**Strategic Advisory Group of Experts (SAGE) on Immunization**

**Interim Recommendations on Vaccination against Ebola Virus Disease (EVD)**

**7 May 2019**

Over the last four weeks, the Ebola outbreak in the Eastern Provinces of the Democratic Republic of Congo (DRC) has deteriorated with a large increase in the number of cases[1]. A major factor in this rise is an increase in critical security incidents that have dramatically affected the ability to identify, follow up and vaccinate contacts successfully. This context challenges the implementation of ring vaccination based on the identification of contacts and contacts of contacts, as recommended by SAGE in April 2017 and confirmed by SAGE during its April 2019 meeting.[2] Further, a potential vaccine shortage may manifest in case the outbreak expands further and/or is prolonged.

SAGE expressed grave concern about the current worsening outbreak epidemiology and completeness of ring vaccination noting that disease transmission continues to occur notably in locations where ring vaccination cannot be implemented and that a large proportion of new cases continue to arise among unknown contacts. SAGE further acknowledged the work of those involved in the Ebola outbreak response in a very challenging context.

SAGE deliberated on the following recommendations on implementation of novel strategies and adjusted dose regimes:

1. **Implementation of innovative operational strategies.**

Innovative operational approaches are being implemented to address security concerns and community tensions. These innovative operational approaches to implement ring vaccination include:

(i) **Pop-up vaccination** – In this approach, already successfully implemented to address security issues and tensions with the community, rather than setting the vaccination site at the residences of contacts and contacts of a given case (which is how ring vaccination is typically done), vaccination is implemented at an agreed and temporary, protected vaccination site, at a distance from the residence of the contacts, often a health facility) and;

(ii) **Targeted geographic vaccination** – In this approach, already successfully implemented to address security issues, all the contacts and contacts of contacts of all cases reported in a given village or neighbourhood are enumerated and invited for vaccination simultaneously. Again, this is done at a fixed location where security to the teams is provided. Besides addressing the security issues, this strategy allows

[1] WHO Ebola Virus Disease. Democratic Republic of the Congo External Situation Report 39. http://newsletters.afro.who.int/icfiles/1/46425/184054/6134450/97816cb57ede15249d4eb5b5/sitrep_evd_drc_20190430-eng.pdf?ua=1, accessed 7 May 2019

[2] The report of the SAGE April 2019 will be published in the WHO Weekly Epidemiological Record (www.who.int/wer/en/) on 30 May 2019.

the teams to catch up with the increased number of cases without vaccination rings in certain locations.

In view of the implementation challenges, SAGE agrees with the proposed innovative operational approaches, tailored to the local situation, should be implemented to address security concerns.

**2. Revised vaccination strategy to adjust the target population for ring vaccination to include a second and third barrier of immunized individuals around each incident case.**

In order to contribute to interrupting the chain of transmission within the current outbreak, SAGE recommends adjusting the target population for ring vaccination to include a second and third barrier of immunized individuals around each incident case with onset of symptoms within the previous 21 days as follows:

(i) Continue to offer as a priority rVSV-ZEBOV-GP vaccine and vaccinate those at higher risk of Ebola including contacts and contacts of contacts and health care workers (HCWs) and front line workers (FLWs) in affected Aires de Santé.

(ii) Offer rVSV-ZEBOV-GP and vaccinate to those who can potentially be involved in the tertiary generation of cases (e.g. 3rd level of contacts) to create a barrier around the contacts of contacts in affected Aires the Santé. This approach also addresses community requests to offer vaccination to additional members of the community that they consider to be at high risk as they believe this is likely to increase overall community acceptability and;

(iii) Offer a vaccine other than rVSV-ZEBOV-GP to those at some risk of Ebola in Aires de Santé with cases, although at a lower risk than those described in (i) and (ii) above. In order to determine suitability of Ebola vaccines for clinical studies, WHO reviewed data generated by Ebola vaccine manufacturers on two candidate vaccines: the adenovirus 26 vectored glycoprotein / MVA-BN (Ad26.ZEBOV/ MVA-BN) vaccine developed by Johnson & Johnson, and the CanSino-Beijing Institute of Biotechnology (Ad5-EBOV) vaccine.[3] SAGE recommends that these lower risk populations would be vaccinated with the J&J vaccine with informed consent. The latter ideally implemented as per the SAGE recommendation from April 2019 which outlines that studies using other candidate vaccines should be done in this context: "*Proposed studies should be scientifically and epidemiologically justified, have appropriate approvals including from all African and other regulatory and ethics authorities, and have defined endpoints including for safety which can contribute to licensure.*" [2,4]

