World Health Organization

WHO R&D Blueprint – Ad-hoc workshop on Ebola Vaccines

Deliberations on design options for clinical trials to assess the safety and efficacy of investigational Ebola vaccines

23 January 2019
Wellcome, London, UK

Summary of deliberations and next steps

R&DBlueprint
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1. BACKGROUND

Evolution of the outbreak in the Democratic Republic of Congo (DRC)

As of 23 January 2019, 715 cases of Ebola Virus Disease (EVD) were reported (666 confirmed and 49 probable) in eastern Democratic Republic of Congo (DRC). This outbreak of EVD is affecting two provinces in north-eastern DRC, which border Uganda, Rwanda and South Sudan. Potential risk factors for transmission of EVD at the national and regional levels include: transportation links between the affected areas, the rest of the country, and neighbouring countries; internal displacement of populations; and displacement of Congolese refugees to neighbouring countries. Additionally, the security situation in North Kivu and Ituri continues to hinder the full implementation of outbreak response activities. Since 28 September 2018, based on the worsening security situation, WHO revised its risk assessment for the outbreak, elevating the risk nationally and regionally from high to very high[1].

Progress with the implementation of the SAGE recommendations regarding deployment of rVSV-ZEBOV-GP using the ring vaccination strategy.

SAGE recommends that "should an EVD outbreak due to the Zaire strain occur before a candidate vaccine is licensed, *rVSV-ZEBOV vaccine should be promptly deployed within the expanded access framework, with informed consent and in compliance with good clinical practice. Ring vaccination, as used in the phase-3 study in Guinea, is the recommended strategy for delivery, to be adapted to the social and geographical conditions of the outbreak areas and include people at risk: (i) contacts and contacts of contacts, (ii) local and international health care (HCW) and front-line workers (FLW) in affected areas and (iii) health care and front-line workers in areas at risk due to extension of the outbreak. A geographically targeted vaccination strategy may be considered when it is impossible to identify the individuals who make up ring vaccination cohorts because of serious security, social or epidemiological issues*". As of 20 January 2019, 440 rings have been defined and 63,906 eligible and consented individuals one year of age and older have received rVSV-ZEBOV-GP vaccine. These include 20,526 health care workers (HCWs) and frontline workers (FLWs) and 15,475 children aged 1-17 years of age. In addition, 2642 eligible and consented HCWs and FLWs were vaccinated in the Ugandan areas bordering the two affected provinces in DRC, and a similar effort is underway in South Sudan and Rwanda[2].

The need to seek opportunities to assess additional candidate Ebola vaccines in the context of this outbreak

The SAGE recommendations further state that "*opportunities should be sought to assess the efficacy of other candidate EVD vaccines, such as in health care and front-line workers in areas that are not at high risk for EVD and are thus not eligible to receive the rVSV-ZEBOV vaccine in current study protocols and SAGE recommendations. Particular consideration should be given to the inclusion of pregnant and lactating women into vaccine research. Data on use of the vaccine in paediatric populations in such trials should be recorded (SAGE 2018).*"

Bearing the above in mind, the World Health Organization invited on 23 January 2019 representatives from EVD-at risk countries, international clinical trial experts and experts in the

[1] WHO SitRep, *issued 16 January 2019*
[2] https://www.afro.who.int/news/south-sudan-vaccinates-health-workers-against-ebola

field of Ebola vaccine RCTs (in particular trialists, and statisticians) and representatives of funding agencies and vaccine developers with the aim to outline study designs and the critical steps towards the evaluation of Ebola candidate vaccines in the context of this outbreak. List of participants and summary of Declaration of Conflict of Interest are in Annexe 1.

The objectives of this consultation were: (i) to review and discuss the existing body of evidence of the most advanced candidate vaccines; (ii) to review trial design options and exchange views on potential study design options to be implemented in the context of the current EVD outbreak; (iii) to discuss criteria that could inform national authorities of affected countries on the adequate candidate Ebola vaccines to be selected for evaluation under the proposed clinical trials and; (iii) to discuss a framework for an efficient and sustainable collaborative approach across countries and this and future outbreaks. The Agenda of the meeting is included in Annexe 2.

