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Establishment of a Research Pharmacy to Support Ebola Clinical Research in Liberia

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Abstract

Objective—This paper describes the establishment of a research pharmacy to support the PREVAIL vaccine study for Ebola Virus Disease.

Setting—This paper describes the establishment of the pharmacy element to support the overall research program during an Ebola outbreak in Monrovia, Liberia in 2014 and 2015.

Practice Innovation—The need to rapidly establish infrastructure to support the Liberian-US joint clinical research partnership in response to the emerging Ebola Virus Disease provided the opportunity for collaboration among Liberian and US pharmacists.

Evaluation and Results—Experiences of the Liberian and US pharmacists involved in the program are described.

Conclusion—The partnership was successful in the conduct of the study, but more importantly, capacity for Liberian pharmacists to support clinical research was established. Additionally, the US team learned several important lessons that will help prepare them for responding to research needs in future infectious disease outbreaks.

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The West African Ebola epidemic of 2014–2015 and the successful response are well documented.¹ Included in the overall response was a clinical research component based on a collaboration between the Liberian Ministry of Health and Social Welfare (MOH) and the US National Institute of Allergy and Infectious Diseases (NIAID).² The challenges of designing and launching the study, “Partnership for Research on Ebola Vaccines In Liberia – PREVAIL,” are also well documented.³

Objective

This paper describes the establishment of a research pharmacy to support the PREVAIL vaccine study for Ebola Virus Disease.

Setting

As noted by Kennedy et al, the Ebola outbreak in Liberia was particularly devastating due to the poor health-care infrastructure, limited expertise in disease surveillance, limited capabilities for rapid response to emerging and re-emerging infectious disease, limited training of health-care workers and emergency personnel in dealing with a highly infectious and deadly disease, and lack of proven vaccine, therapeutics, or preventative measures.³ In November 2014, the Governments of Liberia and the United States established an agreement to form a partnership to conduct clinical research on interventions to prevent, control, and treat Ebola. The first research protocol to emerge from this partnership was PREVAIL.

PREVAIL was designed as a randomized, double-blind, placebo-controlled Phase 2/3 clinical trial to evaluate the safety and efficacy of two Ebola vaccines among healthy volunteers in the midst of the Ebola virus outbreak in Liberia.³ The ChAd3-EBO Z vaccine (Glaxo) consisted of a ChAd3 vector with a DNA fragment insert that encodes the Ebola virus glycoprotein. The VSV G-ZEBOV vaccine (NewLink/Merck) was comprised of a single recombinant (vesicular stomatitis virus) VSV isolate (11481 nt) modified to replace the gene encoding the G envelope glycoprotein with the gene encoding the envelope glycoprotein from the Ebola virus Zaire strain (ZEBOV).

The logistics associated with planning the study presented substantial challenges. Liberia was in the process of recovering from a devastating series of civil wars that ravaged the country intermittently between 1989 and 2003. Basic infrastructure functions such as reliable electricity, clean water, and paved highways were under development at the onset of the Ebola epidemic. Education systems, certain government functions, and the local economy were also disrupted during the outbreak. Both vaccines required storage at or below -60°C . Storage of the vaccines at a location with a reliable power source provided the primary impetus in choosing a location for the pharmacy operation. Additionally, the replicating nature of the VSV G-ZEBOV vaccine requiring serial dilution without a long safety history prompted consideration of preparation in a level II biosafety containment

hood. Given the limited time available to build capacity and the need for reliable electrical power, the study team narrowed down the search to utilization of former office space on the old US Embassy compound in Monrovia.⁴ The team immediately went about ordering various supplies and laboratory equipment as well as transforming a segregated room into a utilitarian clean area for vaccine storage and preparation. Unfortunately, given travel restrictions associated with the epidemic, it was not possible to bring in contractors to certify the Class II, Type A2 biosafety cabinets in the pharmacy and laboratory. However, the US Public Health Service had deployed biomedical engineers that qualified the temperature-control capacity of the freezers against requirements. Additionally, qualification of the cold-chain shipping process from the US and Europe with the respective vaccine manufacturers was completed. While achieving USP 797 standards was outside the realm of possibilities in this situation, the pharmacy team took considerable measures to compound syringes in as clean of an environment as was reasonably possible. Some of these measures included a demarcated, dedicated clean area requiring proper gowning, the use of a horizontal flow hood to prepare placebo syringes and Class II, Type A2 biosafety cabinets to prepare vaccines syringes, daily cleaning, and regular review of aseptic technique. Table 1 describes activities undertaken to prepare the research pharmacy.

