Conducting clinical trials during epidemics

Following issues during the Ebola outbreak, an Expert Committee was convened to deliberate on how science can learn, while not interfering with care and treatment

The conduct of clinical trials of experimental therapeutics and vaccines during an epidemic, is the subject of a recently released report, 'Integrating Clinical Research into Epidemic Response: The Ebola Experience', from the US National Academies of Sciences, Engineering, and Medicine.[1] The report, presented at the Fifth African Health Workforce Forum in Uganda on 20th April 2017, was authored by a committee of sixteen international experts[1] from the US, Europe and Africa, with backgrounds in epidemiology, biostatistics, clinical trials, infectious diseases, tropical medicine, ethics, law, public health, nursing, and public administration. It presents seven recommendations (Box 1) that together, if implemented, can facilitate trials to generate actionable safety and efficacy data on experimental therapies or vaccines when the next epidemic strikes.

Box 1. Report recommendations

1. Support the development of sustainable health systems and research capacities in low-income countries.
2. a. Develop memoranda of understanding to facilitate data collection and sharing.
   b. Provide resources to enable data collection and sharing at the start of an epidemic.
3. Facilitate capacity for rapid ethics reviews and legal agreements.
4. Ensure that capacity-strengthening efforts benefit the local population during an epidemic.
5. Enable the incorporation of research into national health systems.
6. a. Prioritise community engagement in research and response during an epidemic.
   b. Fund training and research into community engagement and communication for research and response.
7. a. Coordinate international efforts in research and development for infectious disease pathogens.
   b. Establish and implement a cooperative international clinical research agenda at the outset of an epidemic.

When the West Africa Ebola epidemic began in 2014 there were a few therapeutics and vaccine candidates in early development, plus a few approved antivirals for other indications that might be repurposed for Ebola. However, there was no human safety or efficacy data in Ebola-infected individuals. The severity, rapid progression of the outbreak, and large number of people with Ebola virus disease (EVD), presented the opportunity to evaluate these candidates in naturally infected and at risk humans who might benefit from effective therapeutics and vaccines.

However, there were major obstacles to rapid mobilisation of personnel and infrastructure for a robust clinical research programme, including the challenge of doing clinical research while working in personal protective equipment without interfering with clinical care of critically ill patients, prioritising what to study, preparing protocols, obtaining scientific and ethical approval in the affected countries, completing legal clinical trial agreements with national authorities, developing the finances and infrastructure to conduct the trials, recruit participants, and collecting and analysing the data. The report emphasises the need to strengthen capacity in low-income countries for response, research and engaging people living in affected communities, and local community leaders to create a partnership with healthcare providers and researchers, local government, Ministry of Health staff, and international experts. It identifies steps needed to improve the speed and effectiveness of planning and implementing clinical trials during an epidemic before the next one occurs, especially where pre-existing healthcare and research infrastructure are limited.

Research and development (R&D) of therapeutics and vaccines is a long and expensive process, currently estimated to take at least 10 years and cost US$2.6 billion, and, on average, just one in 10 candidates will be successfully licensed. Necessary R&D cannot be easily compressed into the course of a rapidly progressing outbreak, so it is essential to set priorities among potential outbreak pathogens and generate substantial public financing for early research before an epidemic breaks. Financial incentives need to exist for the private sector to advance successful products through licensure into manufacture.

The 2014–2015 Ebola epidemic was the longest ever recorded since EVD was identified in 1976, with more individuals involved, and resulted in more deaths than all previous outbreaks combined. By the end, there were 28 616 known cases and 11 310 deaths (case fatality rate 39.5%) in Guinea, Liberia, and Sierra Leone. In contrast, among 27 patients, including 20 international healthcare workers were infected in West Africa but treated in the US or Europe with optimal clinical support and compassionate use of investigational therapeutics. Only 18.5% died. This discrepancy led to rumours of a 'magic serum' being used for expatriates, but not for Africans. Conspiracy theories about the origin of the outbreak followed, complicating the task of gaining trust, explaining uncertainties of benefit vs. risk, and enrolling patients in trials. Discussions within the research and response community were also complex, often contentious, and driven by assumptions rather than actual knowledge of

Keith P.W. J. McAdam and Gerald T. Keusch were co-chairs, and Fred Wabwire-Mangen and Olayemi Omatade were members of the former National Academies of Sciences, Engineering and Medicine's Committee on Clinical Trials During the 2014–2015 Ebola Outbreak.

