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Prevention of Ebola virus disease through vaccination: where we are in 2018

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In 2016, Guinea, Liberia, and Sierra Leone succeeded in interrupting the longest epidemic of Ebola virus disease in global history.[1] Control of the epidemic was primarily achieved by implementation of effective and coordinated public health measures that involved rapid identification, isolation of cases, contact tracing, and isolation of contacts. However, the risk of re-emergence of Ebola virus disease is real, as shown by the 2017 and 2018 outbreaks in

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Declaration of interests

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the Democratic Republic of the Congo. Consequently, along with other public health measures, efforts to develop an effective vaccine against Ebola virus disease must continue.

As of June 18, 2018, 36 completed trials, seven active and not recruiting, and seven recruiting Ebola vaccine studies are registered on ClinicalTrials.gov. The only study that has been able to provide data on clinical efficacy is the Ebola Ça Suffit vaccination trial in Guinea.[2] This open-label, cluster-randomised trial evaluated vaccine effectiveness in case contacts, where clusters of contacts of Ebola cases were randomised for immediate or delayed vaccination with the recombinant, replication-competent, vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Zaire Ebolavirus (rVSV-ZEBOV). Although the authors estimated the vaccine efficacy to be 100% (95% CI 68·9–100, p=0·0045)[2] in individuals vaccinated in the immediate group compared with those eligible and randomised to the delayed group, the extent of this efficacy has been debated.[3,4] A report by the US National Academies of Sciences, Engineering, and Medicine stated that “the results suggest that the vaccine most likely provides some protection to recipients—possibly ‘substantial protection,’ as stated in the final report. However, we remain uncertain about the magnitude of its efficacy”.[4]

Among other studies of this vaccine, the Partnership for Research on Ebola Vaccines in Liberia I (PREVAIL I) randomised, double-blind, placebo-controlled trial assessed the safety and immunogenicity of the rVSVZEBOV vaccine and the chimpanzee adenovirus type 3-vectored Ebola virus vaccine (chAd3-EBO-Z) in 1500 adults.[5] Compared with the placebo group, more participants in each vaccine group reported injection-site reactions and symptoms such as head ache, muscle pain, feverishness, and fatigue during the week following vaccination. These adverse effects were generally mild and time-limited. Over the 12-month follow-up period, a similar number of serious adverse events were recorded among those vaccinated with the rVSV-ZEBOV vaccine (47 participants; 9%), the chAd3-EBO-Z vaccine (40; 8%), and placebo (59; 12%). Most (71%) of the serious adverse events were attributed to malaria. Immunogenicity data at 1 month post vaccination, the time when the maximum antibody response was achieved, indicated that 71% of those given the chAd3-EBO-Z vaccine and 84% of the rVSV-ZEBOV recipients, compared with 3% of those randomised to the placebo group, had an anti-Ebola glycoprotein antibody response. At 12 months, antibody responses were 64% among those vaccinated with chAd3-EBO-Z and 80% among rVSV-ZEBOV recipients.

Additional safety and immunogenicity data on rVSVZEBOV have been generated in the Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) study, which enrolled more than 8000 health-care and front-line workers in Sierra Leone,[6] and in a trial in Guinea (the Front Line Worker trial [PACTR201503001057193] sponsored by WHO and Médecins Sans Frontières). There have also been eight phase 1 trials[7–10] and a phase 3 safety and manufacturing-consistency trial[11] of the rVSV-ZEBOV vaccine conducted in North America, Europe, and Africa. Collectively, trial data indicate that the rVSV-ZEBOV vaccine has an acceptable safety profile, and that it induces immunity that is durable for at least 24 months in adults (antibody responses for 89–100% of recipients depending on the doses administered).[12] Vaccination strategies involving rVSV-ZEBOV, although not yet licensed, are now used during epidemics through emergency authorisation. During May and June of

2018, more than 3000 individuals were vaccinated in the Democratic Republic of the Congo as part of the WHO response to the Ebola virus disease outbreak, according to the country's Ministry of Health.[13]

Another promising vaccine candidate in advanced stages of development is an adenovirus type 26-vectored vaccine encoding Ebola virus glycoprotein (Ad26.ZEBOV), boosted by a modified vaccinia Ankara-vectored vaccine encoding glycoproteins from Ebola, Sudan, and Marburg viruses as well as the nucleoprotein of Tai Forest virus (MVA-BN-Filo). In a phase 1 study of healthy volunteers (n=87),[14] immunisation with Ad26.ZEBOV and MVA-BN-Filo did not result in any vaccine-related serious adverse events. Seroconversion frequencies of 79–89% were observed as early as 14 days after prime vaccination with Ad26.ZEBOV. Boosting with MVA-BNFilo resulted in sustained elevation of specific immunity.[14] Published phase 1 data show that the combination of Ad26.ZEBOV and MVA-BN-Filo confers durable immunity for at least 360 days and is well tolerated with a good safety profile.[15]

