A vaccine against Ebola: Problems and opportunities

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The unprecedented dimensions of the 2014 Ebola epidemic which ravaged 3 West African countries have challenged public health response capacity and urged the availability of safe and effective vaccines. In this context, vectored vaccines already tested in animal models have undergone phase 1 studies in human beings and are now ready for efficacy evaluation in large scale trials. Health care workers and other frontline caregivers are likely to be the target population for both vaccine trials and vaccination campaigns. However, methodological and ethical issues should be considered in plans concerning the conduction of clinical trials and the possible use of licensed vaccines against Ebola.

The large 2014 epidemic of Ebola virus disease (EVD) in West Africa^{1,2} has strengthened the need for an effective vaccine able to prevent the infection at the individual level and to keep outbreaks under control. Relying on such preventive tool is particularly important, since experimental drugs have not been sufficiently evaluated in controlled trials on human beings, thus no evidence based treatment for EVD is available.

Although there is still no effective vaccine licensed, promising results have been gathered from both animal and human studies during the last decade. In particular, animal models showed that it is possible to develop a protective vaccine against Ebola,³ and a phase I trial of a recombinant adenovirus type 5 vaccine encoding the envelope glycoprotein (GP) from the Zaire and Sudan Ebola virus species showed that this vaccine is safe and immunogenic in healthy adults.⁴ However, this vaccine could not

considered an ideal candidate, since it may evoke a diminished immune response in study participants with preexisting neutralizing antibodies.^{4–6}

Current Ebola Vaccine Candidates

The unpredictable evolution of the Ebola epidemic in West Africa favored the speed of human testing of other vaccine candidates under development. First, GSK, in collaboration with the NIAIDS, started a phase I, dose-escalation, open-label, clinical trial (VRC 207), using a replication-defective recombinant chimpanzee adenovirus type 3-vectored ebolavirus vaccine (cAd3-EBO), which showed positive findings in terms of safety and immunological response.⁶ Such bivalent vaccine, encoding the glycoprotein from the Zaire and Sudan species of Ebola, had been tested with success in non-human primate models, offering protection against infection.⁷ However, durable immunity was enhanced only after a prime boosting schedule of cAd3 and a modified vaccinia Ankara (MVA) poxvirus vector encoding Ebola GP.⁸ Recently, a cAd3 monovalent vaccine against Ebola Zaire (a virus strain similar to the one causing the outbreak in West Africa) was also tested in humans with encouraging results.⁹

One of the open questions is whether these results will be replicated in the Africa context, where malaria, which is associated with diminished immunogenicity with other vectorial vaccines, is widespread.¹⁰ A partial answer to this question was provided by a phase 1 trial conducted in Uganda with DNA vaccines encoding different versions of the Ebola virus and the Marburg virus surface glycoprotein. This

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vaccine candidate resulted well tolerated, eliciting antigen-specific humoral and cellular responses; however, the proportion of responders was rather low in this study. Moreover, the DNA vaccine is not able to induce highly acute protective response, thus it is not the ideal candidate to be used in response to an outbreak.¹¹ Nevertheless, the results of this study conducted in Africa are to some extent reassuring about the immunogenicity of other constructs encoding the Ebola glycoprotein, such as cAd3-EBO, which are going to be tested in African populations.¹²

Another experimental vaccine undergoing phase I in humans was developed by the Public Health Agency of Canada in Winnipeg. The license of this vaccine was held by an American company, NewLink Genetics, located in Ames, Iowa, which agreed to develop and manufacture the vaccine with Merck & Co. This is also a vector vaccine, based on an attenuated vesicular stomatitis virus, which is a live-stock pathogen, with one gene replaced by an Ebola virus gene.¹³

Other vaccine candidates are also entering the experimental phase in humans. In particular, New Jersey-based Johnson & Johnson, jointly with a biotech company Bavarian Nordic, has begun testing an Ebola prime-boost vaccine (Ad-Vac plus MVA-NB). After gathering initial safety data from phase 1 trials, GMP (Good Manufacturing Practices) produced vaccine doses will be available for phase 2, to be approved and initiated in affected and non-affected countries at the beginning of the year.¹⁴ Finally, Companies like Novavax, which is testing a recombinant nanoparticle vaccine, and governmental institutions in Russia and China, announced they may have vaccine candidates that would undergo clinical trials.¹⁵

Thus, there are several candidates showing promising results. In particular, viral vectored vaccines appear to be the best candidates, since inactivated Ebola virus and subunit vaccines using recombinant expressed purified viral proteins resulted not protective, or only partially protective, in animal models.¹⁶

However, fundamental questions about correlates of protection still exist, and although humoral immunity (glycoprotein-specific ELISA IgG titers) appears to

have the most important role in conferring vaccine protection, the role of CD4 and CD8 T cells remains to be investigated. Obtaining reliable information on correlates of immune protection is particularly important for applying the so-called “animal rule”, consisting in the use of animal data instead of human trials (as usually requested for traditional regulatory approval), when trials are not feasible because outbreaks occur sporadically and unpredictably.⁷

