and information technology staff have been trained in infection prevention and control practices in coordination with training of the clinicians, laboratory scientists, pharmacists, and hygienists.

To improve training, the team uses novel technologies that increase healthcare workers' awareness and capabilities. For example, color markers (eg, Glo Germ™ and Highlight® by Kinnos) that simulate environmental and personal protective equipment (PPE) contamination have been incorporated into training sessions. These products enable real-time feedback on skill execution, which increases confidence and improves standardization of decontamination practices. Additionally, the preferred (though not exclusive) PPE for the team includes powered air purifying respirators rather than N95 masks. This provides the team with increased comfort and vision, resulting in more effective, longer, safer working intervals, which enables improved clinical observation and documentation.

While staff safety is a priority of the project, a second training challenge emerges when considering the execution of research, particularly research in which an investigational MCM may be used. Training in good clinical practice

and good clinical laboratory practice is resource-intensive and requires practiced learning, repetitive audits, and constant communication with experienced team members. However, high-quality data—including relevant clinical observations and quality-controlled laboratory results—are essential to ensuring the validity of the collected information.

To reinforce the JMEDICC team's training in good clinical practice, good clinical laboratory practice, and related quality control tasks, the team executes an observational clinical research protocol through the Austere Environments Consortium for Enhanced Sepsis Outcomes project. Patients presenting to the emergency department who meet study eligibility criteria have the option to consent to sample collection, sample testing, and clinical data collection by a team of JMEDICC and hospital staff. The team have become well versed in screening potentially eligible patients, reviewing eligibility criteria, obtaining consent from severely ill patients or their legally authorized representatives, and collecting extensive clinical data at multiple time points using direct electronic data capture on tablets. During regulatory audits, the team is assessed at the level of an FDA-compliant clinical trial, ensuring that staff have adopted the higher regulatory requirements of a clinical trial even while conducting observational clinical research. By instilling these principles in the team and integrating their execution into the team's daily operations, these tasks will be second nature to the staff when they are operating in an outbreak, enabling them to focus their attention on their own safety, patient outcomes, and FDA-compliant clinical research.

JMEDICC staff used their training in 2018 when a suspected VHF case, who ultimately was diagnosed with Crimean-Congo hemorrhagic fever (CCHF), presented at the hub site hospital in Fort Portal. The team safely provided high-quality care in a high-containment unit, including blood transfusion and continuous vital sign monitoring; clinical laboratory support for monitoring progress; nutritional support; and ongoing psychosocial support throughout the 3-week admission. Under the care of the JMEDICC team and other hospital staff, the patient recovered and returned home. The experience enabled the team to update and improve processes and procedures based on their personal real-world experience and to have the satisfaction of applying their training to support the recovery of a sick patient in a biocontainment setting.

Several modifications to the project operations were made based on the experience with the CCHF patient, including changes to the psychosocial support structure of the team and to staffing allocations. During the patient's hospitalization, the community engagement officer was the only person with the necessary skills to address the psychosocial issues raised by both the staff and the patient. This proved to be inadequate, and JMEDICC subsequently hired a counselor to lead the psychosocial aspects of patient care and staff welfare. Her immediate task was to provide a course in mental health during humanitarian response. The counselor was available for voluntary staff outreach, which identified issues and stressors that arose over the 3-week patient hospitalization. Additionally, scenarios modeling communication between patients and staff and the use of stress management skills have been drafted for incorporation into the ongoing weekly staff training drills. This effort has been further augmented by strengthening the healthcare worker occupational health program to address fatigue and exposure anxiety. The psychosocial support lead has been valuable to the JMEDICC team but has also advocated at the national level to have psychosocial support incorporated in the national training program for healthcare workers before deployment.

A change to staffing allocations was also made based on lessons learned from treating the CCHF patient: the establishment of a nurse hygienist role. Although the CCHF patient's clinical condition improved substantially within 4 days following admission, persistent viremia posed a risk of transmission. Staff priorities shifted from routine clinical monitoring and medical care to the maintenance of environmental hygiene and communication with the patient. This led the team to advocate for a new cadre of health workers, the nurse hygienists, who would primarily support environmental hygiene tasks while providing a requisite level of nursing skills to enable clinical support in the event of additional patient admissions. The primary roles of this cadre include environmental hygiene, waste management, and mixing of disinfectants.

