Background

The Ebola epidemic 2014-2015 demonstrated that the international community needs to improve the ability to respond to new threats and prepare a new R&D paradigm to address future epidemics. On this background a Blueprint for Research and Development Procedures in the Context of Global Public Health Threats will be prepared by the WHO Secretariat for presentation at the 69th World Health Assembly, in May 2016.

Study design and statistical analyses are key to all aspects of epidemic response and preparedness, from clinical data to vaccine efficacy trials. Tailoring designs and developing new analysis methods are required to improve the speed and better adapt to infections exhibiting large spatiotemporal variation.

In the context of developing a Blueprint, a series of expert consultations have been convened. The recommendations from the meeting in Oslo 16 November 2016 follows on the conclusions from two other meetings; the meeting Generating Evidence for Infectious Diseases with Epidemic Potential arranged by the Wellcome Trust, University of Oxford, the World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR) in London 20 October, 2015 as well as the workshop 9-10 November on Clinical Trial Designs for Emerging Infectious Diseases hosted by the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) in Washington DC. The emerging high level conclusions from these two meetings were:

20 October, London: Generating Evidence for Infectious Diseases with Epidemic Potential

- Include R&D in care as an integral and essential component of epidemic preparedness and response to improve availability of descriptive clinical and epidemiological data
- Facilitate efficient and effective joint working and timely sharing of key information and of specimens. Adaptability and agility are essential to conduct research during epidemics.
- There is no “one-size-fits-all” approach to the generation of evidence during outbreaks, but one need to consider the context on a case-by-case basis in the design of clinical trials of therapeutics or vaccines for epidemic infections.
- Linking up with local resources is the most efficient and appropriate way forward in R&D, and can be facilitated by using established research networks with community knowledge.
- Prepare a toolkit for implementation with protocols, case record forms, consent forms tailored to causative agents and type of outbreak, and include an inventory of research protocols and operational procedures.
- Tailor protocols for unpredictability and involve ethics and regulatory authorities early on to address concerns and regulatory requirements.
- Anticipate not having a vaccine or drug: Research plans and frameworks for outbreaks must encompass a situation where vaccines and therapeutics are less well developed or unavailable.
9-10 November, Washington DC: Clinical Trial Designs for Emerging Infectious Diseases

- Develop a toolkit of options for clinical trial design, rather than a “one size fits all”.
- A number of designs, in addition to those used for Ebola, are being developed.
- Further work needs to be done to develop a decision making framework to select appropriate designs from the toolkit to address the next epidemic infectious disease threat when it emerges.
- Implementing a clinical trial in the heat of responding to an epidemic was recognized as very difficult.
- Complementary study designs on vaccines (individual RCT, cluster RCT, stepped-wedge cluster RCT, ring vaccination) are likely to be useful, whereas there is less consensus on this for therapeutics.
- Vaccine trial design needs to take feasibility, implementation challenges, attack risks etc into account.
- The concept of a flexible, trained R&D workforce that can be deployed to work alongside clinicians providing clinical care in such circumstances is supported.
- Building local research capacity in countries likely to be affected by future highly infectious diseases is the optimal long-term solution.
- Good Participatory Practices as a tool to ensure community engagement should be adequately implemented in future CTs conducted in response to outbreaks caused by highly infectious pathogens.

16 November, Oslo: Modelling and Trial Statistics during Epidemics

Transmission and interventions

- **Improve communication on the usefulness and limitations of infectious disease models**
  Infectious disease modelling was in the current Ebola outbreak useful for clinical trial planning, for mobilizing and exploring scenarios, but we need to improve on communicating the models’ limitations in their ability to predict disease incidence and localized epidemics. Some infectious disease models’ estimates of EVD cases during the 2014-2015 epidemics in West Africa were too high (e.g. up to 1.4 million cases); nearly 50 times more than observed. An explanatory factor is that humans adapt behavior; worst case scenario created awareness and action, and the behavior seen during the early stages of the outbreak changed. Secondly, due to early exponential growth, models may overestimate when using data from this period only to model future epidemic development. It is challenging to predict the spread of EVD, which spreads heterogeneously due to behavioral change and social structure. It is however possible to project a wide range of different scenarios.

