1 October - *WHO Consultation on Ebola vaccines: beyond phase 1 clinical trials*

From 29–30 September, WHO organized an expert consultation to assess the status of work to test and eventually license two candidate Ebola vaccines. More than 70 experts, including many from affected and neighbouring countries in West Africa, attended the event.

The expertise represented among participants ranged from the virology of emerging infections, to regulatory requirements that must be met, to medical ethics, public health, and infectious diseases. Heads of clinical research and other executives from the pharmaceutical industry also presented their views.

Some non-African participants came with more than 3 decades of experience working in Africa on other infectious diseases.

Experts on the use of innovative, cutting-edge trial designs also shared their most recent work.

The overarching objective was to take stock of the many efforts currently under way to rapidly evaluate Ebola vaccines for safety and efficacy. The next step is to make these vaccines available as soon as possible – and in sufficient quantities – to protect critical frontline workers and to make a difference in the epidemic's future evolution.

All agreed on the ultimate goal: to have a fully tested and licensed product that can be scaled up for use in mass vaccination campaigns.

Two promising candidate vaccines

Given the public health need for safe and effective Ebola interventions, WHO regards the expedited evaluation of all Ebola vaccines with clinical grade material as a high priority.

Two candidate vaccines have clinical-grade vials available for phase 1 pre-licensure clinical trials.

One (cAd3-ZEBOV) has been developed by GlaxoSmithKline in collaboration with the US National Institute of Allergy and Infectious Diseases. It uses a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted.

The second (rVSV - ZEBOV) was developed by the Public Health Agency of Canada in Winnipeg. The license for commercialization of the Canadian vaccine is held by an American company, the NewLink Genetics company, located in Ames, Iowa. The vaccine uses an attenuated or weakened vesicular stomatitis virus, a pathogen found in livestock; one of its genes has been replaced by an Ebola virus gene.

Phase 1 trials

WHO and other partners have helped facilitate expedited evaluation of these two vaccines in order to generate phase 1 safety and immunogenicity data for decision-making. A series of coordinated phase 1 trials is currently under way or will soon be initiated with international consortia at more than 10 sites in Africa, Europe and North America.

These studies aim to ensure good communication and harmonization of key design elements to allow for merging of data from different trials of the same candidate products.

The trials, which are being conducted in healthy human volunteers, are designed to test safety and immunogenicity and select the appropriate dose. Two phase 1 trials of the cAd3-ZEBOV started in September 2014 in USA and UK, and the first Phase 1 trial of VSV-ZEBOV is due to start early in October in USA.

The government of Canada has donated 800 vials of rVSV-ZEBOV to WHO. Once data on dosing from phase 1 trials become available, this donation could translate into about 1500 to 2000 doses of vaccine.

Both companies are working to augment their manufacturing capacity. The goal is a very significant increase in scale during the first half of 2015.

No delays

One shared mindset was readily apparent during the two-day discussions. Nothing must be allowed to slow down the goal of making vaccines accessible to people in affected West African countries. The phrase, “Nothing can be allowed to delay this work”, was heard over and over again.

The ambition: to accomplish, within a matter of months, work that normally takes from two to four years, without compromising international standards for safety and efficacy.

In other words: to give the African people and their health authorities the best product that the world’s scientists, working collectively, have to offer.

What the experts considered

Against this background, the meeting looked specifically at the objectives and key design elements for moving in an expedited manner to conduct additional clinical trials (phase 2 trial designs) that will generate additional safety data and evidence that the vaccine confers protection.

Parallel pathways for emergency use of experimental candidate vaccines with data collection, among frontline health care workers and other critical personnel, were also explored.

Apart from the great sense of urgency, the overall spirit of the discussions was characterized

by a strong sense of solidarity with the people of West Africa, their governments, and their medical, scientific, and public health communities.

Equally strong was the insistence on ensuring that evidence on safety, immunogenicity, and efficacy of the vaccines is collected properly.