2. AVAILABLE EVIDENCE FROM EBOLA CANDIDATE VACCINES FOR WHICH DATA FROM PHASE 2 CLINICAL TRIALS IS AVAILABLE.

Thirteen candidate Ebola vaccines have undergone or are currently undergoing clinical evaluation at different trial phases. Evidence on three advanced candidate vaccines that have undergone Phase 2 (but not yet Phase 3) clinical trials were reviewed and discussed at the meeting. A short description for each candidate, as presented by the developers, can be found hereafter. Annexe 3 includes the slides presented by each developer during the consultation.

Adenovirus Type 5 Vector (developed by CanSino Biologics Inc.)

This vaccine is a replication-defective recombinant human type 5 adenovirus expressing Zaire Ebola virus envelope glycoprotein (Makona). Each dose includes two vials (0.5ml/vial) with a total post-reconstitution volume of 1ml, containing 8×10^{10}VP of the replication-defective recombinant human type 5 adenovirus expressing the Ebola virus envelope glycoprotein. Three clinical studies of Ad5-EBOV were completed, including a randomized, double-blinded, placebo-controlled Phase 1a clinical trial among 120 Chinese subjects, an open Phase 1b clinical trial in 61 Africans in China and a Phase 2 clinical trial in 500 Africans in West Africa. In total, 156 subjects were inoculated according to the registration specification (8×10^{10}VP/dose), 78 subjects were inoculated by 4×10^{10}VP/dose and 355 subjects were inoculated by 1.6×10^{11}VP/dose. This vaccine should be stored and transported at 2-8°C.

This vaccine is licensed to use under national reserves by NMPA, China in the event of Ebola outbreak or emergency to prevent the Ebola virus disease caused by the Zaïre strain. A EUAL application was submitted to WHO in July 2018 and is currently under review.

GamEvac-Combi and GamEvac-Lyo (developed by Gamaleya Research Institute)

GamEvac-Combi and GamEvac-Lyo consist of live-attenuated recombinant vesicular stomatitis virus (VSV) and adenovirus serotype-5 (Ad5) expressing Ebola envelope GP of Zaire Ebola virus species (Makona). The formulation of GamEvac-Combi is liquid frozen and that of GamEvac-Lyo is lyophilized. The vaccine regimen consists of a priming immunisation with VSV

followed by a boosting immunisation with Ad5 21 days later. The proposed dose volume of VSV and Ad5 are 0.5ml per dose targeting adults aged 18 to 55 years.

One Phase I/II trial in Russia (84 healthy adults) and one Phase IV trial in Russia were completed for GamEvac-Combi. There is one Phase III trial of GamEvac-Combi in Guinea, Africa (2000 healthy adults) and one Phase I/II trial of GamEvac-Lyo in Russia (220 healthy adults) on-going.

GamEvac-Combi has been licensed in December 2015 by the Ministry of Health of the Russian Federation for emergency use in the territory of the Russian Federation. No EUAL submission was initiated.

Ad26.ZEBOV & MVA-BN-Filo (developed by Johnson & Johnson)

Ad26.ZEBOV is a monovalent replication-deficient adenoviral vector serotype 26 (Ad26) vaccine, which expresses the full-length GP of the EBOV Mayinga variant. MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which expresses the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as Côte d'Ivoire ebolavirus) nucleoprotein (NP). The formulation of Ad26.ZEBOV/MVA-BN-Filo is liquid frozen. The vaccine regimen consists of a prime immunisation with Ad26.ZEBOV followed by a boost immunisation with MVA-BN-Filo 28 or 56 days later. The proposed doses of Ad26.ZEBOV and MVA-BN-Filo are $5X10^{10}$ and $1X10^{8}$ VP/dose respectively. The proposed target population includes adults, human immunodeficiency virus (HIV)-infected adults and possibly children aged ≥ 1 year.
Four Phase I trials were completed: 87 healthy adults in Europe, 164 healthy adults in the United States and 72 healthy adults in Africa. Three Phase II trials were completed: 423 healthy adults in Europe, 200 healthy adults and 200 HIV-infected adults in the United States and Africa, and 669 healthy adults, 142 HIV-infected adults, 132 healthy adolescents and 132 healthy children in African countries. In addition, one Phase II trial in persons aged older than 1 year in African countries and one Phase I/II/III trial on healthy children and adults aged less than 71 years in the United States, Europe and Africa are ongoing. One additional trial was started in 2017, PREVAC (in partnership with NIAID, INSERM, LSHTM), to evaluate the safety and immunogenicity of the vaccine regimen in previously affected countries.