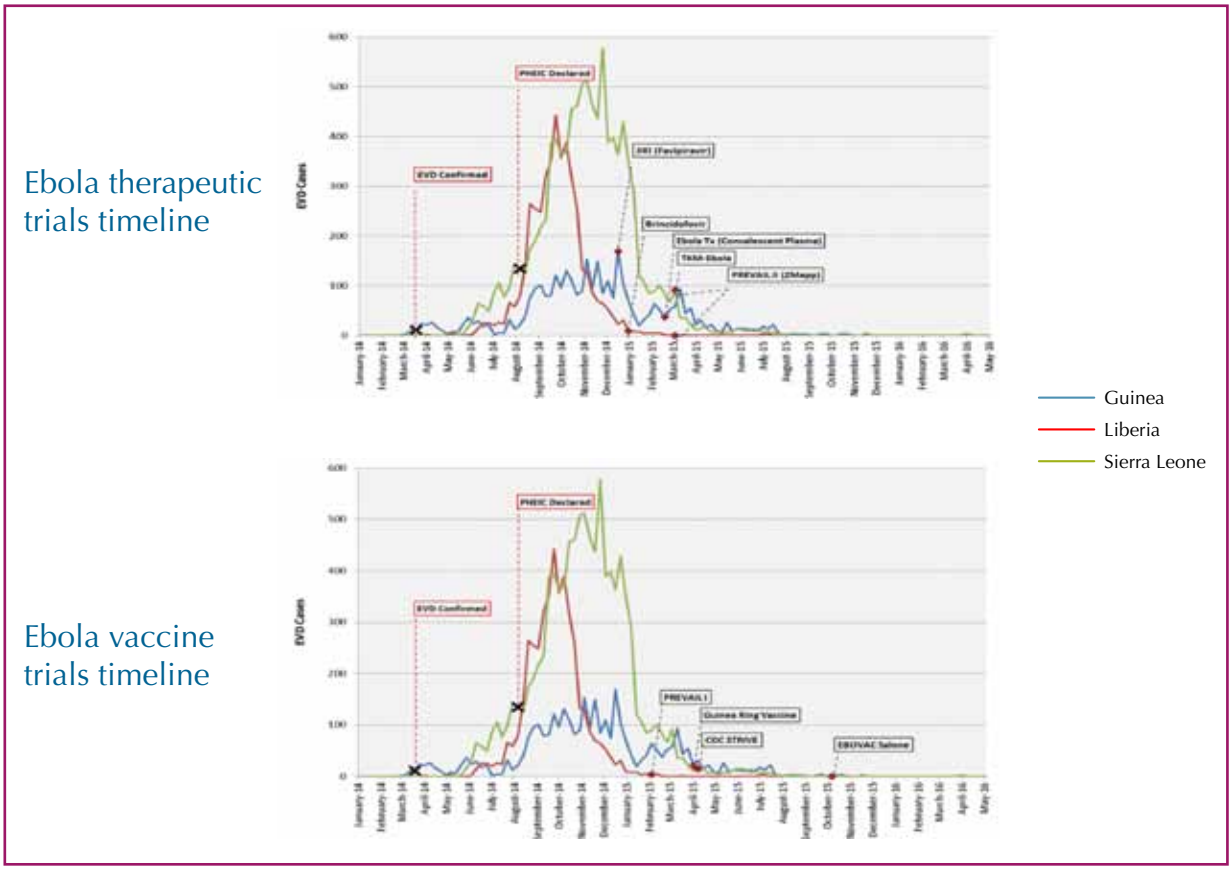
community understanding.