[3] WHO Ebola Vaccines Decision framework. April 12, 2019. www.who.int/blueprint/priority-diseases/key-action/ebola-vaccine-candidates/en/, accessed 07 May 2019

[4] WHO Meeting summary for the SAGE meeting of April 2019 www.who.int/immunization/sage/meetings/2019/april/SAGE_April_2019_meeting_summary.pdf?ua=1, accessed 07 May 2019

### 3. Alternative dosing for the rVSV-ZEBOV-GP vaccine.

To ensure vaccine continues to be available and offered to individuals at greatest risk of Ebola during this outbreak and in order to secure the availability of the rVSV ZEBOV-GP in the mid-term, SAGE revised the following proposal, based on an analysis undertaken by the U.S. Food and Drug Administration (Appendix 1), to exceptionally adjust the vaccine dose for the currently available lots of rVSV-ZEBOV-GP being used in DRC:

(i) For those at higher risk of Ebola including contacts and contacts of contacts including HCWs and FLWs in the affected areas: offer a vaccine dose with a similar potency to that used in the Guinea Ebola ça suffit trial (i.e. $2 \times 10^7$ pfu).

(ii) For those who can potentially be involved in the tertiary generation of case (e.g. 3rd level of contacts), a 5-fold dose adjustment compared with the current dosing of the vaccine is recommended (in relation to the potency of the vaccine lots being used in DRC). The 5-fold dose reduction in the broader population was motivated on immunological considerations related to dose-response analysis using a 4.8-fold dose reduction in various subpopulations and seroconversion rates in those groups at 28 days after vaccination and later, noting this dosing regimen provides a reasonable risk-benefit trade-off for protection.

SAGE supports the adjusted dosing administration as proposed above. SAGE acknowledges, that since the vaccine is available in 10-dose vials at 1 ml/dose, that a 2-fold and a 5-fold reduction in dose could be readily implemented by injection of 0.5 mL and 0.2 mL, respectively.

SAGE stresses that the terminology used should be determined with caution to avoid the impression that the proposed dosing is sub-standard. Training for vaccinators and adequate standard operating procedures (SOPs) and equipment are needed to ensure the success of delivery of the adjusted dosing.

*Research needs*

SAGE requests that it would be helpful to determine the duration of protections conferred by the adjusted dosing. The response of adjusted dosing used in special risk groups, such as HIV infected needs to be assessed.

Immunogenicity studies of the different adjusted doses head-to-head with full dose of rVSV-ZEBOV-GP vaccine should be conducted preferably in Africa. Further, immunogenicity head-to-head studies between the rVSV-ZEBOV-GP vaccine and other available products would be useful.

Further, all possible efforts in such challenging circumstances should be continued to regularly collect and review safety and effectiveness data, particularly for pregnant women and infants 6-12 months.

4. **Proposal to further adjust the protocol to incorporate alternative individual informed consent forms.**

SAGE was presented with a proposal to further adjust the protocol to incorporate alternative individual informed consent forms that while complying with Good Clinical Practice (GCP) guidelines can expedite the vaccination process. These have been adapted to facilitate the consent process while complying with Good Clinical Practice and simplifying the safety follow up by focusing on passive reporting of serious adverse events by phone. Only pregnant women will be actively followed up until delivery date or end of pregnancy, and a single visit at day 21 will take place for infants 6-12 months of age. Plans are also underway to train additional ring vaccination team members who are from the affected areas and speak the local languages.

SAGE approves the proposal of the adjusting the protocol, highlighting that the adjusted dosing will need to be reflected in the protocol.

5. **Implementation of a mass communication campaign.**

Implementation of a mass communication campaign is proposed, targeting community knowledge, attitudes and behaviours regarding Ebola. In particular, this campaign will communicate the evidence on effect on reduced mortality if admitted early to an Ebola treatment unit, the preventative effectiveness of vaccination and the emerging evidence on the reduced mortality due to Ebola among vaccinated individuals.