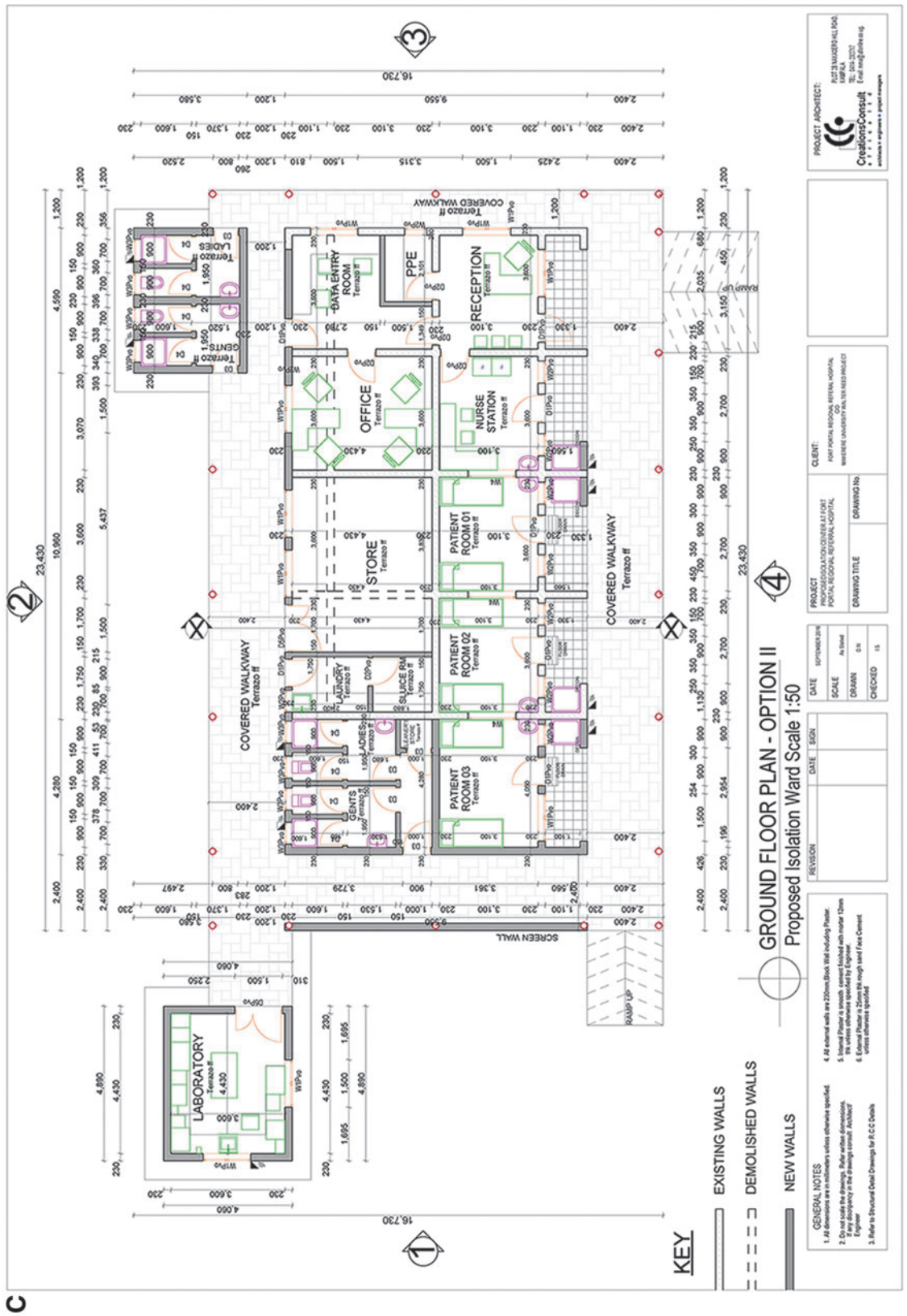
Community Outreach and Stakeholder Engagement

Filovirus outbreaks are highly politicized and publicized events that require proper messaging and communication. Uganda has established one of the most effective national response plans in Africa for suspected and confirmed VHF. The Ugandan plan depends on the centralization of official messaging and diagnostic testing, which aims to reduce erroneous reporting of false-positive results.[27] It also reduces the manipulation of samples from VHF patients at local hospitals, which may not have the biosafety capabilities to manage them safely.