Remarkably, and in record speed from the time trials were first considered, several teams were able to implement formal human clinical trials. None-the-less, all nine conducted in the three Ebola-affected countries began after the epidemic peaked, and all were affected by the diminishing number of eligible subject as the epidemic waned over time. None of five therapeutic trials ended with conclusive results on product efficacy, although a trial of ZMapp, a cocktail of humanised monoclonal antibodies against EVD previously found to be effective in animal models, suggested possible benefit in humans. However, given the resources, time, and effort put into these trials, the limited value of the information obtained was a major disappointment. Results of the four vaccine trials were more fruitful. Two candidates (rVSV-ZEBOV and ChAd3-ZEBOV) appear to be safe and produce a rapid immune response, and the former is most likely protective against infection as well.

Initiating clinical trials during the epidemic also required resolving ethical concerns about conducting clinical trials in the midst of a public health emergency. Some questioned whether randomised controlled study designs were even acceptable, primarily due to the belief that the community would not participate. However, randomised controlled trials (RCTs) are preferred because they allow identification of incremental benefits, in contrast to single arm trials, most useful to detect a major 'blockbuster' effect. Others argued that RCTs would be unethical during the epidemic because individuals randomised to the control group would be deprived access to an agent that could potentially prevent or treat EVD. The report concludes that RCTs are both ethical and acceptable during an epidemic when the community is informed, engaged, gains trust in the researchers, and understands that RCTs are the most reliable and fastest way to identify relative benefits and risks of investigational products. The report recommends that, except in rare circumstances, every effort should be made to implement RCTs during epidemics.

Additional concerns influenced choices about trial design during the epidemic, such as the need to address and overcome community mistrust of authority and potential exploitation, the feasibility and ethical legitimacy of a standard-of-care-only arm, the high and variable mortality rate affecting the reliability of historical controls, limited product availability, and perceived conflicts between research and care. These issues are thoroughly addressed in the report, because they are likely to recur in future epidemics. The report concludes on the importance of using an RCT design.

The committee focused on three main areas to improve national and international efforts to implement clinical trial in the next epidemic—strengthening capacity, engaging communities, and facilitating international coordination and collaboration. All can and should be targeted before the next epidemic strikes. The committee emphasised the essential requirement



Ebola Epidemic 2014-2015 incident cases in Guinea, Liberia and Sierra Leone showing dates of confirmation of Ebola Virus Disease (EVD), declaration of Public Health Emergency of International Concern (PHEIC) and start of Therapeutic and Vaccine Trials (Source: WHO situation reports)

Graphs reprinted with permission from Integrating Clinical Research into Epidemic Response: The Ebola Experience, 2017, by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

for quality and sustainable health and public health systems to improve the prospects for necessary clinical trials, which is optimised by integration of research expertise with healthcare and outbreak response. To proceed rapidly when an outbreak occurs also requires strengthening systems for scientific, ethical and legal reviews of proposed projects, community engagement, streamlined and effective informed consent procedures, the ability to collect and share clinical and epidemiological data, and training clinical research leaders and personnel. These must be improved before the next epidemic so that research and response are primed to work together from the outset.

There was considerable fear, mistrust, and misunderstanding between the affected communities, national and international response, and research staff during the outbreak. Not only did community members fear going to healthcare facilities for diagnosis and treatment, because most who did, died especially early in the outbreak, but international responders and researchers were tarred by the rumours that they deliberately brought Ebola to the region to test drugs and vaccines. Initial response efforts did not respect community traditions and beliefs regarding burial rituals, mandatory cremation policies countered deeply held religious beliefs, and even the colour of body bags (black instead of white, the colour for mourning) incited push back. It is no surprise that successful clinical research during the outbreak depended on a community's understanding of what and why research was needed, engagement with researchers, and involvement in the process of planning and conducting research, and on investigators respecting the community. Prioritising community engagement with the health system now will lead to channels of communication that can be rapidly opened at the onset of another outbreak.