Practice innovation

Identification of the pharmacy team to support the study presented an opportunity to further the goals of the research collaboration.² The trial steering committee included the chief pharmacist from the Liberian Ministry of Health and Social Welfare as well as the regulatory director from the NIAID team who was also a pharmacist. These two determined that at the outset of the study, the utilization of two Liberian pharmacists and two senior pharmacy students from the University of Liberia with mentorship from one US pharmacist would provide the necessary staff for the requisite early morning vaccine preparation each working day. The Liberian team member worked within the overall contract process established by the study team to identify several Liberian pharmacists and pharmacy students with the potential to serve on the team. Working with the contractor, the candidates were interviewed, and two pharmacists and two senior pharmacy students were hired. The University of Liberia, like every other educational organization in the country, was closed during the epidemic as a means of reducing the potential for transmission of the virus.

On the US side, the NIAID Director of the Division of Clinical Research engaged the National Institutes of Health (NIH) community and the US Public Health Service (USPHS) by providing information about the joint effort and encouraging staff to volunteer to go to Liberia on three-week or longer rotations to mentor the Liberian research team. The first pharmacist volunteer, a program officer with the National Cancer Institute (NCI) who was also a retired USPHS Commissioned Corps Officer had prior experience in disaster response and training. The US team established a training program to augment in-country pharmacy training focused on the principles of sterile products preparation and an introduction to the principles of clinical research practice, topics which were not previously taught by the local College of Pharmacy.^{5,6} Training included the preparation of the sterile preparation/hood area, using positive pressure, label bar-code scanners and quality control. Upon completion of training, the team worked through draft standard operating procedures (SOPs) to identify

areas requiring further explanation and revision. A dry run of all study procedures was undertaken prior to the study start to ensure the adequacy of the SOPs. Table 2 describes pharmacy duties during the study.

A challenge faced by the pharmacy team impacting the successful implementation of the study was the process for blinding the vaccines in the pharmacy center at the time of labeling with the unique vaccine identifier and achieving the correct randomization mix. The team established separate production lines for each of the vaccines and a third line for the placebo vaccines. The team alternated roles in vaccine syringe production and quality assurance to ensure that each member had an appreciation of all aspects of the production process. Randomization was achieved through a batch production method that produced twelve syringes, four from each arm, labeled with a unique identification code. The syringes were packaged in a large, clear plastic bag and transported to the study site in a temperature-monitored refrigerated container. At the site, the vaccinator randomly pulled syringes from the plastic bag and tore-off a portion of the three-part label and attached it to the participant's case report form to link the vaccine identification to the study participant. At the end of the day, the case report forms were transmitted to the data management center completing the link in the database. 1,500 participants were successfully enrolled in PREVAIL I and received an injection.

Given that a relatively low production rate was planned at the start, the team also helped out at the vaccination center with a variety of tasks from supporting the clinical laboratory to quality assurance support of data collection. An effort was made to provide educational opportunities to the Liberia pharmacy staff through on-line resources on relevant topics such as infectious diseases (e.g., malaria), industrial pharmacy methods and cold-chain management. US pharmacists also provided in-service training opportunities from their respective areas of expertise.

Evaluation and Results

The study, as initially planned, was to be a Phase 2 expanded safety study of 1,500 participants expanding to a Phase 3 study of 27,000. By the time the Phase 2 portion of the study was complete, 1500 participants were vaccinated and the epidemic had waned to the point that the Data Safety Monitoring Board advised against proceeding to the Phase 3 portion. When the vaccination phase was fully enrolled in late April, the Liberian members of the team continued to support the many follow-up visits at the vaccination center. One of the Liberian team members was motivated through her PREVAIL experience to depart to pursue a master's degree in medicinal chemistry. Another team member was instrumental in supporting the implementation of a pharmacy to support research of the ophthalmologic and neurologic symptoms experienced by Ebola survivors. That team member was also instrumental in establishing a field-preparation process when the PREVAIL study was amended to allow for open-label ring vaccination of a small cluster in an area outside Monrovia following an isolated case of Ebola in November 2015.

