Title: Ebola Vaccines: Biomedical Advances, Human Rights Challenges
(Commentary on: A Randomized, Blinded, Dose-Ranging Trial of an Ebola Virus Glycoprotein (EBOVGP) Nanoparticle Vaccine with Matrix-M™ Adjuvant in Healthy Adults)

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Key Words: Ebola virus disease, Filovirus, *Filoviridae*, Vaccine, Viral haemorrhagic fever

In this issue of the *Journal of Infectious Diseases*, Fries *et al* [1] report results from a Phase I trial of an experimental vaccine for Ebola virus disease (EVD). The vaccine, comprised of a recombinant Ebola virus glycoprotein nanoparticle formulated with a saponin-based Matrix-M™ adjuvant, was well tolerated and immunogenic, as measured by both IgG and neutralizing antibody responses. The highest antibody levels resulted from two doses (days 0 and 21) of adjuvanted vaccine, peaking at day 35 and persisting through one year, the end-point of the study, although with some waning. Nevertheless, based on a pseudovirion neutralization assay, comparatively higher levels of neutralizing antibody were elicited from the nanoparticle vaccine than those reported in trials of the experimental rVSV-ZEBOV vaccine made by Merck & Co, Inc., which has been shown to be highly effective [2].

Unique features of the nanoparticle vaccine platform are the use of baculovirus and insect cell expression technology that can allow for rapid production of properly folded GMP-quality proteins, theoretically inducing an expanded immune response to a range of epitopes, and the use of the Matrix-M adjuvant, which may induce multiple arms of the immune system [3]. However, whether this immune response to multiple epitopes is required remains unclear, considering that protection has already been clearly shown in both humans and non-human primates with more restricted immunogens, although there may be benefits to the expanded approach with regard to dose sparing [2]. Although the nanoparticle vaccine has been shown to be protect mice from EVD [3,4], studies in non-human primates, considered the most predictive model of efficacy in humans, would seem to be a key next step.

Fries *et al's* findings come as the second largest EVD outbreak on record continues in eastern Democratic Republic of the Congo (DRC) with, as of this writing, over 3000 cases and 2000 deaths (case fatality 67%)[5]. Despite tremendous efforts on the part of the DRC Ministry of Health, National Institute for Biomedical Research, World Health Organization, and a host of national and international partners, the outbreak persists now for over a year, with most experts seeing no end in sight. Physical insecurity in the region, a complex cultural and political environment, and ineffective messaging and community engagement on EVD have all presented major challenges to control.

Control of EVD outbreaks has relied primarily on the classic public health measures of rapid case identification for isolation and treatment, and thorough contact tracing. While effective, particularly in rural and isolated populations these measures are relatively slow and labor-intensive, resulting in continued infection and loss of life as they grind transmission to a halt. While none are presently widely licensed and commercially available, experimental vaccines have recently become an important additional tool in the response armamentarium. During the large 2013-16 West Africa outbreak, the rVSV-ZEBOV vaccine, comprised of a replication-competent recombinant vesicular stomatitis virus expressing the Zaire ebolavirus glycoprotein, underwent a Phase III trial using a ring vaccination approach (i.e.,. vaccinating contacts of persons with EVD as well as healthcare and other

frontline workers), with almost 6,000 people vaccinated and a reported efficacy of 100% [2] (although this number has been debated [6]). Over 225,000 people have now received rVSV-EBOV under an expanded use protocol using the same ring vaccination approach in DRC [2,5].

So why is the EVD outbreak in DRC still ongoing over a year after first detection? Virtually all the response measures, including ring vaccination, are predicated on community engagement—i.e., the willingness of community members to self-identify as cases or contacts and accept isolation and care if sick, and to be regularly followed and vaccinated if a contact. Given the fear and stigma often associated with EVD, such cooperation is not a given. Furthermore, rumor, and at times intentional misinformation from suspicious communities, sometimes fuelled by political and financial motivations, may pose formidable challenges, causing persons to deny or hide disease or status as a contact. Indeed, decisions by persons who are cases and contacts to avoid recognition, and sometimes even violent armed resistance by certain segments of the society, have proven to be major impediments to control in eastern DRC; daily epidemiologic data consistently show a considerable proportion of cases, often half or more, to not be previously recognized contacts, with estimates from statistical modeling that perhaps 25% of daily cases go undetected [5]. Furthermore, roughly a third of detected daily cases are community deaths, likely highly infectious persons with ample opportunity for community transmission prior to detection.

