Generating Evidence for Infectious Diseases with Epidemic Potential

20th October 2015, The Wellcome Trust, London, UK

Meeting report

Jointly organised by the World Health Organization, the Wellcome Trust, the University of Oxford, and the Special Programme for Research and Training in Tropical Diseases (TDR)

Background and objectives

Epidemics of emerging infectious diseases are often unpredictable and transient, and commonly flourish in vulnerable populations living in difficult conditions. This poses many challenges to the generation of evidence to improve the prevention and treatment of these diseases. The 2014-15 Ebola virus disease (EVD) outbreak demonstrated that the world is not adequately prepared to respond to an outbreak of a serious infectious disease that threatens regional and global health security. Although this outbreak was in many respects uniquely challenging, it was also a familiar reminder of our limited understanding of many infectious diseases with epidemic potential. For many worrying infections, such as avian influenza and MERS-CoV, there are enormous gaps in our knowledge of the natural history of disease progression, the pathophysiology of disease, and of the effectiveness of standard medical interventions and of experimental therapies and vaccines. Although sometimes extremely demanding, it is possible to generate evidence during epidemic emergencies, as was demonstrated during the 2014-15 EVD outbreak. The experience of previous outbreaks to provide tools to improve the response to future outbreaks needs to be collated and synthesised.

This meeting was convened as part of a process of evaluation of past performance in order to inform future practices, and it feeds into the development of the World Health Organization (WHO) Research and Development Blueprint for preparedness for epidemics. The objectives of the meeting were to:

- Map methods for clinical research (and the usual indications for their use) against epidemic attributes;
- Identify work that needs to be conducted to evaluate the suitability of clinical trial designs to different epidemic types and contexts;
- Describe the elements of a ‘toolkit’ for evidence generation in epidemics.
Meeting proceedings

The participants began by discussing the context of epidemic infections and the difficulties of conducting research in these conditions. The feasibility and value of defining generic components of epidemics to assist in pre-planning of research was discussed, as was the potential value of a ‘toolkit’ to guide decisions about the design and conduct of research during epidemics. The participants then discussed methodological lessons from oncology trials that might be applicable to epidemic infections, the design of field trials of vaccines during outbreaks, and the statistical evaluation of therapeutic trial designs that were used during the 2014-15 Ebola epidemic.

Meeting conclusions

The participants unanimously agreed that research, including observational and clinical research, is essential to inform preparedness and response to epidemics of dangerous and novel infections. Research must therefore be included as an integral and essential component of epidemic preparedness and response.

A high priority must be the strengthening of the quality and accessibility of descriptive clinical and epidemiological data in the early stages of an epidemic, as these are a pre-requisite for designing and conducting informative intervention research.

Research capacity should be strengthened at both regional and national levels, and established research networks should be utilised and expanded to ensure local teams with community knowledge are integral to epidemic response. The presence of existing research capacity in countries affected by epidemic infections is the foundation for efficient, acceptable, and locally relevant research. The paucity of such research capacity in the West Africa EVD outbreak necessitated the involvement of many international partners in efforts to provide it.

Research should ideally be integrated with clinical care and public health responses, not separate from them. However, this will almost always require the provision of additional dedicated resources since clinical and public health teams are usually overwhelmed by the response to an epidemic.

Structures, processes and incentives should be established that facilitate efficient and effective joint working, including timely sharing of key information and of specimens for analytic purposes. As already stated in reports of other WHO-convened meetings, timely sharing of information is essential to design and implement clinical research effectively. This includes a range of useful information, from descriptive clinical data, to experimental data, to protocols and operational procedures. Collaboration, communication, and sharing of data and information between individuals, organisations and countries is essential but is currently inadequate.

There is no obvious one-size-fits-all approach to the generation of evidence during outbreaks. The design of clinical trials of therapeutics or vaccines for epidemic infections must consider context on a case-by-case basis. Epidemics of infectious diseases are one the most challenging contexts in which to conduct research.

Adaptability and agility are essential to conduct research during epidemics. The optimal study design will depend on many factors including the specific question being asked, whether large or smaller effects are being sought, the natural history including case-fatality and pathogenesis of
disease, the intervention options that are available, the epidemiology and stage of the outbreak, and
the specific local context (such as local capacities, security, and the level of community trust).

Community engagement and participation in the development and implementation of research is essential. In addition to establishing a priority list of therapeutics during an epidemic, a participatory process for identifying and assessing trial sites, as well as prioritising the initiation and completion of clinical trials on the ground, is needed. This relieves the pressure on countries to deal with competing research groups when they are in the midst of a public health emergency.

A ‘toolkit’ approach to guiding decisions about epidemic research is recommended. The potential elements of a toolkit should be mapped, current work in the areas identified, and responsibilities agreed. A toolkit could include protocol templates and associated documents (e.g., case record forms, draft consent form) based on epidemic types (e.g. vector-borne outbreak; zoonotic outbreak with limited person to person transmission; an outbreak with significant nosocomial amplification; efficient human-human transmission by blood and body fluids, respiratory, or gastrointestinal routes) and the research questions being asked. These templates should be developed with the involvement of ethics and regulatory authorities. Scenario planning will be of great utility to allow us to prepare, discuss and rehearse different situations.

Protocol templates should not be proscriptive or restrictive, since epidemic characteristics and contexts are complex, may change over time, and are not always predictable. In addition, different approaches may be needed at different stages of an epidemic.

Research plans and frameworks for future outbreaks must encompass a situation where potential vaccines and therapeutics are less well developed or are unavailable. Evaluations should be conducted of vaccine and therapeutic trials implemented for Ebola to derive lessons for the future. During the 2014-15 Ebola epidemic, potential vaccine and therapeutic candidates were available. In fact, far too many therapies were proposed than could be adequately studied, and this required development of a prioritization strategy based on agreed criteria.

An inventory should be established of research protocols and operational procedures prepared for the evaluation of interventions for EVD and other epidemic diseases. As the number of potential pathogens is large, a syndromic approach that covers major disease outcomes (e.g., SARI, VHF) should be considered for selected high-priority representative pathogens (e.g., MERS-CoV, CCHF). These documents should be made publicly available. The work undertaken by McKinsey on behalf of the Bill and Melinda Gates Foundation, the National Institutes of Health, the Wellcome Trust, ISARIC, GloPID-R and WHO is a good starting point. The inventory should document negative and inconclusive data from clinical studies (such as has been developed by the Filovirus Animal Non-clinical Group), and address the potential explanations for such findings.

Next steps

This meeting report will be shared with the WHO Research and Development Blueprint for preparedness for epidemics. A draft contents of a ‘toolkit’ for generating evidence for epidemic infections will be prepared and sent to the workshop participants for comments and input.