Ad26.ZEBOV/MVA-BN-Filo data has been shared with the US FDA and the company plans to request submit a dossier to seek licensure under the USFDA animal rule. A rolling EUAL submission was submitted to WHO in July/September 2016 and is annually updated. In parallel They are having discussions with EMEA on the potential of an emergency approval. This application also includes a proposal for a rolling submission.

3. POTENTIAL STUDY DESIGNS DEBATED AND CONSIDERED.

On the need, and general principles, for evaluating novel Ebola candidate vaccines in the current EVD outbreak in North-Kivu, DRC.

Participants acknowledged the challenges posed by the ongoing EVD outbreak, including knowledge gaps on chains of transmission, and the socio-economic and security conditions of the areas where the EVD outbreak is taking place in DRC. The epidemiological data presented indicates that the EVD outbreak in DRC occurs in an extremely complex environment, marked

by instability and insecurity among affected communities, that challenges the rapid implementation of control measures, and that remains at risk of expansion in neighbouring areas through persistent EVD transmission in nosocomial and community settings.

Nonetheless, they reiterated the need, previously expressed by the SAGE (2018), to evaluate other Ebola candidate vaccines using the highest scientific and ethical standards possible. They also concurred on the desirability of generating robust and reliable evidence to inform global policy and decision-making at national level in affected countries, through whichever trial designs were selected. It would be an advantage if this evidence were also of value to inform regulatory processes towards licensure of candidate Ebola vaccines.

Recognizing that EVD attack rates are extremely low in the general population even during outbreaks, participants also recognized the need for efficient and inclusive study designs in order to increase chances to provide reliable answers that a given trial is designed to address.

The use of a collaborative Master Protocol was endorsed, designed to potentially extend a given vaccine trial across multiple sites and outbreaks, to accommodate changing and unpredictable epidemic features and to incorporate new stakeholders into the trial.

Moreover, participants highlighted the urgency of implementing such studies and agreed that accelerated steps towards the implementation of the evaluation of at least two novel Ebola vaccines must take place as soon as possible to increase chances of evaluation success and to contribute to control the current outbreak provided the vaccines under investigation are effective. Lastly, it was noted such trials could also provide an opportunity to learn more about the rVSV-ZEBOV candidate vaccine as well, especially on the duration of protection.

Participants also agreed that the conduct of such trials must be integrated into the broader efforts to control the spread of EVD disease and should not interfere with the implementation of outbreak control measures in general and specifically with the implementation of the rVSV-ZEBOV ring vaccination strategy. As a consequence, all individuals eligible to receive rVSV-ZEBOV vaccine ring vaccination, as per the SAGE recommendation, should continue to be offered the rVSV-ZEBOV and should not be included as a target population in a new vaccine study.

It was noted that should a case of EVD arise in the vicinity of the trial population, rVSV-ZEBOV would be offered to those in the ring around the case and local frontline workers, which might include trial participants. It was recognised that in such circumstances this could interfere with the assessment of the investigational vaccine, both with respect to efficacy and safety, which would need to be taken account of in analyses. There is a theoretical possibility that prior receipt of an investigational vaccine might impact on the efficacy of rVSV-ZEBOV, which could be evaluated among vaccine (vs. control) recipients who subsequently receive rVSV-ZEBOV. Participants noted that this could be a secondary endpoint of the study, so these participants still will provide potentially useful information However, preliminary immunogenicity data on other Ebola candidate vaccines suggest that the risk of negative interference is low.

Vaccine trial designs discussed during the deliberations to evaluate at least two Ebola candidate vaccines

The R&D Blueprint vaccine trials expert group had earlier deliberations in October 2017 and on 25 May and 7 June 2018 on potential trial designs that could be considered in order to assess additional Ebola candidate vaccines in EVD outbreak settings.