Although most experts believe that rVSV-EBOV vaccination has played an important role in keeping the outbreak from steam-rolling to West Africa proportions, the ring vaccination approach, which relies on the ability to identify nearly all cases and contacts, is unlikely to completely extinguish transmission. Furthermore, most feedback from the community indicates that, while most are in favor of vaccination, the ring vaccination approach, which limits eligibility to a relatively small group, is not always understood and accepted. This has led, in part, to a recommendation by the World Health Organization Strategic Advisory Group of Experts on Immunization to consider use of other experimental EVD vaccines in DRC [7]. In response, a consortium led by the DRC Ministry of Health and National Institute for Biomedical Research is planning a clinical trial with a test-negative design with a considerably broader target population in eastern DRC with Ad26.ZEBOV/MVA-BN-Filo (Janssen Vaccines and Prevention B.V.). This vaccine is comprised of a two-dose regimen consisting of a replication-incompetent recombinant adenovirus 26 expressing the Zaire ebolavirus (Mayinga strain) glycoprotein followed by vaccination with a non-replicating modified vaccinia Ankara-Bavarian Nordic virus vector expressing the glycoproteins of Zaire and Sudan ebolaviruses, Marburg virus, and the nucleoprotein of Tai Forest virus [8 9]. At the dose planned for the DRC trial, this vaccine has shown 100% protective efficacy in non-human primate studies [10] and has been shown to be well tolerated and immunogenic in extensive Phase I-II trials [11-13]. In addition to the planned trial in DRC, a Phase II study in frontline workers is under way in Uganda and a large demonstration project is scheduled to start soon in in Rwanda.

The nanoparticle vaccine, rVSV-EBOV, and Ad26.ZEBOV/MVA-BN-Filo are among at least 13 vaccines for EVD under development. Although we might not need 13, there is advantage to having numerous diverse products in the pipeline [13]; each comes with distinct features with regard to cold chain requirement, coverage of different species of Ebola virus, anticipated adverse effects and duration of immunity, and ease of manufacturing and administration. For example, while single dose live-virus vectored vaccines like rVSV-EBOV have utility in providing rapid immunity during an outbreak, their use to provide durable population-based immunity is confounded by a variety of issues, including cold chain requirements, safety concerns in pregnant women and the immunocompromised, and the potential inability to boost in the face of vector immunity. Other products, such as the nanoparticle and Ad26.ZEBOV/MVA-BN-Filo vaccines, may have less rigorous demands regarding cold chain and might be anticipated to confer long-term protection but require two doses and more time to achieve protective immunity, and thus are less ideal platforms for use in the heat of an outbreak.

Development of an EVD vaccine and seeing it through to regulatory authority approval, full licensure and commercial availability is a particularly arduous journey, one that has yet to be achieved. Although many scientific questions remain even for the most advanced candidates, most daunting are perhaps the logistical challenges of conducting early phase clinical trials in relevant human populations in Africa, where the infrastructure for such trials may be lacking, and ultimately demonstrating efficacy in Phase III trials that can only be done during an EVD outbreak. Noting the challenges of Phase III trials for diseases like EVD, the U.S. Federal Drug Administration has created the “Animal Rule,” allowing products to be licensed after demonstration of efficacy in two relevant animal models. But even this path is not simple, since many questions remain regarding how well the various non-human primate models reproduce human EVD. Nor does the Animal Rule path obviate the need to demonstrate safety and immunogenicity in Phase I-II trials.

Despite these many challenges, it is laudable that so many groups persist in the development of EVD vaccines. The remarkable progress made to date for the most advanced candidates, often under the most difficult and dangerous field conditions, is truly gratifying. It is also important that diverse experimental vaccines and therapeutics for emerging diseases get access to field trials. Research and development of these products are expensive and hold little prospect for large economic return. If the products that are developed never get the chance for field evaluation, it’s safe to assume that pharmaceutical companies will bow out of the endeavor all together.

While not a panacea, vaccines can and should comprise an essential part of the response to EVD outbreaks. We must also look beyond a reactive approach, immunizing and protecting healthcare and frontline workers and vulnerable populations before an outbreak occurs. A robust single-dose vaccine conferring long-term protection against all species of Ebola virus must be the goal. Lastly, we must remember that it is not all about biomedical advancement; the situation in DRC,

where EVD is just one additional problem for a beleaguered population plagued by decades of disease and violence, reminds us that even bigger challenges remain—advocating for health as a human right, and ensuring that the protective power of vaccines reaches its potential by getting to the people most in need [14].

Acknowledgement

The UK Public Health Rapid Support Team is funded by the United Kingdom Department of Health and Social Care. The views expressed in this publication are those of the authors and not necessarily those of the National Health System, the National Institute for Health Research or the Department of Health and Social Care. The authors thank Kerstin Luhn for feedback on the manuscript.

Conflict of interest statement

The London School of Hygiene and Tropical Medicine, with which both authors are affiliated, is the Study Sponsor for numerous clinical trials of the Ad26.ZEBOV/MVA-BN-Filo vaccine. Daniel Bausch is a Co-Principle Investigator for a Phase III study in the DRC. While both authors provide strategic guidance for studies of the Ad26.ZEBOV/MVA-BN-Filo vaccine, neither receives remuneration from the vaccine manufacturer or has a financial stake in the study results. LSHTM and Peter Piot also receive grant funding for clinical trials on the rVSV-EBOV vaccine.

Funding statement: No funding required

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