Multiple challenges

Multiple potential challenges and uncertainties were put forward and assessed. Issues ranging from barriers to rapid implementation of R&D, to the design of trials and their use to guide eventual widespread vaccination, were discussed together with proposed ways to overcome them.

Some of the practical issues discussed included how to address communities' perceptions regarding vaccines in general, and vaccine studies more specifically, public expectations for vaccine availability for widespread use, and whether there is an adequate infrastructure in place to rapidly and safely evaluate and distribute vaccines.

One important technical challenge is the fact that the candidate vaccines must be stored at a temperature of minus 80° C.

Further issues that need to be urgently addressed include identifying staff who can conduct trials meeting international standards, logistical issues (such as cold chain needs for the vaccines), and the resources needed to start the studies quickly.

Some of the scientific challenges include how to conduct studies as safely and rapidly as possible to inform decisions about mass production of vaccines and their administration.

Key questions

Discussions focused on the main questions that studies should help address, which part of the research should be conducted in non-affected areas and which part in affected areas, and how such decisions could either help expedite or delay the availability of robust evidence.

One overarching conclusion was that the international community, joining the affected countries as a whole, has a responsibility and a role to play in accelerating the evaluation, licensing, and availability of the candidate vaccines – if proven safe and effective.

For all these reasons, the actions emerging from the consultation clearly identify a role for each of the main stakeholders.

Randomized controlled trials

Regarding the issue of how to accelerate the assessment and licensure of the vaccines, experts reiterated that, if feasible, randomized controlled trials are the design of choice because they provide the most robust data, in the shortest amount of time, to judge whether a

vaccine is safe and induces protection.

Trials must be expedited, while preserving ethical and safety standards. Efficacy data of high quality must be gathered. Trials need to be carefully designed so that they concomitantly address the most important questions regarding safety, immunogenicity, and efficacy.

While individually randomized controlled trials provide the most robust data, alternative designs should be considered when these trials are not judged feasible. These include cluster-randomized and stepped-wedge designs. As long as the amount of vaccine remains limited, units – such as health or treatment facilities – can be randomized. Regardless of the design chosen, trials should move forward as quickly as possible.

Alternative study designs

Alternative study designs will not delay deployment of vaccine to those who need it. Instead, they will influence the choice of people who receive the vaccine. For some months to come, the critical limiting factor is extremely restricted vaccine supply, and not the need to conduct studies using alternative designs.

Descriptions of the so-called “randomized stepped wedge” design attracted lively interest and much discussion. In this design, a “wedge” (like a slice of a pie or a cake) of the study population is selected for step-wise inclusion in the trials.

As each “wedge” receives the vaccine, all lessons learned or needed to adjust the study design are then applied to the next group to be included in the study. The selection of study populations can be randomized by units, as described above; the entire study population eventually receives the vaccine if trials demonstrate sufficient efficacy.

Such a design makes it possible to roll out vaccinations and evaluate efficacy at the same time. It further has features that meet the explicit objective of fairness.

Other designs will be more relevant when large numbers of vaccine doses are available.

Involving countries

Decisions on study designs and target populations must be made with the active participation of experts from the three hardest-hit countries. Consultations with frontline health workers should be undertaken as a matter of urgency to identify the most feasible approaches to evaluate vaccine efficacy and identify factors influencing acceptability of randomized trials.

The experts discussed the importance of making sure that the trials are appropriately designed to inform the use of these vaccines in all populations, including children, pregnant women, and immunocompromised populations, including people who are HIV positive.

The group also discussed how best to use the doses of experimental vaccine donated by Canada and additional doses that may be available later this year and in 2015.

If vaccine doses are used in the short term, vaccines should be deployed to consenting frontline health workers.

The decision to initiate such deployment should be informed by data emerging from the phase 1 studies, and will occur with data collection on the deployment itself.

Equity is important and therefore vaccine should be made available in an equitable and consensual manner to the affected countries. Maximizing the information gained from the use of these vaccines during this phase is critical.