Under a Master Protocol approach, the Blueprint working group on clinical trial designs proposed the following trial design options which provided the basis for the discussions during this workshop.

Option 1. an individually-randomized placebo-controlled trial (RCT) in those in the highest risk population who are not currently eligible for ring vaccination. The primary objective of this RCT is to evaluate the efficacy of the candidate vaccine in reducing the incidence of EVD. The secondary objective of this RCT is to evaluate the safety and immunogenicity of the candidate vaccine in the target population.
At the meeting, participants discussed the feasibility of using a placebo arm as a comparator in the light of the West-African experience.

Some participants proposed that it may be preferable to use an active vaccine as control, such as measles or hepatitis B vaccine or any other vaccine deemed relevant in the affected area, on the basis that it may be helpful to provide some sort of clinical benefit to study participants not allocated to the investigational vaccine in affected areas.

Other participants argued that a placebo may not be any longer justifiable in relation to Ebola vaccines (Zaire outbreaks), and that these 3 vaccines, however valuable in themselves, amount to a placebo in terms of potential protection against Ebola.

Option 2. a non-inferiority trial against the rVSV-ZEBOV vaccine within rings, provided that there is overall substantial indication of clinical benefit suggested by immunogenicity data of the other candidate vaccines.

Option 2 was reviewed and ruled out because of the acknowledgment that all individuals eligible to receive rVSV-ZEBOV-GP vaccine ring vaccination as per the SAGE recommendation should continue to be offered the rVSV-ZEBOV and should not be included as a target population in a new study.

Also, even if such a trial were conducted in another population, the required study size may be prohibitively large, given the estimated high efficacy of the rVSV-ZEBOV-GP vaccine, at least in the short-term.

Option 3. Administration of Ebola vaccine in a non-randomised way in a target population and then a test-negative case-control study in eligible individuals with Ebola-like symptoms who will be tested for Ebola virus infection in a given geographic area were Ebola vaccination takes place. A test-negative design nested in a randomized study was also discussed. However, experts recognized that randomized clinical trials are potentially much more informative and interpretable than observational studies, and of similar feasibility, and therefore should be used. At the meeting, Option 3 was ruled out for this reason.

In addition to the three trial designs options outlined prior to the workshop, two cluster-randomized designs were also considered at the workshop, noting that randomizing at the

cluster level may increase the acceptability of the intervention compared to an individually RCT, despite their reduced power to answer a research question.

Option 4. A stepped-wedge randomized design. This design would involve the vaccination of HCW/FLWs in health care facilities believed to be at future risk of Ebola, but administer to different groups in a random order, phased over a defined period of time. A list of such facilities would be created prior to study start. Then facilities would be vaccinated with the Ebola candidate vaccine in randomized order according to a predetermined time line.

Vaccine efficacy would be evaluated by comparing the laboratory confirmed EVD illness rate in vaccinated facilities with the rate in unvaccinated facilities not yet vaccinated. The analysis is stratified on time or changes in exposure to Ebola virus over time are modelled.

This trial design has the advantage that all participants would be offered the vaccine by end of the trial and avoids the issue of giving a control injection (placebo or another vaccine). Some participants noted that the order of vaccination must be random within the pre-defined population and using non-random allocation would potentially bias any results.

It has also been argued that the acceptability of the intervention would be higher than with an individual-randomized study. In addition, if vaccine(s) were initially in short supply, randomizing the order of rollout could be considered as a transparent way to allocate vaccine.

This trial design has several disadvantages that were highlighted during the West-African EVD outbreak. The most serious disadvantage is its inflexibility. Study sites and their randomized order must be determined before the first vaccine dose is administered. There is no opportunity to influence the order of vaccination, so that vaccination may start with areas relatively far from the current epidemic. Similarly, it is not possible to add sites in response to changing epidemiology. If the epidemic moves in an unexpected direction, it is possible for the planned trial to be located in the wrong place.

As mentioned above, participants in a stepped-wedge design do not receive a placebo or control injection. Therefore, these designs do not have the strength and robust conclusions of a blinded trial. In an unblinded trial knowledge of vaccination status may change behavior of health workers and the trial participants, and this will confound vaccine effects with behavioral effects.