JMEDICC has prioritized adherence to the Ugandan national processes and integration with the national outbreak response authorities. In Kampala, team members participate in the National Task Force meetings, which lead the national response to outbreak events. In Fort Portal, staff members also participate in the District Task Force, ensuring cooperation and coordination with local plans and procedures.

While the JMEDICC team has onsite diagnostic capabilities for some VHF pathogens, these capabilities are used only within the context of an institutional review board (IRB) and clinical protocol approved by the

Figure 1. Images from JMEDICC site at FPRRH. (A) Image of staff members doffing. (B) Image of staff member in doffing lane utilizing chlorine piping system for hand hygiene. (C) Blueprint of unit design, courtesy of Creations Consult, Kampala, Uganda.



Ugandan National Council for Science and Technology (UNCST) or at the direct request of national authorities. Paired samples of any samples tested at the JMEDICC site specifically for the presence of VHF pathogens are sent to UVRI for confirmation.

Engagement with outbreak response entities outside of the National Task Force has proven critical to JMEDICC. Organizations such as WHO, MSF, and the World Food Program have the resources and partnerships for large-scale outbreak response and Ebola treatment unit management, which JMEDICC lacks. JMEDICC does not have the capabilities or authorization to engage in contact tracing, burials, and other key aspects of VHF outbreak management. Instead, the research project aims to fill a niche in the clinical care and the research aspects of outbreak response in collaboration with teams better positioned for larger-scale activities and logistics. Constant communication about project scope and capabilities has been essential to ensuring that JMEDICC offers a useful and mutually beneficial contribution to partners in outbreak response.

Layering research on top of the complexities of the management of hemorrhagic fevers requires constant community engagement with local leaders. In Fort Portal, JMEDICC has established an inclusive community advisory board as a gateway to the community. Community advisory board members are a diverse group of volunteers that include community activists, professionals associated with health services delivery, Ebola survivors from previous outbreaks, cultural leaders, traditional healers and herbalists, and politicians.

The JMEDICC community engagement officer and a team of clinicians (nurses and doctors) make regular visits to communities where the local population are educated regarding the significance of febrile illnesses and the role of research in combating such threats. The use of information, education, and communication materials such as banners, posters, and brochures complements these efforts. Following the confirmation of Ebola Zaire cases imported from DRC to Uganda in June 2019, the JMEDICC team was invited by representatives of the community advisory board to participate in a radio talk show to sensitize community members on transmission, symptoms, signs, and steps to consider once a suspect patient is identified. The community advisory board reaches community leaders in the geographical area served by FPRRH, the Rwenzori region. The Rwenzori region consists of 8 districts: Bundibugyo, Bunyangabu, Kabarole, Kamwengye, Kyegegwa, Kyenjojo, Ntoroko, and the Kasese District, where the latest importation of Ebola from DRC was reported.

Infrastructure

At FPRRH, JMEDICC renovated a specifically designed research ward with a unilateral work-flow design and other ergonomic and architectural elements to support optimal, high-posture infection prevention and control practice. Infrastructure improvements include the installation of an onsite medical incinerator with a throughput of up to 200 kg/hour of waste and a novel chlorine solution preparation and plumbing system (Figure 1). To support data capture and communication, a secure authenticated wide area network and associated file storage, digital data capture, and communication system are in place. This enables secure communication and electronic storage of patient data, which is critical in a high-containment setting where paper documentation will not be retrievable after decontamination. The system also provides real-time access to patient records and results outside of contaminated zones.