Information sharing

A crosscutting issue is the need for data sharing – in real time – among the research, medical, and public health communities, coordinated by WHO. This was considered of paramount importance to inform decisions on future studies and scaling up the production of those experimental vaccines that look most promising.

Vaccine development normally takes a long time and is notoriously costly. Even under the best conditions and with the massive efforts of many partners, a significant number of doses will not be available until late in the first quarter of 2015.

One important factor for the completion of all the above steps is to secure the funding to ensure the production of the vaccine and to support priority studies. Major international funding partners should promptly pledge or commit the necessary funding so that this critical research is completed without further delay.

The African perspective

The presence of West African researchers, scientists, clinicians, and health officials vastly enriched the discussions, especially concerning the practical dimensions of trial design.

These experts further underscored the importance of communicating with communities and engaging their views, and called for qualitative studies to begin immediately. For example, some cultures are deeply distrustful of “Western” medicine and foreign medical staff in general, and of vaccines in particular.

Interventions from the three hardest-hit countries, Guinea, Liberia, and Sierra Leone, clearly stated that international assistance is both greatly needed and fully welcomed.

Families and entire villages have been shattered. Some communities are on the verge of hopelessness and helplessness. Many do not comprehend what hit them and why, especially as this is the first time that the Ebola virus and Ebola virus disease have been seen in West Africa.

Governments are on board. Clinicians are on board. Researchers and their institutes are on

board.

Statements made by West Africans reminded all participants of what life is really like in these countries. Children do not play in school yards, play pens, fenced back yards, or terraced gardens. They play in the bush.

These realities of daily African life need to be kept in mind when high-risk exposures are considered and defined.

Health workers

Participants were further reminded that the definition of “health care workers” in these African countries includes doctors, nurses, and laboratory technicians but also hospital cleaners, ambulance drivers, burial teams, mortuary attendants, and in some instances, traditional healers.

As hospitals in many areas are overflowing or closed, the number of treatment beds in all three countries is woefully inadequate, and people frequently do not trust the health care system, more and more patients are being cared for by their loved ones in homes or within the community.

These people are also at very high risk of infection and should be considered when priorities for support – in all its forms – are being set. The importance of community engagement cannot be overstated.

Operational changes made since the unprecedented resolutions on Ebola virus disease were adopted by an emergency session of the UN Security Council (on 18 September) and by a UN General Assembly high-level session on Ebola (on 25 September) involve a vast ground-swell scaling-up of international support to affected countries. This support includes a much larger number of medical staff working in countries, thanks to generous support from the governments of China, Cuba, and many others.

Lessons learned

Participants also drew heavily on lessons learned, in the African setting, during trials for candidate malaria, HIV/AIDS, cholera, epidemic meningitis, hepatitis B, and other vaccines.

As some experts noted, never again can the international community allow what boils down to “market failure” to create such catastrophic suffering for humanity in any country, in any region of the world.

The sense of urgency and need for speed, without compromising the integrity of studies or the quality of their data, are fully justified by the dire situation in affected countries and the risk that other countries may soon experience their first imported cases.

The Ebola outbreak currently ravaging parts of West Africa is the most severe acute public health emergency in modern times. Never before in recent history has a biosafety level 4

pathogen infected so many people so quickly, over such a wide geographical area, for so long.

Key expected milestones

October 2014:
Mechanisms for evaluating and sharing data in real time must be prepared and agreed upon and the remainder of the phase 1 trials must be started

October–November 2014**:**
Agreed common protocols (including for phase 2 studies) across different sites must be developed

October–November 2014**:**
Preparation of sites in affected countries for phase 2 b should start as soon as possible

November–December 2014:
Initial safety data from phase 1 trials will be available

January 2015:
GMP (Good Manufacturing Practices) grade vaccine doses will be available for phase 2 as soon as possible

January–February 2015:
Phase 2 studies to be approved and initiated in affected and non-affected countries (as appropriate)

As soon as possible after data on efficacy become available:
Planning for large-scale vaccination, including systems for vaccine financing, allocation, and use.