Ebola vaccines, therapies, and diagnostics

Questions and Answers

21 January 2015

This Q&A provides answers to questions about clinical trials and evaluations of potential vaccines, therapies and diagnostics for Ebola virus disease. Additional information about the epidemiology of the disease, as well as infection prevention and control, treatment, and recommendations for travel, can be found at: http://who.int/csr/disease/ebola/faq-ebola/en/

VACCINES

Is there a vaccine to protect against Ebola virus disease?
At this time, there are no vaccines to protect against EVD licensed for use in humans. On 8 August 2014, WHO convened an Emergency Committee on the Ebola outbreak in West Africa. The Committee concluded that the outbreak constituted a Public Health Emergency of International Concern (PHEIC). Since then, evaluation of the most advanced Ebola vaccine candidates has been accelerated.

- Statement on the first meeting of the IHR Emergency Committee on the 2014 Ebola outbreak in West Africa

Which vaccines are in development?
Two vaccine candidates currently being tested in humans are the ChAd3-ZEBOV vaccine, being developed by GlaxoSmithKline, in collaboration with the United States National Institute of Allergy and Infectious Diseases, and the rVSV-ZEBOV vaccine, being developed by NewLink Genetics and Merck Vaccines USA, in collaboration with the Public Health Agency of Canada. Both vaccines have shown to be safe and efficacious in animals.

Johnson & Johnson, in association with Bavarian Nordic, are developing 2-dose vaccination approaches for Ebola using different vaccines for the first and second doses. This approach is known as heterologous prime-boost. The two vaccine candidates are known as Ad26-EBOV and MVA-EBOV.

Novavax, a biotech company, is developing a recombinant protein Ebola vaccine candidate based on the Guinea 2014 Ebola virus strain.

The Russian Federal Ministry of Health is developing a recombinant influenza candidate Ebola vaccine, as well as other approaches. The recombinant influenza candidate is scheduled to start Phase I trials in the second half of 2015. Other products in development include an oral adenovirus platform (Vaxart), an alternative vesicular stomatitis virus candidate (Profectus
Biosciences), an alternative recombinant protein (Protein Sciences), a DNA vaccine (Inovia) and a recombinant rabies vaccine (Jefferson University).

Phase I clinical trials (to test for safety and for dose selection) are underway for both vaccines. Trial participants are healthy adults in countries with no (or very few) cases of Ebola virus disease. For the ChAd3-ZEBOV vaccine, trials began in the United Kingdom and the United States of America in September and in Mali and Switzerland in October. Results from the trial in the United States were published in late November. No safety concerns were identified. Immune responses of trial participants appeared to be in the range reported from preclinical trials involving nonhuman primates. Results of all other Phase I trials are expected by the end of the first quarter 2015.

For the rVSV-ZEBOV vaccine, trials began in the United States of America in October, in Gabon, Germany, and Switzerland in November, and in Canada and Kenya in December. Preliminary results of the first trial in the USA were presented at a research conference in December 2014. To date, immunogenicity results presented by the manufacturer show Ebola antibodies in those vaccinated. The safety profile reported to date is acceptable and supports further evaluation of the vaccine in larger trials.

In January 2015, Johnson & Johnson announced the start of their first Phase I trial, which is taking place in the United Kingdom.

Phase II clinical trials of the ChAd3-ZEBOV vaccine are expected to take place in February 2015 in several countries in West Africa that have no or few cases of EVD. These countries are Cameroon, Ghana, Mali, Nigeria and Senegal. The Phase II trials will test for safety and the capacity to induce an immune response in larger numbers and in broader populations, including the elderly, children, and persons living with HIV.

Phase III clinical trials are planned to start in early 2015 in Guinea, Liberia and Sierra Leone, the three countries most affected by Ebola. The objectives of these trials will be to assess whether the vaccines protect against EVD and to further document safety.

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<th>Pre-clinical trials</th>
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<td>Pre-clinical trials are carried out in laboratories and animals and aim to: 1) determine whether a vaccine works as intended and 2) to identify any harmful effects.</td>
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<th>Clinical trials</th>
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<td>Phase I trials involve 20 to a few hundred healthy individuals and examine safety and immune response. They also identify commonly-occurring adverse reactions.</td>
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Phase II trials involve several hundred to a few thousand people and determine the optimum vaccine composition for achieving protection while ensuring safety.

Phase III trials involve thousands to tens of thousands of people and examine the vaccine's ability to prevent a disease as intended. They also provide further safety information.

Post-licensure monitoring or formal Phase IV trials involve the target population. These surveillance activities identify, through spontaneous reporting systems to health authorities, less common adverse events, events which could occur after a long time, or events that may occur in specific subgroups of the target population.