Laboratory freezers and refrigerators, critical for sample and reagent storage, require significant electrical support. In addition, the laboratory equipment and portable glove boxes that provide safety to the team in the research ward laboratory require uninterrupted power.[28] All refrigerators and freezers are equipped with temperature monitors to ensure early detection of power failures or cold chain challenges; the monitors are continuous and send an email and text message to designated staff within minutes of detection of power interruption or unacceptable temperature fluctuations. Uninterrupted power supply devices have been installed on all pieces of equipment or instrumentation, and the project has purchased and/or provided maintenance for all hospital generators and inverters. However, electrical stability has continued to be a problem for the team. Problems with the existing electrical wiring at the site, which predated the JMEDICC project, are difficult to address retrospectively, and upgrades to the electrical grid at the hospital have been required to support the additional instrumentation put in place by JMEDICC.

Regulatory

JMEDICC is fortunate to have experienced regulatory personnel in both the United States and Uganda who facilitate conversations with regulatory authorities. On the Ugandan side, regulatory authorities include the IRB, NDA, and the UNCST; for filovirus-related protocols, socialization with the National Task Force is also advised. On the US side, multiple agencies and stakeholders participate in protocol review.

International Guidance

The development of protocols for testing INDs during filovirus outbreaks has been a source of debate dating back to at least the 2014-2016 EVD outbreak in West Africa. Consideration of ethical issues—specifically around the use of placebos—has been the most challenging point, but logistics, quality management, and pragmatism have also featured in those debates.[29] JMEDICC sought to advance a pre-positioned clinical trial protocol for a filovirus therapeutic before the start of the current DRC outbreak.

However, through that process, the team, partners, and other stakeholders faced challenges related to lines of access and authority, communication, and differences of opinion on the ethical weight of study design choices. A significant fact reinforced by this experience was the need to integrate relevant research and response organizations in order to appropriately adapt to rapidly evolving situations. Indeed, implementation of the filovirus therapeutic randomized clinical trial (RCT) PALM in the DRC was the result of extensive consultation and communication led by WHO but supported by numerous international stakeholders. Of note, the RCT design for PALM was enabled by the availability of multiple investigational therapeutic candidates with predicted efficacy against Ebola Zaire, making a comparator design feasible. The number of candidate products for other filoviruses, including Marburg viruses and Sudan virus, are more limited, however, and RCT protocols for those agents are still under discussion.[30]

The Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) clinical protocol framework was devised by WHO in consultation with clinical research experts following the West Africa EVD outbreak.[31] The MEURI framework is essentially a compassionate use protocol that includes a commitment by the executing team to collect and share data collected under the protocol. A MEURI protocol aims to make a drug available to patients and enable collection of data on product safety concurrent with development of a clinical trial approach by the international community.

Local Ethics Review and Regulatory Processes

Clinical trials and clinical research are common in Uganda, and the ethics review and NDA processes are quite clear for conventional clinical trials. However, outbreak clinical trials require accelerated review and consistent communication with multiple execution and guidance partners. There are numerous IRBs in Uganda, and a given committee may find bio-emergency research protocols challenging due to lack of guidelines, inadequate time, and external and internal pressure to approve protocols rapidly.

Uganda recognized these challenges early in late 2018 and initiated a joint review of the JMEDICC MEURI protocol, which brought together all key players in the approval process: the research team, the IRB, the NDA, the UNCST, and the community engagement team. While this joint review expedited initial review of the protocol, processes were still being developed for the follow-up procedures and timelines, and final approval ultimately depended on each institute's individual response and approval.

As a new protocol framework, MEURI posed intrinsic challenges both in Uganda and in the United States. Perceived as falling in between research and expanded access, the MEURI framework was interpreted differently by different partners, delaying approval and therefore access to the INDs for potential patients. The presence of regulatory experts familiar with Ugandan policies and procedures, and a joint history of related conversations on the work of JMEDICC, proved to be essential to navigating the regulatory process and obtaining approval of the protocol. Despite a changing landscape, the preliminary work of JMEDICC allowed all stakeholders to engage in a rigorous conversation regarding research.

