Questions and Answers

*Ebola ça suffit! - Phase III Vaccine Trial in Guinea*

*Updated 8 March 2016*

**Key dates for the Ebola ça suffit! - Phase III Vaccine Trial in Guinea**

The Ebola Phase III vaccine trial in Guinea – *Ebola ça suffit* - began in March 2015. Just four months into the trial, The Lancet and WHO published preliminary results showing a high level of efficacy for the vaccine. Final results are expected in the second quarter of 2016, barely over 12 months after the start of the trial.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>March 23, 2015</td>
<td>Start of trial – Pilot phase</td>
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<td>April 1, 2015</td>
<td>First randomized ring enrolled</td>
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<tr>
<td>July 26, 2015</td>
<td>Randomisation stopped, all rings enrolled after this date were assigned to immediate vaccination</td>
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<td>July 31, 2015</td>
<td>Publication of interim results¹</td>
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<td>November 3, 2015</td>
<td>Last participant vaccinated</td>
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<td>January 29, 2016</td>
<td>Last follow up visit</td>
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<td>March 1, 2016</td>
<td>Locking of the clinical trial database and transfer to the manufacturer</td>
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<td>Second quarter, 2016</td>
<td>Publication of the final results of the trial</td>
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**What is the current status of the trial?**

- The week of 26 October to 1 November 2015, saw the last confirmed case of Ebola Virus Disease (EVD) in Guinea;
- On November 23 2015, the Data Safety Monitoring Board (DSMB) recommended that the trial stop recruiting and vaccinating participants 30 days after the last case of EVD in Guinea;
- On 29 December 2015, WHO declared the end of Ebola virus transmission in the Republic of Guinea (42 days after the date of onset of symptoms of the last confirmed case);
- On December 31 2015, the *Ebola ça suffit!* trial stopped recruitment and vaccination of participants.
- On March 1 2016, WHO transferred the locked clinical trial database to the manufacturer (Merck)

As follow-up of all volunteers for up to 84 days after vaccination is completed as well as completing data entry and validation procedures (see below). The trial team has now been disbanded.

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What are the remaining steps leading to the availability of final results?

In accordance with Good Clinical Practice (GCP)\(^2\), WHO, as the sponsor of the trial, has ensured that GCP and agreed data management procedures were implemented, including those concerning handling of data, data verification, conduct of statistical analyses, and preparation of study reports.

Three main steps have now been completed:

**Step**
1. Data management and data verification
2. Data analyses as per the Statistical Analysis Plan for the trial
3. Preparation of the Clinical Study Report (CSR) for the relevant national Regulatory Authorities

Following data verification, the locked database was transferred to the vaccine manufacturer (Merck) to inform submission to relevant national regulatory authorities for registration of the vaccine.

The final results of the trial will be submitted for publication in an international scientific journal to allow for a peer review process and broad dissemination. In addition, the data and final trial results will be shared with the Government of Guinea and the relevant authorities involved in the national and international Ebola response, and with the communities who participated in the trial. It is not possible to anticipate the exact date of availability of the final results, but it is expected that final efficacy data will become available in the second quarter of 2016 if all goes according to current plans.

What exactly was done to make the trial results available?

As per Good Clinical Practice guidelines, as soon as the last follow-up visit was completed (Jan 29, 2015) the process of data management and data analysis was finalized; in other words:

- Conversion of the data collected using Case Report Forms (CRFs), into electronic data that can then be statistically analyzed;
- Validation to ensure the most accurate ‘clean’ set of data is provided for statistical analysis. This an integral part of the data management process and in this trial it involves 100% independent monitoring of the reported trial data to ascertain that they are accurate, complete and verifiable from source documents;
- Check by independent data management team of data against the pre-defined validation rules to detect missing values, outliers, inconsistencies;

- Data validation using descriptive statistics;
- Rapid query generation and problem resolutions including review validation outputs, confirmation of queries and documentation using query sheets, update of electronic CRFs and data base, with oversight by independent monitors;
- Data analyses as per the Statistical Analysis Plan for the trial
- Preparation of the clinical study report to be submitted by the manufacturer to the relevant regulatory authorities. This includes: the clinical and statistical description, and analyses with appendices containing such information as the protocol, sample case report forms, investigator-related information, information related to the test investigational product including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output.

