Second WHO high-level meeting on Ebola vaccines access and financing

8 January 2015

SUMMARY REPORT

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Introduction

A second high-level meeting, convened by the World Health Organization, was held on 8 January 2015 to take stock of efforts to develop and make Ebola vaccines available to communities that have been ravaged by the disease.

The sense of urgency that characterized the first high-level meeting at the end of October was once again apparent and was borne out by the rapid progress made on multiple fronts — progress that has come at an unprecedented pace in the context of vaccine development. By contrast, with the wide-ranging remit of the first meeting, the second high-level meeting focussed more closely on technical issues pertinent to policy makers, with a strong emphasis on maintaining the momentum that has been built in the few short months since October.

The meeting was attended by more than 90 participants representing national and university research institutions, government health agencies, ministries of health and foreign affairs, national security councils, and several offices of Prime Ministers and Presidents. Also represented were national and regional drug regulatory authorities, Médecins Sans Frontières (MSF) medical charity, funding agencies and foundations (Wellcome Trust), and Gavi, the Vaccine Alliance.

Main conclusions reached

- **In the quest for an effective vaccine, safety remains a top priority**

Despite the urgent need for an Ebola vaccine and the unprecedented speed with which vaccine candidates are progressing through development, safety remains of paramount importance. A brief pause in the Phase I trial of one candidate vaccine was announced in December 2014, after concerns were raised about unexpected side-effects. However, after a thorough investigation, it was concluded that it was safe to resume testing. Newly available safety data from Phase I trials of the two most advanced candidates indicate that they are both safe and well tolerated at the highest doses tested.

- **The vaccine pipeline is promising**

Meeting participants were encouraged to learn that there are a number of vaccines in the development pipeline. Two vaccines are completing Phase I studies and a third is about to start in Phase I trials. Attendants also welcomed the news that a number of other novel vaccines are in earlier stages of development, including vaccines being developed in China and Russia.

- **An effective vaccine will be an asset however the epidemic evolves**

Predicting the course of the epidemic is fraught with difficulty, but there was consensus that an effective vaccine would be an invaluable addition to the armamentarium of those who are fighting the outbreak, whatever course it takes. A vaccine may be necessary to eliminate the disease should, as is hoped, current control measures succeed in bringing transmission down to very low levels, and would act as an insurance policy against future outbreaks. In

the worst case, an effective vaccine could help turn the tide in areas where other control measures fail to halt the spread of the disease.

- **The window of opportunity to prove efficacy may be closing**

The meeting heard that, as a result of the recent and extremely welcome falls in case incidence in Liberia and in some areas of Sierra Leone, and the plateauing of the epidemic in Guinea, a point may soon be reached when there are too few cases to prove the efficacy of a candidate vaccine in Phase III trials reliant on clinical outcome measures. It is therefore imperative that correlates of vaccine-induced protection against Ebola virus be characterized as soon as possible and trial designs be as flexible as is feasible to allow for the changing epidemic.

- **Phase II and Phase III clinical trials are imminent**

In light of promising preliminary Phase I data, preparations for concurrent Phase II and Phase III trials are already at an advanced stage. Three trial collaborations detailed their plans for a ring vaccination trial in Guinea, a randomized-controlled trial in Liberia, and a stepped-wedge trial in Sierra Leone. Each group emphasized the leading role played by affected countries and praised the dedication and diligence of their teams in making such rapid progress. Each trial will test the efficacy of a single dose of one or more vaccine candidates, although decisions on candidate and dose selection will hinge on further detailed analyses of immunogenicity data as they become available in the coming weeks.

- **Adequate supplies of vaccine will be available for clinical trials and roll-out**

The quantities in which the three leading vaccine candidates will be available in the short term depend to a large extent on the doses at which they are deemed most effective — a decision contingent on close scrutiny of immunogenicity data soon to be available from Phase I trials. However, manufacturers of each of the three most advanced candidates — GlaxoSmithKline (GSK), NewLink/Merck, and Johnson & Johnson (J&J) — re-emphasized their confidence that there would be ample supplies of each vaccine for Phases II and III testing, with production capacity for over a million doses of each candidate by year end, if required.

- **Logistical issues and community engagement must be addressed**

As at October's meeting, strong emphasis was given to the importance of effectively communicating and engaging with communities, both to build trust and allay concerns about clinical trials and vaccination campaigns. In several cases, work to sensitize health workers and communities at trial sites has been ongoing for over a month. The meeting also learned more about some of the potential logistical hurdles that will need to be overcome prior to Phase III trials and any putative wider vaccination programme. Two of the three most advanced vaccine candidates have cold-chain constraints that could hamper their deployment outside urban areas. Work is ongoing to determine the stability of the vaccine candidates at higher temperatures.

- **Funding is in place for up to 12 million doses**

In an announcement that was given an enthusiastic welcome by all in attendance, Gavi, the Vaccine Alliance presented details of a US$ 300 million funding envelope, approved by its Executive Board, for the purchase of up to an estimated 12 million doses of vaccine.

- **Regulatory pathways need to be finalized**

The meeting heard that WHO has initiated 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 developing countries and from the African region, including affected countries, reaffirmed their commitment to working closely with WHO and with manufacturers and trial groups to provide guidance. For their part, manufacturers stated their readiness to generate whatever data are required for licensure and their eagerness for greater clarity regarding the nature of regulatory conditions to be met in the current extraordinary circumstances.