Outbreak-Specific Logistical Challenges

Ethics review and scientific approvals are not the only regulatory challenges faced by researchers attempting to conduct clinical trials during outbreaks of high-consequence pathogens. Even after protocol approval, there are logistical challenges as well as communication challenges that must be handled in a pragmatic and ethical manner. In an environment where paper documents cannot be removed from the clinical or laboratory areas, electronic or proxy systems must be established to properly document informed consent. In addition, EVD patients are likely to be severely ill, confined, stigmatized, fearful, and therefore vulnerable. Researchers need to be cognizant of and responsive to patient vulnerability while at the same time adhering to the international requirements of an informed consent process. Involvement of the respective communities in developing the consenting documents, employing staff from the local communities who speak the same language as the prospective participants, shortening the informed consent form, using the legally authorized representative, and constant consultation with the IRB are some of the strategies JMEDICC has used to address these challenges.

From a communications perspective, patients' expectations need to be managed when they enroll in the clinical study, be it MEURI, traditional expanded access, or a clinical trial. In outbreaks like filovirus outbreaks, where the case fatality rate is very high, prospective participants may mistakenly believe that the research intervention is guaranteed to provide relief to the participant; contributions to generalizable knowledge where the individual may not accrue direct benefits may be difficult to communicate. To the extent possible, due diligence should be exercised to minimize the therapeutic misconception during and before the research activities.

Parallel to that challenge, researchers must be vigilant about timely but accurate sharing of research data. The statistical plans incorporated into clinical protocols are necessary to ensure that conclusions are scientific and not reflective of inadvertent biases or trends. Challenges and potential caveats of the study need to be made clear, and researchers should not be faulted for identifying them: The logistical, cold chain, personnel, and technical challenges of

outbreak research are significant. Accurately sharing any caveats that should be attached to interpretation of clinical data is an ethical imperative and should be welcomed by the scientific community as a valuable teaching tool for future preparedness and response efforts.

Conclusions

Improving our understanding of high-consequence pathogens, particularly in the context of human disease, is the best approach to controlling outbreaks and reducing the biosecurity threat posed by emerging and reemerging infectious diseases. Incorporating research into clinical care will, at a minimum, increase our understanding of disease pathogenesis and clinical presentations, enable the refinement of animal models, and help evaluate the impact of clinician-driven modifications to the standard of care. In the best-case scenario, the integration of research into outbreak response will also expedite the clinical development and regulatory approvals of MCMs, leading to general access in future outbreaks.

The complexities of executing meaningful research in austere environments, particularly in the context of high-consequence pathogens, are many. Established collaborative research and operational partnerships created during the "inter-outbreak" period can ensure that research agendas reflect national priorities, that they have community trust and buy-in, and that teams can be deployed immediately at the onset of outbreaks of any emerging or reemerging disease.[32] Moreover, research programs such as JMEDICC make tangible improvements in local infrastructure and capabilities, helping the host nation increase its capacity to respond locally and aiding their efforts to meet International Health Regulations and address gaps identified through the Joint External Evaluations. Areas of the action packages in which efforts like JMEDICC clearly contribute include Biosafety and Security, National Laboratory System, Workforce Development, and of course Medical Countermeasures and Personnel Deployment, but likely disease surveillance, reporting, and zoonotic disease may be affected as well.

JMEDICC was designed to be a broad platform for the conduct of FDA-regulated clinical trials for MCMs targeting high-consequence pathogens in outbreak settings and was specifically funded to conduct clinical trials of therapeutics in the setting of filovirus outbreaks. However, the biosafety and security, infection prevention and control, regulatory challenges, and high political visibility associated with filovirus outbreaks make that aim perhaps the most complex possible iteration of activities in which JMEDICC can participate. The project team is actively interested in building collaborations with other partners, and the technical capability of the team could quickly pivot to vaccine trials, therapeutics trials, or research on other diseases endemic to Uganda.

The JMEDICC team is additionally well poised to support train-the-trainer programs throughout East and Central Africa. By focusing on trainees already conducting clinical research, the team could adapt a "buddy system" to reinforce documentation and adherence to good clinical practice and good clinical laboratory practice while training on infection prevention and control with hands-on sessions at the hub site in Uganda. For staff inexperienced in research and infection prevention and control, the introduction of regular simulation exercises in infection prevention and control principles has the potential to save lives in an outbreak setting. Improving the baseline skills of healthcare workers to execute clinical research with high-consequence pathogens is a substantive step toward creating a path to preparation—one that might allow us to set the proverbial ship to sea in calm water and steady winds.[25]

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