During the course of the Phase 2 portion of PREVAIL, six US pharmacists were able to gain experience with this study. Universally, each reported they gained more from working with

the Liberian team than they were able to contribute. Each of the US pharmacists incrementally improved upon the processes established by their predecessor. From the Liberian side, the pharmacy team quickly acclimatized themselves to the fundamentals of good clinical practice, became competent in the practical and regulatory standards involved in the preparation of sterile products, and learned the process for ethical reviews in research. Moreover, the research partnership opened a window of opportunity to have trained four top-notch pharmacy professionals who are now assets to the Liberian people.

The Liberian-US clinical research partnership resulted in follow-on studies and is helping to identify opportunities for a sustainable clinical research program in Liberia.² As discussions of a study with Ebola survivors and the medication needs associated with that patient population, the Liberian team members noted the limited availability of home storage of refrigerated products resulting in an opportunity for additional consultations with the US pharmacists, especially as it related to ophthalmologic drops stable at Liberian room temperature. Furthermore, the Liberian and US pharmacists have given several lectures at the University of Liberia College of Pharmacy, including a workshop on aseptic technique. Opportunities for a sustained involvement in pharmacy education are being pursued with the University of Liberia.

The Liberian-US stakeholders have agreed to consider moving the PREVAIL pharmacy research center off of the embassy grounds to a more centralized location which will facilitate easier access by Liberian pharmacists, enabling greater control over day-to-day operations by the host country. To accomplish this, many challenges must be overcome, including identifying a suitable location, receiving authorization to relocate to the selected location, ensuring uninterrupted or minimally interrupted power supply, movement of existing equipment and supplies, and training of personnel to manage a larger pharmacy with advanced equipment.

In addition to the establishment of a more accessible pharmacy research center to further develop Liberian pharmacy infrastructure, the University of Liberia and NIAID staff are considering the dual use of the research pharmacy for clinical research and educational opportunities to continue the capacity development of pharmacists with clinical research experience. Pharmacy students at the University of Liberia have limited access to pharmacy equipment, and the Liberian research agenda involving pharmacy is sporadic, leaving opportunity to utilize the space for educational purposes between studies.

Since the conclusion of PREVAIL enrollment, four additional clinical research studies have been launched, three of which involve investigational drugs or vaccines. NIH has committed to assisting with further development of the PREVAIL program in Liberia for the next several years, with the goal of creating a sustainable program through research partnerships and grants. The PREVAIL pharmacists should have an active role in future research as the program has added multiple research sites around Liberia.

Conclusion

The overall pharmacy partnership was successful in its mission to rapidly supply, mobilize, train, and staff the pharmacy for the needs of the PREVAIL vaccine trial. The PREVAIL study was the only randomized, double-blind placebo-controlled trial conducted during the outbreak. The partnership in Liberia extended to research with Ebola survivors leading to the development of sustainable research capacity in Liberia.

There were important lessons learned through the process which similar efforts in the future should take into consideration.

- Disasters such as disease epidemics and pandemics are unpredictable in timing, location, and scale, but are predictable in that they will occur. NIAID plans to establish an emergency research response team in order to capitalize on the lessons learned from the Ebola outbreak, and develop well-defined business processes, personnel, and documents which may aid in rapid study startup for future outbreaks.
- Infectious disease outbreaks of epidemic and pandemic proportions are likely to occur in developing areas of the world, often in hot and humid climates where little reliable infrastructure exists. Trials which involve time and temperature sensitive products such as vaccines and monoclonal antibodies require sponsors to pay close attention to climate control issues, including the availability of backup refrigerators and freezers, and should consider an emergency plan such as the use of transport containers for temporary product storage during a complete and prolonged power failure.
- Local partners may need training to become familiar with certain advanced pharmacy practices such as aseptic technique, working in biosafety containment hoods, and record keeping requirements for clinical trials. Plan to have experienced staff available and allocate time for any needed training.
- Rapid mobilization will likely require an “all hands on deck” mentality where job descriptions become unusually fluid. Pharmacists may need to become competent in a variety of fields such as principles of cold-chain, laboratory procedures, and basic electrical principles, as well as be willing to learn how to install and qualify equipment for use in a regulated trial. While a clear command structure should be maintained, even the senior personnel on the team may need to assist with laborious tasks such as moving supplies around a warehouse, or re-familiarize themselves with how to operate a mop and broom.
- Experienced staff may be temporarily mobilized to support operations where needed, but well-trained, less experienced local staff who will be available for the duration of the trial may be preferable to frequently rotating experts. More experienced staff should focus on building in-country capacity by training local staff, so that operations may continue smoothly after they depart. This also contributes to future capacity building within the country and sustainable operations.