Another key disadvantage is that the stepped-wedge design is a clustered design whose analysis relies on adjustment for temporal trends, which can increase the variance associated with the results. In addition, because a placebo vaccination is not used, the trial would not be blind and the possibility of differential behaviour between vaccinated and unvaccinated individuals may introduce potential bias. Since randomization is at the cluster-level rather than the individual-level and, the design is statistically less efficient, requiring substantially larger sample sizes (see the sample size calculations in Annexe) than a comparable individually randomized design. If by the end of the trial only a small number of the randomized clusters have experienced Ebola exposure, the information from the trial will be further limited.

Option 5. a *traditional* cluster randomised design where the unit of randomization would be a village, area and/or a health facility, with half of the units left unvaccinated until the end of the study period.

A more traditional cluster randomized design was discussed, in addition to a stepped-wedge approach, noting that acceptability among the affected communities and HCWs and FLWs may be higher than with an individually RCT. The potential enhanced acceptability of such design must be balanced against the substantially larger sample size required compared to an individually RCT. Many of the advantages and disadvantages of this design parallel those discussed above for the stepped-wedge design. Similarly to option 4, the lack of blinding may change behavior of health workers and other trial participants, and this may confound vaccine effects with behavioral effects.

Table 1-Summary of trial designs options that were reviewed at the meeting

	Trial Design	Proposed target population
Option 1	Individually-randomized controlled trial (RCT), using another vaccine or placebo in the control group	1a. In affected areas, people who are listed within a ring but who are not eligible to receive the rVSV vaccine (e.g. pregnant women)
		1b. HCW and FLWs in areas where the outbreak is likely to spread.
Option 2	Non-inferiority trial against the rVSV-ZEBOV	In affected areas, perhaps population eligible to rVSV-ZEBOV and another candidate vaccine
Option 3	Test negative case-control study	A population offered vaccination (without randomisation). Cases and controls will be drawn from those presenting at ETU with EVD-like symptoms in vaccinated areas.
Option 4	Stepped-Wedge cluster randomized trial	In areas where the outbreak is likely to spread, HCW and FLW
Option 5	Cluster-randomized trial	5a. In areas where the outbreak is likely to spread, HCW and FLW 5b. In areas where the outbreak is likely to spread, individuals at high risk of EVD spread (e.g. military, UN peacekeepers, moto taxi drivers and traditional healers)

At the meeting there was consensus that an individually-randomized controlled trial (RCT) in the highest risk population – **Option 1, designs a and b** – among those who are not eligible to receive the rVSV-ZEBOV under the current SAGE recommendations- **should be the design of choice**.

Option 1 was therefore proposed for implementation in two potential studies targeting two different high-risk populations.

Option 1a - Study population would include people at risk of Ebola and who are listed within a ring, as defined by the ring vaccination teams, but who are not eligible to the rVSV-ZEBOV vaccine. This includes pregnant and breastfeeding women and, depending on the selected vaccine, the possibility of including children under age 1 year and other immunocompromised

individuals. In this study, the proposed intervention was a non-replicating Ebola candidate vaccine likely to protect rapidly after the first dose.

NB. In the week following the meeting, a special communication from Ethics Review Committee from the DRC - not available at the time of the meeting - recommended the use the rVSV-ZEBOV in pregnancy after the first trimester and lactating women and children under one year of age within rings. Therefore, the inclusion of these special populations into a vaccine efficacy trial has been subsequently ruled out as an option.

Option 1b - Study population would include HCWs and FLWs not currently eligible to receive the rVSV-ZEBOV vaccine. In this study, FLWs include any workers who, as a function of their profession, may be exposed to an EVD case, such as those serving in the military, UN peacekeepers, moto taxi drivers and traditional healers.

Primary endpoint (all study design options) – laboratory-confirmed EVD illness

There was a consensus that laboratory-confirmed EVD illness should be the primary endpoint of trials and should be used to determine the efficacy or effectiveness of a vaccine in support of the primary objective of any RCT. Laboratory confirmation should be made by PCR at a trial reference laboratory and assessment of EVD illness should build on the current EVD case definition and its assessment procedures. This primary endpoint is similar to the primary endpoint used in the vaccine trial conducted during the 2014-2016 West-African EVD outbreak.