A Race Against Time

As already mentioned, until the 2014 West African outbreak, Ebola could be considered as a neglected tropical disease, and research on drugs and vaccines was rather slow. Although several basic and translational studies conducted by governmental institutions led to the identification of a few candidates, the interest of the industry to develop a vaccine for human use was limited. Now that the epidemic is outpacing the speed with which vaccines may be produced, governments and companies are exploring different ways to plan clinical trials and to scale up vaccine production.¹⁷ Thus, the big challenge is how to expedite a process that may take years to protect frontline workers and to cut down the epidemic. In particular, the main question is how to go ahead after phase 1 trials, in order to get efficacy data and make a safe and effective vaccine available as soon as possible.

The occurrence of a large and long-lasting epidemic is providing an opportunity to test vaccine candidates on the field in large scale trials. In this case, phase II and phase III trials might be conducted simultaneously, in order to provide safety and efficacy data. However, phase 3 trials may not be feasible since incidence rates are declining.

At the beginning of January 2015, WHO announced that, as soon as safety data and dosing information have been accrued, a large 3 arm (cAd3 vs. rVSV vs. placebo), randomized trial on 30,000 front-line workers will start in Liberia. In other 2 trials, different designs will be adopted, using only one vaccine: a stepped-wedge, cluster randomized design

in Sierra Leone, and a ring vaccination design in Guinea.¹⁵ In the stepped-wedge design, clusters of participants are assigned to receive the vaccine sequentially, at one of several times,¹⁸ whereas in the so-called ring vaccination design, an outbreak containment strategy first pioneered during the smallpox eradication program, rings (consisting of about 50 people around each infected individuals) will be randomized to either immediate or delayed vaccination.

Caveats, Obstacles, and Ethical Constraints

There are several obstacles that need to be overcome in order to make a safe and effective vaccine available in the short term. Firstly, one of the main question is whether vaccine candidates should go through the whole experimental phases, up to phase 3 trials. To this purpose, the RCT model is the gold standard to get reliable data on vaccine efficacy. However, with such high fatality rates, administration of a placebo raises ethical problems. As mentioned above, the stepped-wedge design can mitigate this problem, since it compares rates of infection in vaccinated and unvaccinated groups that would be vaccinated at different timepoints, thus avoiding the use of placebo.¹⁹ But a stepped-wedge design could face serious limitations, since the rate of spread of the infection may differ between sites.^{20,21} Moreover, independently on the study design, clinical trials plans should consider the possibility of fluctuating or decreasing Ebola incidence, which could make difficult to estimate correctly the sample size needed to detect vaccine efficacy.²² Another critical point is about possible trial participants, in particular whether they should include only HCWs or all front-line caregivers.²¹ Furthermore, vaccine production and stability issues (i.e., Ebola vaccines require cell-based production and storage at low temperatures [-80°C cold chain distribution and storage]) which may limit the feasibility of trials and future vaccination campaign should be also evaluated^{15,23}. Finally, preparedness for vaccine trials is essential. In the African context, it is important to

communicate with communities and to engage their views, taking into account that some cultures are deeply distrustful of “Western” medicine and foreign medical staff in general, and of vaccines in particular. To this regard, in accordance with WHO recommendations, behavioral scientists, and in particular anthropologists, should be engaged in order to produce results through qualitative research.

At last, post-licensure challenges which may jeopardize immunization programs should be taken into account. The identification of the target population for vaccination is key. Frontline populations, such as health care workers, which include doctors, nurses, and lab technicians, but also hospital cleaners, ambulance drivers, burial teams, mortuary attendants, and, to some extent, even traditional healers are those who should be offered vaccination. With regard to the general population living in areas at risk of emergence of the Ebola virus, decision should be made on the basis of cost-benefit analysis. However, local communities could become upset if international HCWs or politicians are prioritized. In that case, vaccine supplies will require protections.²⁴ Moreover, a few of the vaccinees may be incubating Ebola at the time of vaccination; this may be a problem for vaccine evaluation and community perception.²⁴ Other challenges include modalities of vaccine administration, the communication approach to risks and benefits of the vaccine, and the impact of vaccination strategies on fragile health system, including costs.²⁵

Conclusions

The limited success of traditional public health measures in the containment of the 2014 West African Ebola epidemic has fuelled research and development of safe and effective vaccines. Vectored vaccine candidates, which were demonstrated to confer protection in animal models, have been tested in phase 1 studies and are ready to initiate efficacy evaluation in

phase 2/3 studies. Whether the accelerated process of research, development, and production of effective vaccines will contribute to control the current Ebola epidemic in Guinea, Liberia, and Sierra Leone is unpredictable; however, the availability of such vaccines might be useful in order to protect health care workers and other frontline caregivers in high risk areas.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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