


COMMENTARY



Challenges and perspectives on the use of mobile laboratories during outbreaks and their use for vaccine evaluation

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ABSTRACT

Mobile laboratories provide diagnostic capabilities for routine surveillance and patient identification during an outbreak. In either situation, they face many challenges including identification of the appropriate assay(s) to employ, logistical arrangements, and providing for the health and safety of the laboratory staff. Great strides have been made over the last decade in the development of mobile laboratories with assays that require minimal infrastructure and technical experience. This knowledge and expertise have been developed in partnership with many researchers and public health officials who live in regions prone to infectious disease outbreaks. Mobile laboratories should now also be used in the evaluation of novel vaccines and therapeutics in remote locations. Clinical mobile laboratories will include similar diagnostic capabilities as outbreak response mobile labs, but will also include additional point-of-care instruments operated under Good Clinical Practice guidelines. They will also operate rigorous data management plans so that the data collected will satisfy regulatory agencies during the licensure process. Failure to deploy an adequate clinical mobile laboratory when administering a novel biological product in a remote location is a significant limitation to any collected scientific data that could ultimately undermine clinical development and availability of life-saving interventions.

KEYWORDS

Mobile laboratory; outbreak response; diagnostics; vaccine and therapeutic evaluation

Mobile laboratories have been in use for decades for the surveillance and detection of infectious diseases as part of regular research activities and for outbreak response. The contents of a mobile lab have evolved with time, for example from a simple sample collection kit and light microscope used during a melioidosis outbreak in northern Australia in 1997¹ to fully self-reliant and equipped vehicles containing the latest in molecular diagnostic and biocontainment equipment used during the West Africa Ebola virus outbreak in 2014–2016.^{2–4}

The contents of a mobile laboratory will be dependent on the type of work to be conducted and the environment in which it will be conducted. In “peace time”, those periods in-between outbreaks when the goal is to perform routine surveillance of pathogens circulating in the environment and/or the local animal populations, researchers have time to establish study sites from the fixed National laboratory, and to obtain all the necessary approvals for sample collection and transportation. Researchers also have the time and the capacity to bring in replacement equipment if, or more likely when, a piece of equipment invariably breaks down. A researcher’s ability to transport samples to a fully equipped lab for additional testing may be diminished during an outbreak however. There are several reference laboratories available in Africa capable of testing for filoviruses, for example, the National Institute for Communicable Diseases (NICD) in Johannesburg, South Africa, the International Center for Medical Research in Franceville (CIRMF) in Gabon, and the

World Health Organization (WHO) Reference Center for Yellow Fever at the Institut Pasteur de Dakar (IPD) in Senegal. However, these laboratories are typically removed from filoviral outbreak sites and while they are adequate for confirming the emergence of a filovirus and thus a new outbreak, they are inadequate for onsite outbreak control efforts.

The solution to the lag time for testing potentially highly contagious infectious pathogens is to have the capacity for this testing at the site of the outbreak. While having a fully equipped biosafety level 3 or 4 (BSL-3 or 4) laboratory in all of these locations is unrealistic, bringing the lab to the outbreak or “hot zone” to provide early detection capabilities is not. In order for this to happen, there are many decisions that must be made and challenges that need to be overcome in order to provide adequate and most importantly, rapid, diagnostic laboratory support in an outbreak. Indeed, onsite laboratories must be able to turn around test results within 3 hours or less of receiving samples to efficiently inform clinical management teams, epidemiologists carrying out contact tracing, community communication, outreach, and engagement, just to name a few activities that are essential to breaking chains of transmission. Ideally, mobile laboratories would be equipped with several specific tests and be able to offer differential diagnostic support, all while safely following strict biosafety guidelines. Detection of Ebola virus infection, for example, can be accomplished through viral isolation, serology and molecular techniques such as real-

