WHO Ebola R&D Effort – vaccines, therapies, diagnostics

30 January 2015 update

Since August, when the Ebola outbreak was declared a global public health emergency, WHO has convened a series of consultations and high-level meetings with key experts and stakeholders involved in the research, development, regulation and funding of potential medical solutions for Ebola. Based on concerted expert advice, the best evidence available, and ethical oversight, WHO has prioritized a number of products for further investigation through human testing. These products now include three lead candidate vaccines (with a possible fourth slated for clinical trials in the near future), a shortlist of antivirals and experimental drugs, and convalescent whole blood and plasma. In addition, WHO is working on a number of emergency procedures with countries and other partners for assessment and fast-track development of adapted diagnostics, as well as joint reviews of vaccine clinical trial protocols to expedite study approvals and potential large-scale introduction.

Vaccines

Two vaccine candidates started human clinical trials in September and are about to enter phase II and III trials in a number of African countries, including the three affected countries. The vaccines are cAd3-ZEBOV, developed by GlaxoSmithKline (GSK) in collaboration with the United States National Institutes for Health, and the rVSV-ZEBOV vaccine, developed by the Public Health Agency of Canada and licensed to NewLink Genetics, who recently licensed the product to Merck Vaccines USA. These two vaccines' manufacturers presented promising safety data at a WHO high-level meeting on Ebola vaccines on 8 January this year.

A third vaccine candidate developed by Johnson & Johnson (J&J) is in phase I trials in the United Kingdom and is planned to start further studies in Africa in the coming weeks and potentially a large-scale efficacy trial in Sierra Leone in the second trimester of 2015.

A number of other vaccines are in the development pipeline. These include a vaccine being developed by Novavax and others being developed in China, Russia and the USA.

Phase II and III trials imminent - The GSK and Merck vaccine candidates are about to enter phase II and III trials in a number of African countries, including the three affected countries. Three phase III trial collaborations are planned: a ring vaccination trial in Guinea, organized through a large international collaboration including WHO and MSF; a randomized-controlled trial in Liberia, under a Liberian government – US-NIH collaboration; and a stepped-wedge trial in Sierra Leone under a Sierra Leonean-US-CDC collaboration. Each trial will test the efficacy of a single dose of one or both vaccine candidates. In the meantime, phase II trials of the GSK vaccine are slated to start in Cameroon, Ghana, Mali, Nigeria and Senegal in the coming weeks.

Production capacity adequate - At a WHO high-level meeting on Ebola vaccines on 8 January the manufacturers assured the international community that enough supplies would be available for testing, with production capacity for several million doses, in case of deployment.

An effective vaccine will be an asset however the epidemic evolves – While the current course of the epidemic may be narrowing the window of opportunity for testing the vaccines' efficacy, there is consensus that an effective vaccine would be an invaluable addition to the tools currently used to end the outbreak. A vaccine may be necessary to eliminate the disease should current control

measures succeed in bringing transmission down to very low levels, and would act as an insurance policy against future outbreaks.

Continued efforts in community engagement - Strong emphasis is being given to effective communication and engagement with communities, both to build trust and allay concerns about clinical trials and vaccination campaigns. Work to sensitize health workers and communities at trial sites has been ongoing since November, in collaboration with UNICEF and civil society.

Funding for up to 12 million doses - A December meeting of Gavi's (the Vaccine Alliance's) Executive Board endorsed a US$ 300 million funding envelope for the purchase of up to an estimated 12 million doses of vaccine.

Regulatory pathways are being finalized - WHO is facilitating a process to devise an emergency regulatory pathway, with the aim of enabling the rapid introduction of vaccines for clinical trials and general distribution without any compromise of scientific standards or rigour. Regulators from the affected countries and from the wider African region have committed to working closely on these matters with WHO and with manufacturers and trial sponsors. For their part, manufacturers have stated their readiness to generate whatever data are required for licensure.

http://www.who.int/medicines/ebola-treatment/emp_ebola_vaccines/en/

Treatments

Blood and blood products

Convalescent whole blood donated by Ebola recovered patients is currently being administered in Sierra Leone in a trial run by the government. A trial of convalescent plasma has begun in Liberia – under the auspices of ClinicalRM (a clinical research organization) with the US government and the Bill and Melinda Gates Foundation; and Guinea is planning to start a plasma trial in the next weeks through a partnership between its National Blood Transfusion Service, institutes in Belgium, the UK, France and MSF.

So far, plasma trials have not managed to enroll a sufficient number of patients to provide evidence of efficacy. Efforts are being made to identify alternative sites for the studies, but preparation of clinical trial sites is technically and operationally complex. Data from whole blood trials in Sierra Leone is currently being analyzed.

Assessments of national capacities for delivering safe blood products outside of clinical trial settings and plans for recovery and strengthening of national blood transfusion services in the three countries are expected to continue in the coming months. In addition, WHO in collaboration with partners is establishing standards for the therapeutic use of antibodies.

Medicines

A number of pre-existing medicines already approved for treating non-Ebola diseases have been considered for re-purposing to treat Ebola because they have demonstrated efficacy against the virus in test tubes (in vitro). The advantage of considering re-purposing of drugs is that these are readily available, and their safety is known.

A clinical trial of the drug favipiravir (Toyama, Japan), has started in Guinea. Trials are being run by Inserm, MSF and the Guinean government and initial results are expected in the coming weeks. One other re-purposed drug, amiodarone, has been used to treat patients in Sierra Leone outside of a clinical trial setting, but it is unclear whether it provides any benefit.

Other products that are still under development and are not registered for any disease are also being taken into small efficacy trials early in 2015. One of these is brincidofovir (Chimerix, USA), which was originally developed for treating cytomegalovirus but has activity against Ebola virus.

Others are medicines that were specifically developed for Ebola, including the monoclonal antibody cocktail ZMapp (Leafbio, USA) and small inhibitory ribonucleic acid (siRNA) (Tekmira, USA, Canada). All of these have been used compassionately in a few expatriated Ebola patients.

Sierra Leone is planning an ethics review for trials involving both siRNA and brincidofovir. ZMapp is being tested in a small-scale clinical trial in the UK under the auspices of Oxford University. Initial data from this trial should be available in February.

The scientific community is currently testing in non-human primates a wide range of other drugs that have been proposed as potential therapies and will be taking the most promising into clinical trials.

http://www.who.int/medicines/ebola-treatment/emp_ebola_therapies/en/

Diagnostics

In September, WHO introduced an emergency procedure under its Prequalification Programme for rapid assessment of Ebola diagnostics for UN procurement to affected countries. The first diagnostic was accepted in November. In the same month, WHO called on manufacturers to develop rapid and easy to use point-of-care 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, where diagnostic experts joined WHO and the NGO FIND to plan for accelerated development, production and deployment of adapted and rapid Ebola tests.

As a result, two types of rapid diagnostics are expected to be ready for clinical trials in early 2015. The most promising type is a rapid, integrated nucleic acid PCR test, which is believed to be more effective in case finding. The other type is an antigen test that is easier to use but may be less reliable.

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Looking forward

Sustained alignment between partners carrying out clinical trials is of paramount importance. WHO will continue its facilitator role as trials move forward, in particular by ensuring that national regulatory oversight and patient safety remain top priorities. To that end, a high-level meeting on R&D efforts across preventive and therapeutic areas is being planned for April this year to build on progress so far.

At the same time, WHO is working with Ebola affected countries, development partners and financing institutions to finalise national plans for recovery and building resilient health systems.