- Research responders should be prepared to work within the context and pace of the local environment, as clinical research is a relatively long-term effort, and short-term successes may translate into long-term struggles if relations are soured in the process.
- While autonomy is a core ethical principle of research in individuals, it is also a core principle when conducting research in foreign countries. Sovereign nations have the right and ability to support or prohibit any research within their borders, for any reason. Foreign researchers should abide by all host country laws, regulations, and bureaucratic processes.

While casual observers may conclude the threat of Ebola is gone as it has not occupied headlines in the past year, health professionals in West Africa are cautiously optimistic that the lessons learned regarding the importance of responding quickly will not be forgotten. Evidence from sporadic cases transmitted by survivors indicates that in Liberia, readiness to respond with public health measures, including a ring-vaccination strategy with oversight from the World Health Organization, has proven effective. A cadre of well-trained Liberian pharmacists from PREVAIL will help ensure this capacity exists for the foreseeable future.

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Importance of this paper to the pharmacy literature

A literature search revealed a dearth of information on the challenges of establishing a research pharmacy operation in (1) an outbreak of a deadly disease; (2) conducting any sort of pharmacy operation in a country with economic and infrastructure challenges; and (3) the development of capacity in West African pharmacists in the areas of sterile products preparation and the principles of Good Clinical Practices. This paper represents an initial description of the experiences in all three areas. We also describe several considerations for pharmacists who have the opportunity to respond to future outbreaks in resource deprived settings.

Key Points

Background

- A US-Liberia research collaboration and infrastructure needed to be rapidly established in Liberia to support research on Ebola vaccines and treatments during the recent Ebola outbreak.
- No known clinical research capacity in Liberia existed prior to establishment of the research collaboration.

Findings

- Deploying experts for relatively short durations proved an effective method to rapidly establish research infrastructure and personnel in the middle of an outbreak.
- Local partners may need training to become familiar with certain advanced pharmacy practices such as aseptic technique, working in biosafety containment hoods, and record keeping requirements for clinical trials.

Table 1**Pharmacy Team Duties During PREVAIL**

Establish standard operating procedures
Preparation of investigational products
Preparation of randomization bags / QC check labels against randomization schedule
Accountability / temperature monitoring of investigational agents
Accountability of anaphylaxis / needle-stick kits
Delivery of investigational products to site under cold-chain
Site Assistance: quality assurance activities / record keeping / laboratory procedures

Table 2

Activities Per Phase of Trial

Early Pre-Study Activities	Late Pre-Study Activities	Post-Study Activities
Investigational product literature search, input into protocol	Preparation of site Receipt of equipment Receipt of back-up generator Qualify freezer	Transition Liberian pharmacy team to assist in follow-up activities
Assist in selection of facility for storage/prep	Training pharmacy staff on investigational product characteristics, sterile products, good clinical practice, procedures	Establish plans for research pharmacy of Ebola survivors at different site
Order equipment (freezers/hoods)	Receipt of investigational products	Establish plans for outreach to University of Liberia College of Pharmacy
Liaison with pharmaceutical companies on shipping / import permits	Mock-study procedures and after-action review	Continue accountability and temperature monitoring of remaining investigational agents
Liaison with contract employer on selection of pharmacists	Kick-off study and after-action review	
Standard operating procedures development	Continuous assessment and training on other pharmacy topics	