When will these vaccines be available?
For the candidate vaccines, wide-scale introduction in affected countries will depend on the results of the clinical trials and review by regulatory authorities of vaccine safety and efficacy. Data from all trials is being gathered and analysed as rapidly as possible.

Who will receive the vaccines once they become available?
Clear criteria are needed on how the first treatments and vaccine doses will be allocated. Approaches to prioritization of vaccines and treatments are being developed to identify strategies that will contribute the most to control of the epidemic.

Final decisions on introduction are made by ministries of health. While target populations for mass vaccination are being discussed, experts agree that front-line workers should be among the first to be offered the vaccine.

Will there be a sufficient number of doses available to vaccinate all people in the areas of highest risk?
Efforts to accelerate and scale up vaccine production are ongoing and modelling of vaccine supply and demand is underway. However, it cannot be known at this point how many doses of vaccine will be required to bring the epidemic under control. The number of doses required and their availability will depend on the outcome of clinical trials as well as recommendations and decisions on populations to be vaccinated beyond the trials.

How will the costs of Ebola vaccine introduction be covered?
Intensive discussions have taken place during the last months between Ebola-affected countries, WHO, UNICEF, the Gavi Secretariat, the African Development Bank, the US Centers for Disease Control and Prevention, the World Bank, vaccine manufacturers, civil society organizations and donors to discuss the financing of the purchase and introduction of Ebola vaccines, in the event that the clinical trials are successful and they are recommended for use.

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1 Gavi is an international organization which brings together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world’s poorest countries.
In December 2014, the Gavi Board endorsed plans that could see up to US$ 300 million committed to procure the vaccines, to be used to immunize at-risk populations in affected countries. Up to an additional US$ 90 million could be used to support countries in introducing the vaccines, to rebuild health systems and to restore immunization services for all vaccines in Ebola-affected countries.

Which other treatments, therapies, or devices are available or being evaluated?

CONVALESCENT BLOOD AND PLASMA

Transfusion of convalescent whole blood and plasma has been prioritized for use as an investigational therapy. Convalescent whole blood donated by EVD recovered patients is currently being administered in some Ebola treatment centres in Sierra Leone. Trials using convalescent plasma are underway in Liberia and in planning phase for Guinea.

DRUGS AND MEDICINES

Of the pre-existing medicines that were considered for re-purposing to treat Ebola, many are either being tested or considered for testing in patients with EVD or have already been used in patients with EVD. Several therapies have also been considered for use in treatment, but have been deemed not to be appropriate for further investigation. These drugs have been evaluated by the WHO Science and Technical Advisory Committee on Emergency Ebola Interventions (STAC-EE) and categorized as follows:

- Drugs already under evaluation in formal clinical trials in West Africa. These include favipiravir and brincidofovir.
- Drugs that have been prioritized for testing in human efficacy trials, but for which such trials are not yet underway. These trials may include the following: Zmapp, TKM-100802, AVI-7537, BCX-4430, and interferons.
- Drugs that have already been given to patients for compassionate reasons or in ad hoc trials, including: Zmab; amiodarone; irbesartan + atorvastatin +/- clomiphene; and FX06.
- Drugs that demonstrate promising ant-Ebola activity in vitro or in mouse models, but for which additional data should be generated prior to proceeding to clinical trials. These include: azithromycin; chloroquine; erlotinib/sunitinib; sertraline; and clomiphene.
- Drugs that had been prioritized or considered for prioritization and have now been deprioritized based on new data or more detailed analysis of old data. There is a single drug in this category, namely toremiphene.

Categorization and prioritization of drugs for consideration for testing or use in patients infected with Ebola
WHO continues to work closely with all relevant stakeholders on each of the potential therapies and vaccines to continue to accelerate identification, verification, development, and, if safety and efficacy are found, deployment.

- [Statement on the WHO Consultation on potential Ebola therapies and vaccines](#)
- [WHO Meeting on the Scientific and Technical Advisory Committee on Experimental Ebola Interventions – Briefing Note](#)

**DIAGNOSTICS**

**How is Ebola virus disease (EVD) diagnosed?**
The symptoms for EVD are similar to the onset of many diseases, including influenza and malaria. The best way to diagnose whether someone with suggestive symptoms is infected with EVD is by taking a body sample, such as blood, and sending it to a laboratory that is properly equipped to handle potential Ebola specimens. In some cases, this may be a biosafety level (BSL) 3 or 4 laboratory in a neighbouring city or country. In field situations, mobile laboratories can be established in order to reduce the time between transport of the specimens and return of results. In the case of EVD, the delay caused by the need to transport specimens creates significant logistical problems with the management of potential but unconfirmed cases of EVD.