- **Simplify data collection by defining a minimal set of clinical and demographic parameters required for infectious disease modelling for outbreak.**
  If research is to be integrated with outbreak response and clinical care, predefined case record forms intended for research data collection must be unified with response-based data schemes not overly comprehensive to facilitate data completion in setting of an epidemic.
• To ensure rapid access to reliable epidemiological data from early phase of outbreaks, allocate resources for labor-intensive cleaning and processing of source data documents

Anticipate that data collection in early phase of outbreaks in developing countries will be paper-based line lists or case record forms and derived from multiple sources, requiring labor-intensive cleaning prior to use in modelling. The WHO should streamline the data collection, cleaning and entry of outbreak data from these sources, in order to make data available as early as possible for decision making and modelling.

• Access to epidemiological data from countries should be facilitated by making data sharing an opt-out decision.

Access to data following data cleaning should be governed by a transparent and rapid application process through WHO, where applicants state the intended analyses. Existing mechanisms are seen as non-transparent and having many prerequisites, and exclude confirmatory or complementary analyses by different groups. An international safe house for data should be established, preferably the WHO.

• Mandatory involvement and acknowledgement of scientists or doctors from outbreak countries in analysis and interpretation of data.

Access to data for analysis must have the prerequisite of involving scientists from the country where data originated, to ensure appropriate context interpretation, ownership and capacity building as an integrated part of the processes.

Clinical trials

• Innovation in clinical trial design for drugs or vaccines will expand the toolbox for rapid trials

Innovation in clinical trial designs for vaccines or drugs against highly infectious pathogens must be intensified, to ensure that trials can be conclusive in as short time as possible. The feasibility of designs should be simulated and assessed ahead of time for new epidemics. Novel trial designs should be pre-vetted for potential bias in interpretation, to ensure data on these are collected prospectively. In order to be accepted, trial designs should be prepared, pre-approved and documented by the international community at large, by an expert meeting convened by WHO.

• Implement clinical trials in locations where there is ongoing transmission to enable a scientifically valid assessment of new interventions

Location and timing of trials in relation to ongoing transmission is critical: put the trial where transmission occurs, and include a valid and representative control group. All basic protocols should include this component. Each infectious disease has its own parameters that will affect trial design.

• Initiate a framework for allowing centralized and effective interaction between regulatory sponsor and ethical approval authorities
The relative benefit of pre-approval of protocols with national regulatory agencies and ethical committees must be explored, taking into account that each new outbreak will be different in terms of location, causative pathogen and safety-efficacy profile of the investigational new drug. Focus should also be placed on rapid and coordinated, expert evaluation for each trial, as the “regulatory bar” for approval may be specific for each situation.

- **Involve regulatory agencies in assessing ability of trial designs to contribute to licensing**

  To ensure that study outcomes can inform the licensing process of a vaccine or drug, the requirements from regulatory authorities must be taken into consideration in design and implementation of trials. Regulatory authorities may not be limited in their willingness to assess documentation from new trial designs, however the strict scientific assessment ensures that the balance between epidemic risk and vaccine efficacy and safety is maintained to ensure overall health benefit for the population.

- **Reassess criteria for efficacy in trial during PHEIC**

  The ring vaccination trial in Guinea had a dual purpose: to evaluate the vaccine efficacy and to be part of the Ebola-response. The efficacy estimate was assessed on a ring-basis, not an individual level as is the typical outcome for traditional individually randomized placebo controlled trials. This strategy posed some challenges for the communication in how to interpret efficacy, however the Hawthorne effect (i.e. individuals modify behavior in response to awareness of being observed) has been taken into consideration and further analyses will be performed in this trial. A commonly used method for adjusting the alpha spending for multiple testing in clinical vaccine trials is the O’Brien Fleming method. This was also the choice of method in the preliminary analysis of the Guinea ring vaccination trial. It was, however, proposed that this may be an overly conservative methodology; resulting in significance thresholds that are unnecessarily strict in a situation where there is an urgent need to provide early indications of efficacy. Time and capacities to perform trials, as well as the number of promising treatments, are then limiting factors. In an outbreak, this may lead to needlessly eliminating candidate vaccines with partial to high efficacy.