- **Coordination and alignment among multiple partners must continue**

There was consensus that WHO has assumed a lead coordinating role and a widespread appreciation that the presence of ministers, ambassadors, and senior staff from various institutions and companies at the second high-level meeting had added welcome impetus to the discussions. Both high-level meetings have provided valuable forums for the sharing of information and coordination of action; there was agreement that a further such high-level meeting should take place in the coming months in order to build on progress so far.

- **Crisis must be a catalyst for change**

The meeting concluded that all efforts to develop, test, and approve Ebola vaccines must be followed through to completion at the current accelerated pace, even if dramatic changes in the epidemic's transmission dynamics meant that vaccines were no longer needed to control the current outbreak.

Looking ahead, there was a strong sense that the current crisis presents the world with an opportunity to change how it prepares for and responds to future disease outbreaks. Strong statements were made that the current rush to develop vaccines and therapies for Ebola is a direct consequence of market failure. The meeting heard that, over the past decade, much of the thinking had already been done about how to reconfigure mechanisms for vaccine, drug, and diagnostic development and outbreak readiness to avoid a repeat of the situation the world finds itself in today. What has been lacking is the political will to enact serious reform and there was an impassioned plea for WHO Member States to grant the organization's Director General, Dr Margaret Chan, a mandate for change.

Overview of the meeting's discussions

The senior executives of the three pharmaceutical companies (GSK, J&J, and Merck) whose candidate vaccines are in the most advanced stages of development presented a summary of their latest data, including safety data from the Phase I trials of the two most advanced candidates: GSK's Chad3-ZEBOV vaccine and Merck's rVSV-ZEBOV vaccine. Based on these data, both candidates appear to be safe and well tolerated. Representatives from each company also gave estimates of production capacities to year-end.

Comprehensive Phase I data on the nature of the immune response elicited by the two most advanced vaccine candidates (their immunogenicity) were not available at the time of the meeting. Decisions on which doses are most likely to confer protection, and whether or not an additional booster dose would provide additional protection, must therefore be deferred until a complete analyses of the immunogenicity data has been undertaken. Companies again expressed their willingness to have their vaccines tested alongside each other in the same trials.

Time is of the essence

Widespread appreciation of the startling progress made so far was accompanied by a growing recognition that, as case incidence shows promising signs of declining in the three affected countries, it may soon be too late to demonstrate an effective vaccine if trials are not able to move to the field quickly. There was also widespread acknowledgement that it cannot be assumed that any of the most advanced candidates will be effective. A summary of the many candidates currently in preclinical development, a number of which will soon be ready to progress to Phase I trials, provided some reassurance that there is now a strong pipeline of first-generation candidates.

As was clear during the first meeting, the world's scientific, pharmaceutical, regulatory, and public health communities are aiming to condense a process that normally takes several years into 6 months, with no compromise of international standards for vaccine safety and efficacy. In an effort to move as swiftly as possible to testing the vaccine in the field, each of the three planned Phase III trials will most likely test candidate vaccines using the simplest possible single-dose regimen. Concerns were raised that, on the basis of preliminary analyses of immunogenicity data from Phase I trials, results from human trials of similar vectors, and data from studies in non-human primates and other animals, the levels of immune response elicited by the two most advanced vaccines might not confer durable, complete protection. Points raised in favour of a single-dose regimen were its simplicity, bearing in mind the limited infrastructure available for administration and the potential difficulty of ensuring compliance with a prime-booster schedule. Points raised in favour of a prime-booster schedule were the greater likelihood of such a schedule conferring lasting protection on recipients, and strong arguments were made for the use of a prime-boost schedule for frontline health-care workers, given that compliance is likely to be especially high in this population.

Industry again stressed its commitment to generate whatever data are required to inform regulatory decisions, but they also made clear that, at this time, it is far from clear what

those data requirements are. The meeting was told that an Ebola vaccine target product profile (TPP) would greatly assist manufacturers in ongoing vaccine development and WHO was requested to develop this TPP. Further clarity is also required on what additional data may or may not be required pertaining to the efficacy of vaccine candidates in special populations, such as children and immunocompromised individuals. Work is ongoing at WHO to produce guidelines on emergency regulatory review to support use in an emergency situation. At present, the African Vaccine Regulator Forum (AVAREF) provides a platform for the joint review of Ebola clinical trial applications and work is ongoing to further streamline the process.

Remarks by Dr Chan stressed that decisions about whether or not to introduce a vaccination programme or allow a trial to be undertaken can only be made by countries themselves. WHO will facilitate and support the decision-making process, but ultimately the toughest choices about which technologies to prioritize must be made by governments in consultation with their own experts.

A generational opportunity

On the question of why the world is now rushing to produce a vaccine against a virus that has been known to the scientific and medical community for nearly 40 years, the unanimous answer was that the usual market mechanisms that govern the development of vaccines and therapeutics had failed. Dr Chan called for the world to take advantage of the current crisis and turn it into an opportunity.

Reports from the principal vaccine companies

The meeting heard from senior executives of three pharmaceutical companies (GSK, J&J, Merck, and Novavax) whose candidates are in the most advanced stages of development. The meeting also heard details of Novavax's recombinant glycoprotein nanoparticle vaccine and a Russian candidate vaccine based on an attenuated influenza virus, by researchers at the Influenza Research Institute in St Petersburg with support from the Russian Ministry of Public Health. The Novavax candidate vaccine is due to go into Phase I testing in Australia this month.

Safety