Research and response efforts were also greatly affected by the relationships among international stakeholders and their ability to coordinate and collaborate with one another, and with national and local stakeholders in the affected countries. A mechanism is needed to improve international coordination and collaboration in the future. This should include assembly of a tool box which includes identifying and convening stakeholders, model clinical trial design templates for different circumstances and settings, guidelines on prioritisation of products for trial, checklists for community engagement and communication, authority to regulate this environment, and the responsibility to identify expert teams to be rapidly deployed to assist in early assessment and research decisions during an outbreak.

In summary, the report highlights seven critical steps to launch successful clinical trials early in the course of an epidemic, when there are enough patients to enroll in trials and reach interpretable results, including: 1. To collect and share patient information, 2. Establish standards of care, 3. Engage communities in a relationship of mutual trust, 4. Integrate research efforts into response and clinical care, 5. Facilitate stakeholder coordination and collaboration, 6. Prioritise which vaccines and therapies to study, and 7. Select trial design, help negotiate contracts, consult with regulators, and perform independent ethics reviews.

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Reference

1. National Academies of Sciences, Engineering, and Medicine. 2017. *Integrating clinical research into epidemic response: The Ebola experience.* Washington, DC. The National Academies Press. DOI: 10.17226/24739.

Strengthening capacity for responding to filovirus outbreaks

National preparedness for epidemics is critical. Mohammed Lamorde and colleagues describe measures being taken currently in Uganda

The Ebola virus disease (EVD) outbreak 2014–2015 was the largest filovirus outbreak in history, with 28 616 cases reported and 11 310 deaths in Guinea, Liberia, and Sierra Leone.[1] In the absence of evidence-based therapies, experimental treatments were used with some patients, highlighting a failure in drug development for a disease that had been recognised for decades. The recently released report[2] '*Integrating clinical research into epidemic response: The Ebola experience*' found that none of the therapeutic trials conducted during the outbreak were able to reach definitive conclusions about efficacy. Barriers to the success of the overall research effort included weaknesses in national health systems to comply with International Health Regulations (IHR) 2005 targets and inadequate research capacity within countries and local organisations. Notably, these weaknesses are not restricted to the West African countries most affected during the outbreak. The lessons learned from the West Africa outbreak present a unique opportunity for African institutions to prioritise emerging infectious disease threats and implement strategic and operational plans to promote global health security. While the need for capacity strengthening is clear, institutions need optimal and evidence-based frameworks to address the challenges posed by EVD.

Established in 2002, the Infectious Diseases Institute

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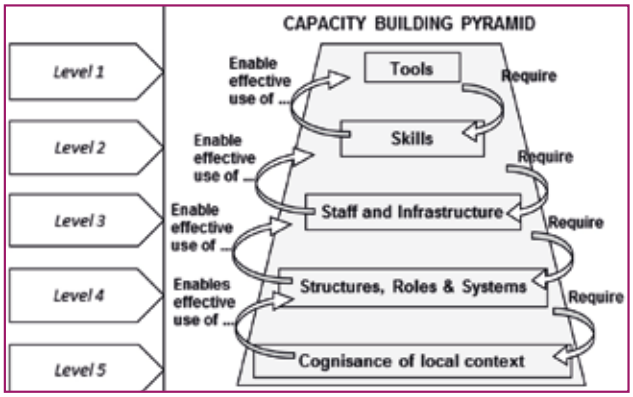