time reverse transcription polymerase chain reaction (RT-PCR). Live virus isolation from patient samples requires up to two weeks and a BSL-4 facility containing large pieces of equipment such as an incubator. Live virus isolation is therefore not practical for a mobile laboratory and rapid diagnosis. Serological testing, on the other hand, is relatively easy to do and all the necessary reagents and equipment can be transported into the field. Serological assays such as enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assays are advantageous for the testing of disease states that have progressed beyond those capable of detection via molecular methods (convalescence).⁵ While some believe that serological testing is unlikely to occur as part of routine outbreak response,³ cases were identified in real-time at the site of the outbreak using serological testing in conjunction with epidemiological data during the 2017 Ebola outbreak in Democratic Republic of Congo (DRC).⁶ Serological testing can also be used to identify the source of an outbreak through the testing of animal carcasses or to identify the index case through back tracing of suspected cases who have recovered. One caveat to this is that many patients who succumb to Ebola virus infection do so without producing a detectable humoral response and as such, would produce false-negative ELISA tests.⁷ For this reason, molecular testing capable of detecting virus within blood, urine, from a swab and other bodily fluids in acute patient samples is therefore the first line within the diagnostic algorithm during an outbreak.

Real-time RT-PCR can also be used to test environmental samples, for example, inanimate objects in the house of a suspected patient to help confirm suspected chains of transmission from epidemiology data when patient biological samples are no longer available, or to confirm that disinfection of an area is complete (or not).⁸ Furthermore, real-time RT-PCR can be used to offer differential testing (malaria, Q fever, typhoid fever, etc) of patient samples in a bid to help identify the causative agent of disease within an inclusive platform. Various groups have noted the value of differential testing but warn that in large outbreaks it can be extremely difficult if not impossible due to a lack of time and resources.^{3,9}

While real-time RT-PCR has become the gold standard in molecular testing for mobile laboratories, this technique still has a number of drawbacks. For example, moderately large and sophisticated pieces of equipment are required for running and analyzing samples. These pieces of equipment need a consistent source of power protected from unexpected surges. The equipment must also be protected from the elements, i.e. rain and extreme heat and humidity, to ensure their proper functioning and to prevent breakdowns.³ Real-time RT-PCR also requires specific primers/probes in order to accurately identify the pathogen. Should the outbreak pathogen significantly mutate over the course of time or another pathogen emerge in the meantime, the protocols established for a specific pathogen may no longer be adequate.

It is for this reason that in large, spatially dispersed, prolonged epidemics, mobile laboratories should, either individually or more likely in concert with a network of mobile labs, provide samples for genome sequencing. Quick et al.¹⁰ demonstrated during the West Africa Ebola outbreak that

genome sequencing can be portable and performed in real-time for Ebola surveillance. Genome sequencing provides the health-care community with the ability to not only characterize the pathogen and its evolutionary rate, but also helps shed some light on the potential need for a change in diagnostic targets and on the effect, if any, of vaccines and therapeutics. Furthermore, genomic surveillance allows for the matching of cases with transmission chains and can reveal the introduction of a new virus into the outbreak.¹¹ While conducting specialized analyses such as genome sequencing can be very helpful in providing additional data to help manage an outbreak, efforts to this end should be conducted with particular attention to not disrupt the normal functioning of the mobile diagnostic lab and its ability to provide quick turnaround times on patient samples.

The challenges associated with the use of molecular diagnostic techniques in remote locations that lack significant infrastructure has led some researchers to develop alternative tests that do not require sophisticated operational and analysis equipment, nor access to refrigeration equipment to keep reagents cold. Commercialized kits or in-house developed assays with lyophilized reagents eliminate the need for reagent freezing, while the development of rapid lateral flow assays that can be performed directly at the bedside eliminates the need for specialized equipment, highly trained technical staff and reduces the turnaround time for results from hours (approximately three hours with real-time RT-PCR)^{9,12} to minutes (approximately 30 minutes).^{13,14} The ability to obtain a reliable result directly at the patient's bedside also removes the need for the diagnostic laboratory to communicate test results with the doctors and support staff actually caring for the patients.

Our ability as researchers and outbreak responders to improve the molecular assays available for use during an outbreak is exemplified by a field team from IPD in Senegal and their collaborators.¹² Over the course of as little as five years, they went from using the standard infrastructure reliant real-time RT-PCR assay to a real-time recombinase polymerase amplification (RT-RPA) assay that has many of the same benefits as the lateral flow assays mentioned above. This team was able to respond to outbreaks of Dengue virus in Cape Verde Islands, Rift Valley Fever virus in Mauritania, Yellow Fever virus in Uganda and Ebola virus in Guinea using a similar mobile laboratory setup and evolving diagnostic assay platform.

