Emergency Ebola response: a new approach to the rapid design and development of vaccines against emerging diseases

Claire M Tully, Teresa Lambe, Sarah C Gilbert, Adrian V S Hill

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Jenner Institute, University of Oxford, Oxford, UK (C M Tully BA[Mod], T Lambe PhD, Prof S C Gilbert PhD, Prof A V S Hill DM)

Correspondence to: Claire M Tully, Jenner Institute, University of Oxford, Oxford OX3 7DQ, UK **claire.tully@ndm.ox.ac.uk**

The epidemic of Ebola virus disease has spread at an alarming rate despite containment efforts. As a result, unprecedented large-scale international response efforts have been made in an attempt to gain control of the outbreak and reduce transmission. Several international consortia have been formed in a remarkable worldwide collaborative effort to expedite trials of two candidate Ebola virus vaccines: cAd3-EBOZ and rVSV-EBOV. In parallel, both vaccines are being manufactured in large amounts to enable future rapid deployment for management of the crisis.

Introduction

On March 23, 2014, WHO reported a rapidly emerging outbreak of Ebola virus disease in Guinea in west Africa.[1] Zaire ebolavirus (referred to hereafter as Ebola virus) was quickly identified as the cause, by which time, suspected cases were being investigated in border areas of neighbouring Liberia and Sierra Leone.[2] By June, the situation was described as "out of control" by front-line Médecins Sans Frontières health workers who had been treating patients since March.[3] WHO declared a public health emergency of international concern on Aug 8, and priority response protocols and implementation strategies were quickly published in the *Ebola Response Roadmap*.[4,5]

The outbreak has since become a major humanitarian crisis. Eight countries have been affected so far, and more than 8000 deaths—a figure widely thought to be underestimated—have been recorded.[6] Conservative forward projections estimating that more than 20 000 people would be infected before the disease could be contained have already been surpassed.[5,6] As the crisis has escalated, extraordinary measures to contain and treat infections have been implemented.

World first

In a world first, international consortia have been formed to accelerate collaborative multisite trials of two candidate Ebola virus vaccines: cAd3-EBOZ, codeveloped by GlaxoSmithKline and the US National Institutes of Health (NIH); and rVSV-EBOV, from NewLink Genetics, developed by researchers at the Public Health Agency of Canada.[7,8] Additionally, a combination prime-boost vaccination regimen, which is based on adenovirus (AdVac; Crucell, Netherlands) and modified vaccinia Ankara (MVA; MVA-BN; Bavarian Nordic, Denmark) vectors, developed by Janssen Pharmaceuticals of Johnson & Johnson, started a phase 1 trial in Oxford in late December, 2014.

Prioritisation of the ethical and regulatory approvals for these trials has increased the speed at which trials have begun. By the end of January, 2014, sufficient safety data should have been collected about cAd3-EBOZ, and possibly about rVSV-EBOV, for phase 2 safety and phase 3 efficacy trials to begin in early 2015. The phase 3 trials will be in Liberia, Sierra Leone, and Guinea, with phase 2 trials mostly in surrounding west African countries. Parallel production of more than 24 000 doses of the cAd3-EBOZ vaccine from GSK, and probably larger amounts of the Johnson & Johnson Ad26-MVA vaccine regimen, is underway and, depending on phase 1 dose selection, NewLink Genetics expect between 52 000 and 5·2 million doses to be available by April, 2015.[9,10] These vaccines are being produced and stockpiled in parallel with phase 1 trials in progress, to ensure that trials can proceed without delay and that any successful vaccine can be available for immediate widespread use.

Therapeutic interventions

Investigational therapies have already been used to treat a few patients on a compassionate basis. ZMapp (Mapp Biopharmaceutical; CA, USA), an experimental treatment comprising three humanised monoclonal antibodies recognising non-overlapping Ebola virus glycoprotein epitopes has been given to several medically evaluated patients with Ebola virus disease, but the clinical effectiveness of this treatment is uncertain.[11] Additionally, current supplies of ZMapp and the ability to scale up supply in the short term are extremely limited.[12–14] Similarly, brincidofovir (Chimerix; NC, USA), an oral antiviral with in vitro activity against Ebola virus, has also been given to medically evaluated patients.[15,16] Clinical trials of brincidofovir and a second antiviral drug, favipiravir (a pyazinecarboxaminde derivative; Toyama Chemical, Japan), are ready to begin at several sites across affected areas hosted by Médecins Sans Frontières.[17] Several novel Ebola virus-specific antiviral therapies are also under consideration, including TKM-100802 (Tekimira pharmaceuticals; BC, Canada), a lipid nanoparticle delivering small interfering RNA (siRNA); AVI-7537 (Sarepta therapeutics; MA, USA), a phosphorodiamidate oligonucleotide; BCX4430 (BioCryst; NC, USA), an adenosine analogue; and interferon therapies.[13]

The alternative to drug therapies is to use convalescent blood products from patients who have recovered. Convalescent blood products have previously been used in other diseases with promising results, and in a small

group of Ebola cases.[18–20] However, in the case of Ebola, the numbers treated so far have been small, and efficacy is uncertain.[20] Phase 2 trial protocols of convalescent whole blood and plasma therapies are in the final stages of development, and are scheduled to begin in several sites in affected areas.[17] Although convalescent blood products are theoretically scalable, there are substantial operational constraints on identification of suitable donors, production and ensuring of a safe product, and delivery of infusions in overstretched Ebola treatment centres.