Figure 1: Capacity building pyramid

(IDI) is a not-for-profit organisation wholly-owned by Makerere University, Uganda. Its mission is to strengthen health systems in Africa, with a strong emphasis on infectious diseases, through research and capacity development. Throughout its operations, the institute works in close alignment with national structures. The IDI works closely with the Ugandan Ministry of Health and serves as the implementing partner to the ministry on various projects. Originally focused on the HIV epidemic, the institute expanded its mandate to include other infectious diseases in 2006. In the wake of the EVD outbreak, IDI implemented changes to its strategic plan to prioritise global health security and harmonise its existing efforts in this field into a coherent programme. The capacity development framework used by the institute is the capacity pyramid (Figure 1). The model provides a systemic approach to capacity building, recognising that there is a hierarchy of inter-related capacity building needs. Notably, investments at the bottom of the pyramid (e.g. structures, delineating roles and supporting systems) are expected to yield dividends at the top of the pyramid (e.g. supporting skills acquisition by training or technical assistance).

Clinical research during an EVD outbreak must occur within the framework of a national health system. In this regard, national diagnostic, disease surveillance, reporting and response capacity as well as biosafety and biosecurity, infection prevention and control and medical countermeasures systems are all important. With local and international partners, IDI is conducting acute febrile illness surveillance in six health facilities in Uganda to identify causative agents among children presenting with non-malarial fevers. Syndromic surveillance of this nature can complement national integrated disease surveillance and response (IDSR) to facilitate earlier identification of cases that could signal an outbreak. Furthermore, at the national level, IDI is supporting a whole-of-government approach to biosecurity by supporting policy development and legislation within the One Health conceptual framework. These policies are needed to govern a national pathogen inventory, support pathogen consolidation efforts to a minimum number of secure laboratories, and to prevent unauthorised use of select agents. Alongside this effort, a harmonised curriculum for biosafety and biosecurity has been developed and 48 national trainers trained.

The paradigm for the management of EVD has evolved to emphasise supportive clinical care.[3] To deliver high quality supportive care, health workers must come in close proximity with patients to execute clinical procedures. To safely and confidently deliver care, high levels of competency must be achieved for infection prevention and control, a process that requires ongoing mentorship and supervision by highly experienced personnel.[3] The IDI is part of the Joint Mobile Emerging Diseases Intervention Clinical Capabilities (JMEDICC) consortium comprising local and international partners. This project is developing research capabilities for improved sepsis patient management and capacity to conduct therapeutic research in a filovirus (Ebola and Marburg) outbreak setting.[4] In this project, IDI supports clinical care, infection prevention and control aspects. To attain and sustain competencies, staff receive ongoing training in infection prevention control through supervised drills and exercises.

Research capacity needs are also apparent. Site investigator capacity is needed to engage with international clinical trials during an outbreak setting. Ethics committees and competent authorities should be prepared and have clear guidance for oversight of clinical trials during an outbreak. With funding from the World Health Organization Tropical Diseases Research (WHO TDR) and the European and Developing Countries Clinical Trials Partnership (EDCTP), IDI is implementing a series of measures to support early phase clinical trials on investigational drugs for viral haemorrhagic fevers, including investigator training for early phase studies, clinical trial systems support and clinical trial quality management.

While IHR obligations are primarily within the mandate of the government, the IDI experience suggests that it is feasible for African non-government institutions to adapt contribute significantly to national efforts for preparedness for EVD outbreaks. Organisations with mission statements and strategic plans aligned with national priorities can leverage prior health investments to support response and research during an EVD outbreak. An often-cited challenge is the lack of funding to conduct these activities. During, and in the immediate aftermath of, the West African EVD outbreak, funding opportunities relevant to EVD response and/or research were provided by several organisations including, but not limited to, the United States Centres for Disease Control and Prevention, the EDCTP, the WHO TDR, the Canadian Institute for Health Research, the UK Department for International Development, and the Wellcome Trust. However, funding is likely to gravitate to the few centres of excellence in Africa where reliable grants management and financial capabilities are already in place. In the inter-epidemic period, attention to systemic and sustainable capacity strengthening of African institutions should be a priority.

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