The handling of logistical requirements is another challenge of any mobile laboratory. For routine field surveillance, mobile laboratories have the luxury of time to ensure a smooth deployment and operation. During an outbreak, time is of the essence to control and stop the spread of a dangerous transmissible pathogen. Partnership between international organizations such as the WHO, the United Nation (UN), Médecins Sans Frontières (MSF), The Red Cross, UNICEF and different public health and research laboratories in North America, Europe and Asia (e.g. US-CDC, Public Health England, etc) who are capable of contributing important logistics, expertise and support on all aspects is critical. Logistical considerations include medical facilities, medication, accommodations, transportation into and around the outbreak area, access to electricity, food and

clean water, and in some unfortunate situations, access to security personnel.¹⁵ An additional logistical requirement that needs to be taken into consideration before deployment is the infrastructure status of the region. Since most mobile laboratories are still operating real-time RT-PCR assays, they require some form of standing structure and access to a reliable power supply. Ideally the mobile laboratory will be able to set up in a pre-existing structure that has all the necessary amenities; however, it is not uncommon for the necessary infrastructure to be commissioned upon arrival.¹⁵

When a pre-existing structure is available for laboratory setup, additional bio-safety/bio-containment equipment can be employed. For example, the NICD in South Africa established a modular high-biosafety field Ebola diagnostic laboratory (SA FEDL) near Freetown, Sierra Leone during the West Africa outbreak that included a negative pressure biological containment system for sample processing.³ On the other hand, when a tent structure is commissioned on site, the “clean” and “dirty” laboratory areas necessary for molecular diagnostics may be separated only by tarps.¹⁵

Access to the affected region is another potential obstacle that must be met. First, transport of equipment and reagents into the affected area, or as close as possible, may need to occur by air with helicopters when no roads or even trails can support movement of off-road vehicles. Humanitarian organizations like the UN World Food Programme have been able to help with moving equipment and personnel.³ While many groups have designed their mobile laboratories to fit into a varying number of durable crates,¹⁶ others utilize multiple large vehicle containers (i.e. semi-trucks)⁴ to provide the necessary infrastructure and equipment, when there are roads that can accommodate them. The downside to self-contained motorized laboratories such as these is that outbreaks can and have occurred in such remote locations that road access leading to the affected area is negligible and at best, a motor bike can be used to transport the diagnostic technician carrying a back pack. This reinforces the need to develop assays that are independent of the trappings of traditional laboratory assays and that can be carried by an individual into an infected area.

Once established, mobile laboratories may also face challenges associated with sample collection and maintaining the safety and security of its personnel. Local populations affected by an outbreak may be hesitant or even fearful of providing a sample for diagnostics.⁹ They may be averse to providing a blood sample, in which case swabs can be taken, or they may be resistant to the idea of entering a hospital/isolation unit where they would normally provide a sample for diagnostics for fear of never leaving the area alive.¹⁷ Also, the ongoing Ebola virus outbreak in DRC, now the second worst in the history of filovirus outbreaks, only after the devastating outbreak in West Africa that lasted for over 2 years, has seen a number of security incidences where response teams have been physically attacked, have had their equipment destroyed and have been kidnapped.¹⁸ This heightened risk for violence adds another layer of complexity to the running of a mobile lab during an outbreak and as such, the personnel being deployed must be physically and mentally fit for the job.

When identifying personnel for deployment to an outbreak one must not only consider the training and expertise of an individual, but they must also consider a person's attitude and ability to adapt to the type of situations and circumstances one will find in the field. The individuals that make up a field team will hopefully consist of people able to not only work, but live, together for extended periods of time under conditions that can be both emotionally and physically draining. During an outbreak, first responders often work very long hours every day of their deployment, which tend to be weeks, if not months, at a time.