This is required to ensure compliance with Good Clinical Practice and document that all data is collected, verified and analyzed in the appropriate manner to preserve the scientific integrity of the study.

**Besides the clinical trial in Guinea, are there other clinical trials using the VSV-EBOV candidate vaccine being conducted in Africa?**

Yes, there are five clinical trials being conducted in Africa using the VSV-EBOV candidate vaccine. Below is a summary of their status using the information that is publicly available.

For information on other vaccine trials with this vaccine and other vaccines in Africa and elsewhere please consult the International Clinical Trials Registry Platform[^3].

[^3]: [http://apps.who.int/trialsearch/default.aspx](http://apps.who.int/trialsearch/default.aspx)
## Overview of VSV-EBOV candidate vaccine trials in Africa as of Jan 20, 2015

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Country</th>
<th>Study type/Primary outcomes</th>
<th>Date of first enrollment</th>
<th>Status</th>
<th>Results publicly available?</th>
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<tr>
<td>STRIVE (Sierra Leone Trial to Introduce a Vaccine Against Ebola)⁴ ⁵</td>
<td>Sierra Leone⁶</td>
<td>Phase 2: 3/ Laboratory-confirmed Ebola &gt; 21 days following vaccination; occurrence of Serious Adverse Events during 6 months following the vaccination</td>
<td>April 2015</td>
<td>Closed to recruitment, follow up continuing</td>
<td>No</td>
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<tr>
<td>Ebola ça suffit! Ebola Vaccine Ring Vaccination Trial⁷</td>
<td>Guinea</td>
<td>Phase 3/ Laboratory-confirmed Ebola &gt; 10 days following vaccination</td>
<td>March 2015</td>
<td>Closed</td>
<td>Methods published in July 2015⁹ Preliminary results published in August 2015⁸</td>
</tr>
<tr>
<td>PREVAIL (Partnership for Research on Ebola Vaccines in Liberia)¹⁰</td>
<td>Liberia¹¹</td>
<td>Phase 1 and, Phase 2-3 Adverse events. [Time Frame: One month] Immunogenicity measures (ELISA and neutralization antigen-specific assays for antibody. [Time Frame: One month]</td>
<td>January 2015</td>
<td>Recruiting</td>
<td>Preliminary results for Phase 1 announced in a news release in March 2015¹² Design procedures and challenges published on January 2016¹³ Results presented at CROI meeting (February 2016)</td>
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<tr>
<td>Study to Evaluate the Safety and Immunogenicity of the Ebola Virus Vaccine Candidate¹⁴</td>
<td>Lambarène, Gabon</td>
<td>Phase 1/ Open-Label, Dose-Escalation/Safety and tolerability</td>
<td>January 2015</td>
<td>Closed to recruitment, follow up continuing</td>
<td>Preliminary results published on April 2015¹⁵</td>
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<tr>
<td>A Study to Find Out if the New Ebola Vaccine is Safe and Stimulates Immunity That</td>
<td>Kilifi, Kenya</td>
<td>Phase 1/ The nature, frequency, and severity of adverse events and/or serious adverse events with causal link to the study</td>
<td>December 2014</td>
<td>Closed to recruitment, follow up continuing</td>
<td>Preliminary results published on April 2015¹⁷</td>
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⁴ Source: International Clinical Trials Registry Platform⁴  
⁵ [http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02378753](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02378753)  
¹⁰ [http://apps.who.int/trialsearch/Trial2.aspx?TrialID=PACTR201403001000000](http://apps.who.int/trialsearch/Trial2.aspx?TrialID=PACTR201403001000000)  
¹³ Kennedy SB, Neaton JD and Lane CH (2016)  
[http://ctj.sagepub.com/content/early/2016/01/08/1740774515621037.long](http://ctj.sagepub.com/content/early/2016/01/08/1740774515621037.long)  
When will the vaccine be available to all the populations in the affected countries?
The VSV-EBOV candidate vaccine is not a licensed product, and it cannot therefore be recommended at this time for use in a public health setting. Current evidence from the trial suggests that the vaccine is effective against Ebola and that “ring vaccination” (vaccinating contacts and contacts of contacts of an Ebola case) is a promising approach to halt transmission.