If any of these treatments prove to be safe and efficacious, they could potentially play a part in de-escalation of the current situation. However, these treatments are expensive, do not provide prophylaxis, and need medical supervision from already overstretched frontline workers. Treatment with convalescent blood products has a small risk of infection with blood-borne pathogens, and Ebola virus infection could theoretically be enhanced by antibody therapies, similar to complement-dependent enhancement of HIV-1 infection by autologous non-neutralising antibodies.[20,21] These issues raise obvious questions about the long-term sustainability of such expensive therapeutic interventions in countries with already fragile social, political, and economic conditions. Beyond this outbreak, continued surveillance of Ebola virus in wildlife will be necessary to prevent future outbreaks, and individuals at risk from such work will need to be protected. Effective vaccines are potentially the most cost-effective and practical long-term means of tackling the crisis.

Experimental vaccines

Unlike therapeutic interventions, the aim of vaccination is to achieve long-term, preferably life-long, protection against infection to prevent future morbidity and mortality. In addition to protection of vaccinated individuals, unvaccinated individuals in the community are protected by herd immunity so that further incidences of the disease become self-limiting. Results of preclinical Ebola vaccine studies in non-human primates have shown several vaccine platforms to be remarkably efficacious, including DNA, human adenovirus serotype 5, virus-like particles, recombinant vesicular stomatitis (rVSV), rabies, and human parainfluenza virus type 3.[22–27] The Ebola virus glycoprotein is the sole viral surface protein and, as such, is a major immune target. The candidate vaccines being fast-tracked encode the glycoprotein of the Zaire strain of Ebola virus expressed by a simian adenovirus, chimpanzee adenovirus serotype 3 (cAd3), in the case of cAd3-ZEBOV, or by an rVSV vector, in the case of rVSV-EBOV.[28] A related bivalent vaccine, cAd3-EBO, composed of two recombinant cAd3 vectors expressing Zaire and Sudan species glycoproteins in a 1:1 ratio is also being tested in a phase 1 trial at NIH (NCT02231866).

Replication-deficient chimpanzee adenovirus vectors have a good safety record in clinical trials, although none has yet been licensed.[29–32] The first replication-defective chimpanzee-origin vectors tested in human beings were derived from serotype 63 (ChAd63), and were used to express the pre-erythrocytic malarial antigen ME-TRAP.[29] By 2014, more than 600 individuals had been immunised in Africa with ChAd63 ME-TRAP vaccine, and many hundreds in the UK had been immunised with ChAd63 encoding HIV or malaria antigens.[29,31–35] Similarly, the cAd3 vector (usually known as ChAd3) expressing non-structural proteins from hepatitis C virus (HCV) genotype 1b successfully induced a T-cell response against HCV in healthy volunteers, and is in a phase 2b efficacy trial in the USA (NCT01436357).[30,36] The encouraging safety profiles from these trials show that simian adenoviruses are well tolerated in healthy individuals.

Much less is known about the tolerability of rVSV vectors in human beings. However, phase 1 trials assessing a candidate HIV vaccine (NCT01859325) and a potential liver cancer treatment (NCT01628640) using rVSV vectors, albeit with somewhat different viral backbones, are underway in the USA. The Ebola candidate vaccine rVSV-EBOV has previously been given as a post-exposure experimental vaccine in a laboratory worker after an Ebola virus-contaminated needlestick injury.[37] Although fever and a low-level rVSV viraemia were detected, the vaccine was otherwise well tolerated, and IgG antibodies to Ebola virus glycoprotein were detected.[37] Diagnostic RT-PCR for the Ebola virus-specific L gene was negative, and no additional serological evidence indicative of an Ebola virus was detected, suggesting that these IgG responses were vaccine-induced.[37]

No licensed medication or vaccine exists for any Ebola virus infection, and conventional treatment strategies rely on intensive interventional support.[38] The candidate vaccines being taken into clinical trials have shown striking single-dose efficacy in animal models.[39,40] If either vaccine has clear efficacy in human beings, administration to front-line workers could help to strengthen and sustain human resources and response capacities, which are crucial for short-term and long-term transmission control. However, if vaccine immunogenicity or efficacy is suboptimal, a booster vaccine based on MVA could be used, on the basis of studies of vectors for Ebola vaccines in macaques, and many clinical trials for other disease indications.[36,39,41]

Ethical questions

Vaccine development is guided by strict regulatory processes to ensure new vaccines are assessed ethically and transparently. The clinical trial system is designed to test the safety and efficacy of interventions in human beings that have previously only been validated in the laboratory, or in animal models. Progress of a vaccine candidate from design to deployment routinely takes many years.

However, the exceptionally high case-fatality rate of infections, intense transmission, threat of endemism, and the profound effect of the outbreak on societal