**Which in vitro diagnostics (laboratory tests) are needed in the current epidemic?**
Laboratory support, including the use of accurate diagnostic testing, is crucial for the interruption of transmission of EVD and is necessary to confirm suspected cases, guide triage and clinical decisions, aid contact tracing, and facilitate early detection of cases in individuals with previous exposure. It also underpins effective case detection and quarantining of patients.

Ideally, in vitro diagnostics for EVD should be rapid, sensitive, safe, and easy to use. Testing procedures should involve fewer than three steps, produce results in 30 minutes, and have no biosafety requirements beyond the wearing of personal protective equipment. Additional operational specifications pertain to the easy storage and reconstitution of reagents and staff training that takes less than half a day. In general, the ideal test and related portable equipment should need no power supply and require no maintenance.

**Urgently needed: rapid, sensitive, safe & simple Ebola in vitro diagnostic tests**

In September 2014, WHO called on manufacturers to develop rapid and easy to use point-of-care in vitro diagnostics that are better suited for use in the affected countries, where health infrastructure and trained personnel are largely lacking. The call was followed by a consultation, on 12 December 2014, where diagnostic experts joined WHO and the NGOs FIND and MSF to plan for accelerated development, production, and deployment of adapted and rapid Ebola tests.
As a result, two types of rapid in vitro diagnostics are expected to be ready in early 2015. The most promising type is a rapid, integrated nucleic acid PCR in vitro diagnostic, which is believed to be more effective in case finding. This type of test detects the virus’ nucleic acid. The other type is an antigen detection test that is easier to use but may be less reliable. Several in vitro diagnostics of each type (and from multiple companies) are already in early phases of evaluation.

What is WHO doing to ensure that in vitro diagnostics for diagnosing Ebola are of good quality?
In September 2014, WHO’s Prequalification Team introduced an emergency procedure under its Prequalification Programme for rapid assessment of Ebola virus in vitro diagnostics for UN procurement to affected countries. The first in vitro diagnostic was accepted in November 2014. The invitation to submit an application for assessment is still open. It can be found at the following website: http://www.who.int/diagnostics_laboratory/procurement/purchasing/en/

What types of in vitro diagnostics will be assessed in the Emergency Use Assessment Mechanism?
Although there are a variety of in vitro diagnostics that will be used during the current outbreak, WHO is prioritizing those applications for in vitro diagnostics that detect either Ebola virus RNA or Ebola virus antigen in symptomatic patients.

What aspects will be assessed by the Emergency Use Assessment Mechanism for in vitro diagnostics?
WHO assesses the following:
- documentary evidence of the applicant’s manufacturing capability and competence (through evidence of an effective quality management system);
- any documented performance and stability data generated during development of the product; and
- potential biohazards associated with the use of the product (including how the manufacturer ameliorates residual risks).

If the product is considered of acceptable quality, WHO will then organize an independent evaluation of the claimed limit of detection, as well as conduct a limited evaluation of its clinical performance using specimens from the current outbreak.

What other devices or equipment are available for treatment of EVD?
Integral to the safe and effective treatment of EVD is the need for appropriate personal protective equipment and essential medicines for providing supportive care to persons with Ebola. A list of equipment and medicines can be found below.
- Medical devices and biomedical engineers needed in response to the Ebola outbreak
What are the ethical considerations for use of unregistered interventions?

On 11 August 2014, WHO convened an Ethics Panel to consider and assess the ethical implications of the potential use of unregistered interventions. The panel reached consensus that in the particular circumstances of this outbreak, and provided certain conditions are met, it is ethical to offer unproven interventions for which the safety and efficacy have not yet been demonstrated in humans as potential treatment or prevention. Key conditions relate to the evidence and ethical basis for the assessment of each intervention. There should be a strong scientific basis for the hypothesis that the intervention will be effective against EVD in humans: the unregistered interventions to be offered should have been demonstrated to be safe and efficacious in relevant animal models, and in particular, in non-human primates. In addition, use of such interventions should be based on the best possible assessment of risk and benefit from the information available at a given time.

Ethical criteria must guide the provision of such interventions and should include: transparency about all aspects of care; informed consent; freedom of choice; confidentiality; respect for the person; preservation of dignity; and involvement of the community. The panel advised that there is a moral obligation to collect and share all data generated, including from treatments provided for compassionate use. In addition, several areas where identified that need more analysis and discussion:

- ethical ways to gather data while striving to provide optimal care under the prevailing circumstances;
- ethical criteria to prioritize the use of unregistered experimental therapies and vaccines; and
- ethical criteria for achieving fair distribution of therapies and vaccines in communities and among countries.