One way of potentially minimizing the fear or resistance among the infected population is through the engagement of local personnel. Despite the progress in local capacity building however, outbreaks are sporadic in nature and occur all over the globe. As such, the training a local team may receive during an outbreak needs to be maintained if their skills are to be used in future response efforts. It is therefore better when research groups with mobile laboratory capabilities establish “peace time” research projects with local researchers to help them maintain and expand their skill sets. Many of the same techniques used to diagnose a patient can be applied to environmental and/or animal sampling. This form of active surveillance not only provides continual training and improves local capacity, but may also prevent a possible outbreak. For example, identification in the rise of a particular pathogen in the animal population (or environment), which could lead to a spillover event, would be possible and as such, decisions on how best to handle the situation (i.e. increased vaccinations, culling of animal populations) can be made. The small investment cost to education and training of local residents would be well offset by preventing an outbreak.¹⁹

Now that mobile lab use has become “routine”, their capacity must be expanded beyond diagnostics and now needs to include the testing of samples arising from the administration of vaccines or therapeutics either as part of official clinical trials or when administered under compassionate grounds. While some progress was made to this end during the West Africa Ebola outbreak,²⁰ we are currently missing an important data collection opportunity as the 10,000's of individuals who have been vaccinated with the rVSV-ZEBOV vaccine in West Africa, and recently in DRC under compassionate grounds, are not being followed extensively with analyses of T and B-cell immune responses that could help better identify and understand mechanisms of protection. This also means that we will not be able to determine the long-term efficacy of the vaccine anytime soon and will have to continue to use the animal models of human disease with the caveats that this entails.

While the knowledge and expertise that accompanies a mobile laboratory could and should be put to use in the evaluation of experimental vaccines and therapeutics, one must ensure that the specific assays used are either comparable or identical between sites as it has been demonstrated that variability exists between assays.²¹ This is particularly important when one wants to compare the effectiveness of different products. De la Vega et al.²² is one of several groups that have demonstrated that Ebola viral load upon admittance to a treatment center is predictive of outcome (survival). In

order for treatments to be accurately compared for efficacy, the average viral load among patients between the treatment groups must be comparable. The test(s) used to determine these viral loads must therefore be equivalent so as to ensure that the products being tested can be compared with reasonable precision.

If, and more likely when, novel vaccines and therapeutics are tested during an outbreak, a second mobile laboratory must be deployed specifically for clinical evaluations. The analyses and documentation of samples during a clinical trial should be carried out independently of rapid diagnostic for clinical management so as to not interfere with diagnostic timelines. This then requires additional coordination between two labs where the diagnostic lab receives the samples first to run simple but rapid diagnostic assays followed by the clinical lab running additional point-of-care tests that utilize qualified procedures and a robust data management system. Point-of-care instruments are capable of analyzing a variety of hematology and chemistry parameters (ex: iSTAT and Piccolo Express) and being light and rugged they are compatible with mobile laboratories. The additional data generated from such devices could prove invaluable when evaluating novel biological products. In addition, all tests conducted in this second mobile laboratory must be conducted under Good Clinical Practice (GCP) guidelines and managed using data management protocols specific for clinical trials. This would ensure that the data generated are robust and reliable and would be accepted by regulatory agencies in a licensure application. A failure to follow GCP guidelines would likely result in a significant lost opportunity to advance promising product(s) toward licensure.

There are many challenges associated with the setup and operation of a mobile laboratory in an outbreak, including identification of the appropriate assay and required equipment needed for a particular situation, the required infrastructure needed to operate, as well as the many logistical issues that must be dealt with in order to simply arrive at your destination and to maintain operations over time. Additional challenges include high sample volume (e.g. >200 samples per day requiring differential diagnostic), the possibility of resistance in the local population and security risks. Despite these many challenges, numerous groups have successfully established mobile laboratories across the globe and continue to improve their functioning with every deployment. These groups now need to increase their involvement with local capacity building so that in future outbreaks local communities can intervene from day one. In addition, mobile laboratories now need to move beyond simply providing diagnostic capabilities for patient identification to participating in the evaluation of novel vaccines and therapeutics. Tremendous progress was achieved at a fast pace during the Ebola outbreak of 2014–16 in West Africa, including on-site real-time sequencing, real-time serology, ecological sampling, and testing of clinical parameters (blood chemistry, cell counts), just to name a few. Setting up a mobile lab during an outbreak without this full complement of assays and capabilities would be similar to treating an Ebola patient with only oral hydration when we now have additional treatment tools at our disposal. The continuous development of mobile laboratories for public health as well as basic, applied and clinical research during

outbreaks is inevitable and will certainly prove to be invaluable going forward.

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No potential conflict of interest was disclosed.

Publication Statement

This material is original, has not already been published, and has not and will not be submitted for publication elsewhere as long as it is under consideration by HV&I.

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