# Out of Control

**Epidemics like the Ebola virus in 2013 are extremely hard to contain. With the clinical trial process often taking many years to obtain authorisation, new and innovative designs need to be explored to ensure that vaccines can be approved as soon as possible**

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The first documented outbreak of the Ebola virus disease – more commonly known as Ebola – occurred in 1976 in South Sudan and the Democratic Republic of the Congo. Nearly 40 years later in 2013, the most widespread outbreak of Ebola in history started in the West African country of Guinea and quickly spread to the neighbouring countries of Liberia and Sierra Leone.

While previous outbreaks were brought under control within a matter of weeks, this one became an epidemic that raged on for over two years, resulting in more than 11,000 deaths and significant social disruption. A number of factors contributed to the failure to control this flare-up, including extreme poverty in the affected areas; a dysfunctional healthcare system in affected countries; a population with enormous distrust of government officials after years of armed conflict; several months of delay in government agency response to the outbreak; and the unprecedented spread of Ebola to densely populated cities.

Even with previous Ebola epidemics on record, there were no licensed vaccines, no treatments with proven efficacy in humans and no diagnostics that met the WHO's target product profile for a rapid, simple Ebola virus disease test at the start of this spread. The lack of effective treatments, combined with the severity of the breakout, triggered an unprecedented global response to tackle the epidemic that provides a compelling case study for accelerated drug development models.

## Speed Up the Process

Approval for clinical trials by health authorities and regulators usually takes years, as does implementing the gold standard of randomised controlled trials. In the US, an average of 12 years is needed for an experimental drug to reach the market, if at all (1). Although there are other routes that can expedite the procedure (referred to as fast-tracking), this is the typical journey for a drug from invention to market, which often means that outbreaks tend to end before trials can even begin. Clinical research is also normally conducted in well-equipped research hospitals, and robust trials have generally been considered impossible to carry out in the gruelling field conditions of deadly outbreaks (2).

The urgency of the Ebola eruption beginning in 2013 changed all of that. In a matter of months, promising candidates moved from preclinical studies to human trials. After initial Phase 1 safety and dosage studies in North America and Europe, investigations with tens of thousands of African volunteers began in earnest by early 2015. From the international collaborative consortia organised to fund, conduct and share the outcomes of clinical trials to the support from regulatory agencies, the WHO, non-governmental organisations and African governments to loosen the restrictions on the use of experimental agents in affected populations, the acceleration of vaccine development for Ebola has been unprecedented. Just 20 months after the outbreak, a vaccine was created that seems to provide total protection against infection, according to the preliminary results of a trial in Guinea that were published in July 2015 (3,4).

Along the way, the WHO-supported collaboration pulled out all the stops to accelerate the testing of treatments and vaccines that had shown promise in animal studies, cutting through the red tape and coming up with innovative trial designs to quickly provide data informing of efforts to control the outbreak. How did these new designs work and, perhaps more importantly, could this fast-tracked approach be applied to other diseases?

## Adaptive Trial Designs

Evaluating the efficacy of novel therapeutics in the context of epidemics is challenging to say the least, with situations

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evolving rapidly and heightened ethical concerns regarding research during public health emergencies. Remarkably, the fast-tracking of production was characterised by a deliberate robustness. A series of multi-agency, international consultations were organised at the WHO to consider the appropriateness of placebo, randomisation and informed consent for investigations in an outbreak context. Ultimately, adaptive trial models were designed to balance the urgent therapeutic needs of the afflicted populations with the regulatory imperatives that require the generation of robust safety and dosage data.

An adaptive clinical trial is a study that evaluates a medical treatment by observing participant outcomes – and possibly other measures, such as side effects – on a prescribed schedule, and modifying parameters of the trial protocol and/or analysis in accordance with those observations. The flexibility inherent in these trials makes them a more attractive option over traditional ones for an accelerated drug development process. The benefits vary with trial design but, in general, the adaptive format can often provide a shorter trial duration, better ability to demonstrate the effect of the drug if one exists, and broader dose-response information. A few of the adaptive trial designs used in the 2013 West Africa Ebola epidemic were:

**Cluster Randomisation/Ring Vaccination**

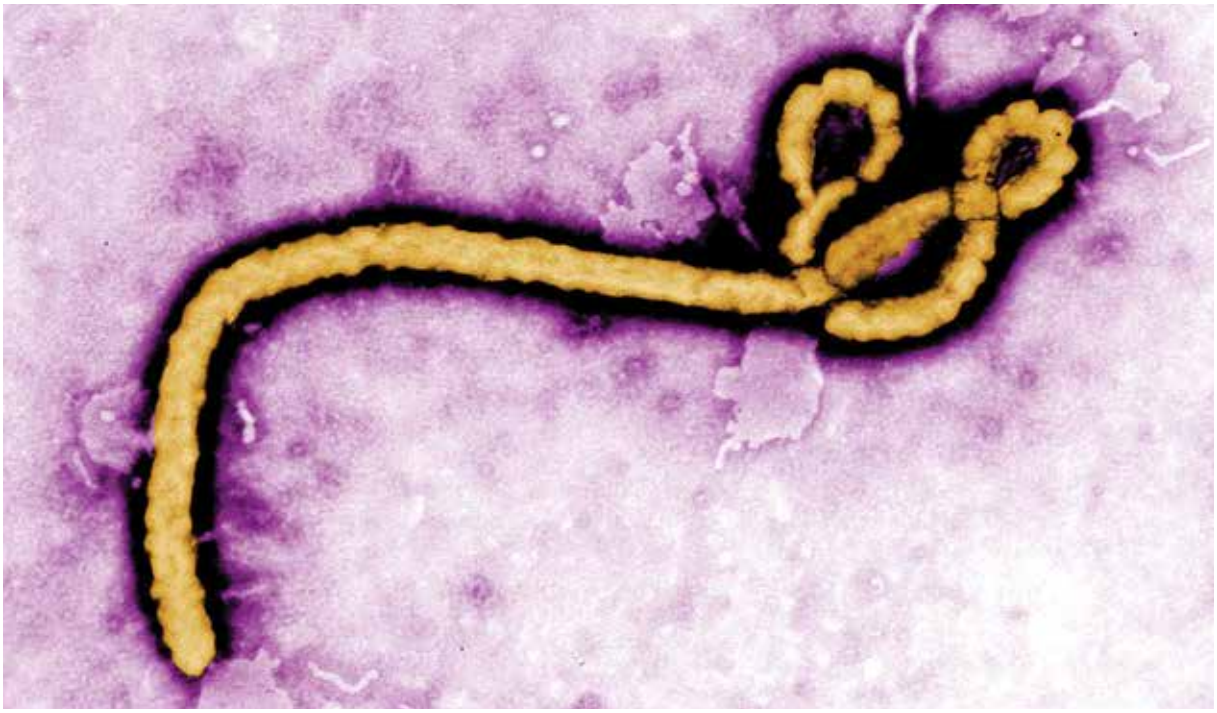
These studies rely on the 'ring' vaccination of individuals at high risk of infection due to their social or geographical connection to a known case. In the recombinant vesicular stomatitis virus-Ebola Zaire Ebolavirus vaccine (rVSV-ZEBOV) trial, for example, rings were randomised 1:1 to (a) immediate vaccination of eligible adults with single dose vaccination or (b) vaccination delayed by 21 days (5). The incidence of disease is compared between the two arms over equivalent time periods measured from the time of randomisation of each ring. Comparing the hazard ratio in those enrolled in the study allows estimation of a vaccine's efficacy, while its overall effectiveness can be estimated by comparing incidence across all members of the rings, including those not eligible for vaccination.

Ring vaccination trials are adaptive, can be run until disease elimination, allow interim analysis and can go dormant during inter-epidemic periods. An added benefit is that a ring vaccination trial tracks the epidemic, recruiting individuals at raised risk of infection due to their connection to a case. This design may both contribute to transmission interruption and have a higher power to detect vaccine efficacy than other study designs.

**Stepped-Wedge Studies**

In a stepped-wedge design trial – like the Sierra Leone Trial to introduce a vaccine against Ebola trial of healthcare workers, also known as STRIVE – the Ebola vaccine is sequentially rolled out to participants in clusters, such as in clinics or hospitals, throughout several time periods (6). By the end of the study, all participants have received the vaccine. The design mitigates the ethical dilemma of non-treatment, such as in the case of a parallel control group, or withdrawal of treatment as would occur in a standard crossover study (7).

One benefit of this study design is the robust statistical power achieved through several comparisons, both within and between groups. Although a stepped-wedge trial has no placebo group, direct comparisons are still made between the bands receiving the treatment and those who are not, and groups can act as their own controls before



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and after the intervention meaning that fewer vaccines are needed. In addition, the design assesses the intervention effectiveness in the context of the community and takes into consideration temporal changes such as seasonality. Studies can be randomised, whereby the order of administering the intervention is established randomly or observationally, thereby increasing flexibility in design (8).

### Lessons Learned

What can we discover from these innovative designs? It may not be the specifics of the designs that matter as much as the principle that is important. Other adaptive trials that convey different benefits may be more suitable in other situations. The key is that researchers should consider these and other innovative adaptive trial structures to identify optimal regimens that are short, safe, efficacious and can be used to treat patients rapidly.

The FDA is supportive of this approach, having published an industry guidance document in 2010 entitled *Adaptive Design Clinical Trials for Drugs and Biologics*, which details potential challenges and benefits of a variety of adaptive trial designs (9). Research during outbreaks requires the acceptance of a methodology that reorders traditional clinical trial phases to accelerate drug development, without losing sight of the traditional benchmarks by which promising drug candidates must be assessed for activity, safety and efficacy.

Can this fast-track approach be applied to other breakouts? Adrian Hill, Director of the Jenner Institute at the University of Oxford who is involved in testing Ebola vaccines, thinks so. When referring to rVSV-ZEBOV's success, he expressed hope that it will provide a model for dealing with future outbreaks: "This is illustrating that it is feasible to develop vaccines much faster than we've been doing" (10). He recommends that research on vaccines against dangerous pathogens be accelerated so that clinical trials can be carried out now to test their safety; those that show promise would be stockpiled and ready for efficacy tests as soon as an outbreak occurs.

Pathogens considered epidemic threats by the WHO, listed as "needing urgent R&D attention", include: Crimean-Congo haemorrhagic fever, Ebola virus disease and Marburg, Lassa fever, Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome and Nipah and Rift Valley fever. Other diseases designated as "serious", requiring action by the WHO to promote R&D as soon as possible were: chikungunya, severe fever with thrombocytopaenia syndrome and Zika (11).

Beyond the research community, support for the fast-track approach is also coming from the WHO, which recently announced that it is developing a 'blueprint' for accelerated development of measures to counteract potential epidemics. The goal is to reduce the time from the recognition of an outbreak to the availability of countermeasures to four months or under, and the plan would include putting trial designs and regulatory approvals in place in advance of an outbreak. As Margaret Chan, General Director of the WHO, recently stated: "No one wants to see clinicians, doctors, left empty-handed ever again" (10).


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