Secondary endpoints (all study design options)

Secondary endpoints should support the primary research question. Immunological endpoints should be measured to assess the immune response to an investigational vaccine in potentially exposed populations and with potential pre-existing immunity to Ebola virus. Such measures might also give better insights on the duration of protection and assist in the determination of correlates of protection. This requires the collection a baseline blood specimen, probably only feasible in a subset of participants, and blood sampling of these participants at different time points after vaccination. The assessment of cellular response was deemed to be unfeasible in such resource-limited settings, although participants recognized that different vaccines may protect through different mechanisms of protection.

In each study option, a subset of participants should be defined to assess the immunogenicity of the investigational vaccine and to account for pre-existing immunity to ZEBOV in the analysis.

Data Monitoring Strategy (all study design options)

It was agreed that study data would not be released unless the trial was stopped, for efficacy or futility, under close DSMB oversight, or by reaching its targeted number of endpoints, to preserve the integrity of the trial and to prevent any premature interpretation of the findings.

The use of a Master Protocol will be essential to allow the continuation of the trial in settings of future EVD outbreaks and to increase the chances of reaching the targeted number of endpoints. Interim analyses to assess efficacy or futility should be based on a statistical monitoring plan agreed *a priori* and can be timed to occur at after reaching a targeted number of events.

The primary analysis will be based on an assessment Per-Protocol and will use a log-rank test for equality of the survival functions, testing the null hypothesis that the investigational has no effect compared with the active control. Vaccine efficacy will be estimated by Cox proportional hazards regression.

CONCLUSIONS

1. In the context of the ongoing EVD outbreak in DRC and in response to the SAGE recommendations that encourage the assessment of the efficacy of novel Ebola vaccines, the group of experts discussed and exchange their views and agreed on clinical trial options.

2. Deliberations were informed by the current SAGE recommendations on the evaluation of novel vaccines, EVD outbreak circumstances in DRC and the characteristics of the most advanced Ebola candidate vaccines.

3. There was consensus that the people currently eligible to receive the rVSV-ZEBOV-GP Ebola vaccine should not be enrolled in any study assessing another Ebola vaccine during the present outbreak and should continue to be offered the rVSV-ZEBOV as part of the EVD outbreak response.

4. Participants agreed that it would be desirable to evaluate at least two Ebola candidate vaccines in populations at-risk of EVD transmission and not eligible to the rVSV-ZEBOV vaccine, as per the SAGE policy, and the trial design must be implemented under a Master Protocol.

5. There was a large consensus that an individually-randomized placebo-controlled trial (RCT) in HCW and FLWs in areas at risk of EVD spread is the preferred approach. In this study, FLWs could include, in addition to medical personnel, any workers who, as a function of their profession, may be exposed to an EVD case, such as those serving in the military, UN peacekeepers, motor taxi drivers and traditional healers.

6. In each study option, a subset of participants will be defined to assess the immunogenicity of the investigational vaccine and to enable account to be taken of any pre-existing immunity to ZEBOV in the analysis.

7. Participants suggested that the suitability of vaccines to be deployed in trials should be should be assessed using a version of the selection framework presented at the meeting.

NEXT STEPS

The agreed overall aim was to promptly develop all the steps and work towards the initiation of trials within 4 weeks if possible.

1. All participants – send comments within one week on the draft framework for selection of a second Ebola Vaccine for use during the outbreak in North Kivu, DRC and areas at risk of outbreak expansion

Within one week, the group will help finalize the criteria presented for selection of candidate vaccine(s) for the study by sending writing comments to the WHO Secretariat. Another independent expert group will be selected to discuss the information provided on each vaccine, together with an update from the manufacturers on the doses available.

The selection of an Ebola candidate vaccine in a given study will be made based on the finalization of the framework for selection.

Once the framework and criteria are finalised, WHO will explore with the manufacturers of the three Ebola candidate vaccines presented at the meeting whether sufficient doses are available for the proposed studies and, if needed, whether a greater supply of their candidate can be produced in order to perform a large-scale study.