The single-dose chAd3-EBO-Z vaccine regimen has also been studied in clinical trials,[16,17] with less-promising results, particularly regarding antibody responses.[5] One trial tested a prime-boost strategy with chAd3 vaccine followed 2–3 months later by an MVA-BN-Filo booster.[18] This strategy proved to be safe. Regarding its immunogenicity, the chAd3-EBO-Z vaccine boosted with MVA elicited B-cell and T-cell immune responses to ZEBOV that were superior to those induced by the chAd3-EBO-Z vaccine alone, and antibody responses remained positive 6 months after vaccination.[19]

Finally, the recombinant adenovirus type 5-vectored Ebola vaccine was safe and immunogenic in different trials.[20–22] The GamEvac-Combi vaccine (live-attenuated recombinant vesicular stomatitis virus and recombinant adenovirus type 5 expressing the envelope glycoprotein of Ebola virus/*H sapiens*-wt/GIN/2014/Makona-C15 strain) was safe and induced strong humoral and cellular immune responses in up to 100% of 84 healthy adult volunteers.[23]

There are a number of unknowns regarding vaccination against Ebola virus. For example, few data have been generated in children. During the Ebola virus disease epidemic in west Africa, about 21% of patients with the disease were children aged 16 years or under, and the case fatality rate was more than 80% for children under 5 years of age.[24] The index case of the epidemic was probably in a child aged 2 years.[25] Thus, it is essential that these vaccines are assessed in children. In the 2018 outbreak in the Democratic Republic of the Congo, on the basis of the perceived risk–benefit ratio and some preliminary data, children as young as 1 year of age were vaccinated.

Collection of data from pregnant women from past and ongoing studies is also important; very few safety data are available at present, as pregnancy is almost always an exclusion criterion in clinical trials. During the 2018 Ebola virus disease outbreak in the Democratic Republic of the Congo, pregnant women continued to be excluded from vaccination strategies.

Furthermore, few data have been generated among high-risk immune-compromised populations, especially individuals infected by HIV. In the PREVAIL I trial, 5% of participants were HIV-infected, and, compared with non-HIV-infected individuals, their antibody response was lower at 1 month post vaccination: 48% for the chAd3-EBO-Z vaccine group and 62% for rVSVZEBOV vaccine group (*vs* 72% and 85% in non-HIV-infected individuals).[5] Additional data on safety and immunogenicity are needed in specific populations, including elderly people.

The durability and rapidity of immune responses also remain important areas of investigation. Whether the different vaccine approaches, including a prime-boost vaccination strategy, are able to confer longer-term protection remains to be shown. This information is especially important when considering a preventive vaccination strategy for at-risk populations, and specifically for health-care and front-line workers. Ongoing studies are assessing the durability of immunity, but only a small amount of data is available for up to 24 months after vaccination. Additionally, rapidity of an effective immune response is likely to be an important determinant of the relative effectiveness of a vaccine in the context of ring vaccination. In the Ebola Ça Suffittrial, all clusters showed that, at 10 days or more after randomisation, there were no cases of Ebola virus disease among immediately vaccinated contacts and contacts of contacts; however, the majority of cases occurred before 10 days after randomisation in the immediate vaccination group.[2]

The correlation between immune response and clinical protection also remains a crucial, unanswered question. For Ebola virus disease, there is, as yet, no known correlate of protection. However, it remains important to do clinical trials investigating the durability of Ebola-specific immune responses. Ongoing efforts to assess possible correlates of protection include studies of vaccine efficacy and immunogenicity in non-human primates, and studies aiming to elucidate the interactions between Ebola virus disease and the immune system in humans (eg, in Ebola survivors). Should a correlate of protection be shown on the basis of these efforts, the immunogenicity data generated in vaccine studies in humans will be assessed according to that understanding.

Efficacy data from the Ebola Ça Suffit clinical trial show that no cases of the disease were reported more than 10 days after vaccination with rVSV-ZEBOV, whereas most phase 1 and 2 studies have shown that titres of anti-Ebola virus glycoprotein IgG antibodies are not appreciably increased when measured 7 days after vaccination.[5] These findings suggest that whatever early protection vaccines provide against Ebola virus might depend on immune mechanisms that are not measured by serum IgG antibody titres in currently available assays. Development of antigen-specific T cells and their cytokine profiles, as well as the induction of innate immune responses, will need to be directly analysed to understand earlier immune responses.[26,27] Additionally, the correlates of immunity that reflect long-term clinical protection, and whether they are similar or different from those mediating immediate protection, need to be understood.[28] Data from non-human primate models and clinical phase 1 studies of combined Ad26.ZEBOV and MVA-BN-Filo vaccination[15] provide evidence of an important role for cellular immunity, particularly CD8-positive T cells producing tumour necrosis factor α and interferon γ (with or without interleukin 2). To date, no data have been published on cellular immune responses to the rVSV-ZEBOV

vaccine. T-cell responses to Ebola virus glycoprotein could be detected in 80% of volunteers after the prime Ad26.ZEBOV vaccination, were increased after the boost, and were sustained for at least 12 months after the prime in about 90% of volunteers vaccinated with Ad26.ZEBOV and MVA-BNFilo with a 56-day interval.[15]