What will happen between now and the time the vaccine is licensed, should there be new cases?
WHO is currently assessing the vaccine manufacturers’ dossier under its Emergency Use Assessment and Listing (EUAL) procedure.18

The EUAL process is designed to expedite the availability of vaccines needed for public health emergencies such as eventual future outbreaks of Ebola, or other diseases for which there are no proven or registered medical interventions. It was established to fast-track assessment of medical products during public health emergencies. Once ‘accepted’ through the EUAL, United Nations’ procurement agencies and Member States may purchase the vaccine for emergency use. EUAL is not prequalification by WHO, but a special procedure implemented when there is an outbreak of a disease with high rates of morbidity and/or mortality and no treatment or prevention options. In such instances, WHO may recommend making a vaccine available for a limited time while further clinical trial data are being gathered for formal regulatory agency review by a national regulatory authority.

Until the vaccine receives regulatory approval, MSF has committed to conducting emergency ring vaccinations in any country in Africa affected by a new Ebola outbreak.19 These emergency ring vaccinations will be carried out under the umbrella of Expanded Access/Compassionate use, and the vaccine will be offered only to individuals who give informed consent, in compliances with Good Clinical Practice principles.

How can you ensure safety while fast-tracking the process?
Information on safety is already available from a number of Phase I, II and III clinical trials performed in Africa, Europe and North America. Some of these data have already been published. The WHO Global Advisory Committee on Vaccine Safety, international experts as well as the ethics and regulatory authorities of the countries concerned have examined the data and concluded that the vaccine is safe and induces an immune

16 http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02299683
18 http://www.who.int/en/
response. Fast-tracking of the process has therefore not resulted from cutting corners in the science, but from reducing procedural time lags: for example, by conducting phase II and III trials in parallel; facilitating multi-country joint reviews of trial data by the concerned authorities; accelerating data sharing between reviewers and manufacturers; and harmonizing the requirements of the different ethics and regulatory committees.

If the vaccine supply is limited, how will access be prioritized?
The principles used to prioritize allocation of potentially limited doses of the vaccine should be fully transparent and involve the governments of the affected countries and communities in a participatory, inclusive manner. WHO and partners (MSF, the International Federation of Red Cross and Red Crescent, UNICEF, Gavi the Vaccine Alliance and others) have been working on an International Coordinating mechanism to achieve this.

In brief, using the experience from vaccines for epidemic-prone diseases like Yellow fever, meningococcal disease or cholera, the proposed mechanism aims to put in place a sufficient amount of vaccines and other supplies. Affected countries would have rapid access to this stockpile based on a set of pre-established criteria.

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) will provide scientific and technical advice on the most appropriate vaccination strategy.

Who will fund the vaccines if large-scale vaccination is recommended?
Financial resources are in place to procure and make vaccines available to the Ebola-affected countries. 300 000 doses, if necessary, will be funded by Gavi (the Global Vaccine Alliance) under an agreement it has made with the drug company Merck. In addition, Gavi’s Executive Board approved a US$ 300 million funding envelope in December 2014 to finance roll-out of the vaccines. There are also US$90 million earmarked to support vaccine deployment.

What are WHO and its partners doing to accelerate implementation of vaccination strategies using Ebola vaccines once they are licensed?
A Global Ebola Vaccine Implementation Team (GEVIT) has been created under WHO’s leadership in order to facilitate the collaborative planning for the potential introduction of Ebola vaccines. This team currently associates countries most affected by the current EVD outbreak and important partners (CDC, GAVI, UNICEF, USAID, BMGF), who will be involved in procuring and introducing an Ebola vaccine. The team has been following two main objectives: (1) to support development and dissemination of tools and guidelines, syntheses of evidence to inform

strategies and policies, and community engagement strategies; (2) to provide capacity and work with Ministries of Health and partners to develop and implement their country plans, to enable and facilitate in-country planning, management, and coordination mechanisms including Emergency Operations Centres.