2. A protocol writing team - will develop DRAFT protocols within one week.

Within one week, the backbone of a study protocol will be produced, based on the study designs agreed at the meeting and using protocols and SOPs already available from ongoing or planned studies and the protocol will be shared with all participants for their comments. MSF/Epicentre (Option 1a) and the LSHTM teams (Option 1b) offered to help draft one of each of the two protocols selected as best options.

During this timeframe, WHO will provide any necessary information to each team to refine assumptions and calculations as needed in the protocol and will organize TCs to discuss any major issues if they arise.

Within two weeks, WHO will organize a follow-up meeting in DRC to review and discuss with the national authorities and the research partners in the ground representatives from the national regulatory authority and ethics review committee the proposed DRAFT protocol(s) and to assess and address any implementation, logistical, and acceptability issues that may occur.

3. WHO will facilitate interactions among participants and other interested parties to promptly identify sponsors and investigators for the two studies

Within four weeks, in parallel of the drafting of protocols, WHO will convene a consortium of partners and investigators who will implement the studies under a consortium governance framework and in compliance with the Master Protocol approach.

Deliberations among a subgroup of stakeholders after the meeting

The points included in this section do not form part of the deliberations during the workshop in London. They are presented here for transparency purpose and given that they have direct implications for the next steps cited above.

A subgroup of the meeting stakeholders interacted on a bilateral fashion during the days ensuing the consultation. The WHO Secretariat did not participate in the same.

Below is the list of those who were recipients of a message addressed to the WHO Secretariat by the Director of the Wellcome Trust on February 1, 2019.

The main driver of those interactions as reported to the WHO Secretariat was to propose that it was their view that an individually randomised trial was not feasible or desirable in the areas around the outbreak. Most of the deliberations related to the Secretariat. Some of the arguments related include:

- Critical to keep the focus of this on the Public Health and Humanitarian response - Public Health is the defining issue
- Need for clear and urgent plan on implementation – agreement on leadership and coordination from DRC with national and international consortium to support
- A question of prioritisation if/as resources limited – response and support in the 'epidemic zone' itself and/or prevention in wider geographic area to prevent spread.
- Need for the vaccine to be used as part of a study - as pragmatic as possible
- Agreement on a "stepped-wedge" design – detail to follow of the definition of the 'wedge' – health care facilities, geographical area, other
- Continued and where needed enhanced surveillance critical
- Johnson & Johnson have 1.5M vaccine regimens to donate and play full part in consortium
- Based on the scientific rationale (non-replicating nature of the vector); the reassuring outcome of developmental and reproductive toxicity, and the human data, consensus is that the safety risk to pregnant women with the J&J vaccine is low and therefore supports its use in pregnant women in the context of the current outbreak in DRC. To allow proper interpretation of adverse events in this group, further discussions are needed about choice of control groups to allow proper interpretation of any safety signal to compare it to background incidence.

This sub-group of stakeholders argued that if an individually RCT is deemed unfeasible for whatever reasons, then cluster-randomized trials, such as a stepped-wedge design, should be considered. In brief the proposal made can be summarized as follows:

- Open label, stepped-wedge design study in a broad geographical ring around the epidemic zone to enhance health care and frontline workers immunity to prevent further spread of the epidemic.
- "To establish a curtain or barrier around the epidemic".
- Consistent with discussions following WHO meeting
- Needs a DRC led, national and international consortium to come together to lead, coordinate, design and fund the implementation
- Potential discussants/partners – DRC, WHO, LSHTM, UK PHRST, MSF, EU, CanSino, J&J, Wellcome, GloPiD-R, CDC, Antwerp, INSERM, and others

A set of questions have been proposed by this group:

- Who will provide the leadership and coordination for the study?
- What work and planning needs to be done to deliver this, who will do that and by when?
- Who will provide resources – human, logistic and financial?

List of recipients of message addressed to WHO Secretariat (AM Henao-Restrepo) by Dr J Farrar on February 1, 2019, which indicated that a group came together by teleconference on that day includes:

- Prof JJ Muyembe (INRB, DRC),
- M Serafini (MSF, Switzerland),
- M Tatay (MSF),
- R Grais (MSF/Epicentre, France),
- P Piot (LSHTM),
- P Stoffels (J&J, Belgium),
- D Bausch (PHE, UK),
- C Schmaltz (European Commission),
- M Klimathianaki (European Commission),
- J Hoegel (European Commission),
- J van Hoof (J&J), Belgium),
- J Golding (Wellcome, UK),
- P Hart (Wellcome, UK),
- J Farrar (Wellcome, UK).