Another unknown regarding vaccination relates to adverse events. Although few (if any) serious vaccine-related adverse events have been observed, and vaccines are at different stages of development, only additional large-scale trials will enable the overall safety of these products to be fully elucidated. This information is especially important given that the pathway to licensure for an Ebola virus vaccine, in the absence of definitive efficacy data in human clinical trials, might involve alternative regulatory pathways and could require postlicensure assessment of safety and clinical benefit. It is also important to better understand the mechanisms that lead to some of the observed adverse events, especially when these events have not been observed in all clinical trials homogeneously. In a Swiss cohort study[7] investigating the effect of dose on the safety and immunogenicity of the rVSV-ZEBOV candidate vaccine, dose reduction from 10^7 or more plaque-forming units (pfu) to 3×10^5 pfu decreased the occurrence and magnitude of recombinant vesicular stomatitis virus viraemia and reactogenicity, but did not prevent vaccine-induced oligoarthritis in ten (19%) of 53 vaccinees.[7] The incidence of arthritis in the other phase 1, 2, and 3 trials of rVSV-ZEBOV has been lower (<5%) across a large dose range, including doses of 1×10^8 pfu or higher.[2,7,8,10,11,29] A multivariate analysis indicated female sex (OR 2·2, 95% CI 1·1–4·1) and a medical history of arthritis (2·8, 1·3–6·2) as risk factors for the development of arthritis post vaccination. This analysis was done on results from a study conducted in the USA, Spain, and Canada with 1197 participants,[7] and the analysis is now mentioned in the investigator's brochure of the rVSV-ZEBOV vaccine.

The final unknown relates to community engagement and ongoing trust-building throughout the clinical trial process, which are crucial for participant retention and overall community support for the trial.[30] Distrust towards a vaccination trial might exist in the population and negatively affect cooperation with the trial or even lead to suspension, as occurred in Ghana, where two Ebola vaccine trials were suspended because of negative rumours.[31] Embedding social science research in the context of clinical trials can provide valuable insights that can mitigate distrust and support cooperation.

To build on the vaccine research studies that have been done thus far, the outstanding questions on the rapidity and durability of the immune response in adults, safety and immunogenicity in children, and the nature of the responses in immunocompromised and pregnant individuals using different vaccine strategies must be addressed. Improved understanding of humoral and cellular immune responses to Ebola vaccines is needed to identify correlates of protection. Answering these questions will require improvement of global capacity to continue research on Ebola vaccines, and collaborative partnerships are needed to optimise the chances of success. Several Ebola vaccine clinical trials in Africa, North America, and Europe have been done using such partnerships, including the EBOVAC projects, the Ebola Ça Suffit vaccination trial consortium, STRIVE, and PREVAIL.

Against this backdrop, the Partnership for Research on Ebola Vaccinations (PREVAC) was established as an international consortium, including research and academic institutions (the French Institute for Health and Medical Research [Inserm], London School of Hygiene & Tropical Medicine, the US National Institutes of Health, and the Universities of Bordeaux and Minnesota), health authorities and scientists from four Ebola-affected countries (Guinea, Liberia, Sierra Leone, and Mali), nongovernmental organisations (the Alliance for International Medical Action and Leidos) and pharmaceutical companies (MSD, Johnson & Johnson, and Bavarian Nordic). This partnership was built to focus on Ebola research activities to prevent or respond effectively to the next potential Ebola outbreak. This consortium is currently conducting a randomised, double-blind, placebo-controlled trial of three Ebola vaccine strategies in adults and children (aged ≥1 year): (1) rVSV-ZEBOV prime without boost; (2) rVSV-ZEBOV prime followed by a rVSV-ZEBOV boost; and (3) Ad26.ZEBOV prime followed by MVA-BN-Filo boost. As of June, 2018, more than 2350 adults and children have been recruited, and an additional 2500 enrolments are planned to achieve the target enrolment.

In summary, it is important to investigate different scenarios for vaccination strategies and different vaccines to respond more effectively to future outbreaks. These strategies include contact and post-exposure vaccination, targeted preventive vaccination, and widespread preventive vaccination of at-risk populations such as health-care workers and those residing in areas of re current outbreaks.

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