Annexes

Annexe 1. summary of Declaration of Conflict of Interest

Annexe 2. Agenda

Annexe 3. Presentation on Ebola candidate vaccines

Annexe 4 – Preliminary Sample Sizes calculations for different designs options discussed at the meeting

1. Individually-randomized placebo-controlled trial

Log-rank test using the Freedman method implemented in Stata. All calculations assume two-sided alpha=0.05 and 80% power. The calculations are not adjusted to censoring due to losses to follow-up or censoring due to vaccination with rVSV.

Vaccine efficacy (VE)	# of events	Cumulative incidence over trial period in placebo arm	Sample size per arm
80%	18	0.5%	2943
		1%	1471
		2%	735
90%	12	0.5%	2132
		1%	1066
		2%	533
95%	10	0.5%	1827
		1%	913
		2%	457

2. Non-Inferiority trial to assess candidate vaccine B against the rVSV-ZEBOV

Let p_C be the probability of developing disease in an unvaccinated (control) population. The probability of developing disease in a population vaccinated with rVSV-ZEBOV A is p_A=(1-$\mathrm{VE_A}$)p_C, and the probability of developing disease in a population vaccinated with a candidate vaccine B is p_B=(1-VE_B) p_C.
Sample size calculations are prepared assuming 80% power at the alternative $\mathrm{VE_A}$=VE_B. We assume an exact Poisson test with one-sided Type I error of 0.025. The calculations are not adjusted to censoring due to losses to follow-up or censoring due to vaccination with rVSV.

$\mathrm{VE_A}$	δ	VE_B	# of cases in both arms	p_C	Sample size per arm
90%	20%	70%	65	1%	16,250
				2%	8,125
				5%	3,300
	10%	80%	112	1%	37,334
				2%	18,667
				5%	7,334
	5%	85%	255	1%	102,000
				2%	50,800
				5%	20,800
95%	20%	75%	52	1%	17,334
				2%	8,667
				5%	3,467
	10%	85%	65	1%	32,500
				2%	16,250
				5%	6,500
	5%	90%	111	1%	74,000
				2%	37,000

3. Test negative design

Approximate sample size (# of unique tests) to achieve 80% power to assess $H0$: VE=0 or equivalently $H0$: OR=1 with a two-sided alpha=0.05 test. Assumes that, among the unvaccinated, 50% will test positive and 50% will test negative. The vaccination coverage is the coverage among individuals testing negative.

	Vaccination coverage	Sample size (# of tests)
VE = 70%	5%	798
	10%	390
	20%	202
VE = 90%	5%	324
	10%	162
	20%	81

4. Stepped-Wedge design

NB: This sample size was not discussed at the meeting but is included for ease of reference. Log-rank test using the Freedman method implemented in Stata, adjusted using the design effect for cluster randomized trials. It is assumed that the cluster size will be 200 participants, and the ICC = 0.05, resulting in a design effect of 10.9. All calculations assume two-sided a=0.05 and 80% power.

Vaccine efficacy (VE)	# of events	Average cumulative incidence over trial period to unvaccinated	Number of steps (clusters)	Total number of participants
80%	196	0.5%	160	32079
		1%	80	16034
		2%	40	8012
90%	131	0.5%	116	23239
		1%	58	11619
		2%	29	5810
95%	109	0.5%	100	19914
		1%	50	9952
		2%	25	4981

5. Cluster randomised trial

NB: This specific sample size was not discussed at the meeting but is included for ease of reference.
Calculations of the number of clusters required in each arm were done for attack rates of 1%, 2%, 3%, 4% and 5%, vaccine efficacies of 90%, 70% and 50%, and cluster sizes of 50 individuals, assuming 20% loss to follow up, and power fixed at 90%, with a two-sided alpha=0.05 test.

Vaccine efficacy (VE)	Attack rates within clusters				
	1%	2%	3%	4%	5%
50%	432	215	142	106	84
70%	191	95	63	47	38
90%	98	49	33	24	20