SAGE supports the recommendation to undertake a mass communication campaign targeting community knowledge, attitudes and behaviours regarding Ebola. The need for ongoing communication efforts is obvious and investment in social sciences is needed to understand how trust can be built.

**Appendix 1: Summary of data relevant to consideration of adjusted dosing of VSV-ZEBOV (rVSVΔG-ZEBOV-GP) Ebola vaccine**

**Introduction**

To increase the supply of the rVSVΔG-ZEBOV-GP Ebola vaccine in order to provide broader vaccine coverage to at risk individuals, manufacturing data, animal protection data, and immunogenicity data from Phase 1 and 2 clinical studies conducted in various subpopulations were analyzed to inform considerations of adjusted immunizing doses. Adjustment of dosing is associated with potential risk of reduced vaccine effectiveness. However, tolerance for any risk to effectiveness should be informed by risks associated with other options and the number of vaccine doses projected to be needed.

**Manufacturing data**

Potency data for the currently available vaccine lots could support an adjustment in dosage of 2-fold, while still on average approximating the dose that was used in the Guinea Ebola ca suffit ring vaccination clinical endpoint efficacy study (referred to as the "Guinea dose").

Of note, this calculation may be subject to revisions pending release potency data of future rVSV-ZEBOV-GP lots.

**Animal and human immunogenicity data**

Human immunogenicity data derived from six clinical studies (all of which followed subjects for 6 months to one year) in which both the "Guinea dose" and a 6.7-fold adjusted lower dose were evaluated suggest a trend towards higher immune responses with the "Guinea dose;" however, in most of these studies the differences in antibody titers were modest. In two of these studies a dose-response relationship was not observed, moreover vaccination at a lower dose resulted in higher immune responses compared to vaccination with one or more higher doses.

In the two larger studies a major difference in immune responses induced by the "Guinea dose" and the 6.7-fold adjusted lower dose was not observed, while in the four smaller studies, two had results consistent with a difference in immune responses, and two did not show a clear difference.

Since protective response soon after vaccination is critical for ring vaccination, the kinetics of response may be especially important. The trend (albeit with overlapping confidence intervals) towards higher GMTs when using the "Guinea dose" compared to the 6.7-fold adjusted lower dose is also observed at 14 days after vaccination in three studies where this time point was evaluated. This trend in GMT response was consistent with reduced day 14 seroconversion rates at the 6.7-fold lower adjusted dose, which was observed in 2 of the 3 studies. At times 28 days or later post vaccination, human immunogenicity data from these small studies suggest a modest to negligible dose-response relationship in this dose range.

While the relationship between immunogenicity and effectiveness is not established in humans or animals, data from non-human primate challenge studies are generally consistent with immune response and protection being insensitive to immunizing dose.

This also is consistent with the mechanism of action of replicating live-virus vaccines, for which protection is usually considerably less sensitive to immunizing dose than it is for other types of vaccines.

Together, the clinical immunogenicity data and non-human primate challenge study data could support a 2 to 5-fold adjustment in immunizing dose with some uncertainty about using the limited clinical data to support adjustment of potency in settings where rapid immune response is critical (e.g., ring vaccination).

While linearity of the immune response has not been demonstrated, a 2-fold reduction in immunizing dose might be expected to yield immune responses closer to the "Guinea dose", while a 5-fold reduction would still be expected to yield immune responses greater than the 6.7-fold adjusted dose.

In summary, adjustment of rVSV-vectored Ebola vaccine (rVSVΔG-ZEBOV-GP) dosage in the above-described ranges is unlikely to be associated with a reduction in vaccine effectiveness in the context of outbreak control. This assessment is based on the data analyzed. If feasible additional data (for example, from the field) addressing the impact of using adjusted doses of rVSVΔG-ZEBOV-GP should be obtained. Based on a review of the potency data for currently available rVSVΔG-ZEBOV-GP vaccine lots, vaccine could reasonably be considered for ring vaccination at potency adjustment reduction of 2-fold compared to the current dose in use in DRC (so it is comparable to the "Guinea dose"). For more general use (e.g., when rapid evolution of immune response is less critical), based on an analysis of a combination of manufacturing, clinical, and animal data, potency reduction of 5-fold (or half of the "Guinea dose") could be considered.

The following is important in considering adjustment of rVSVΔG-ZEBOV-GP dosing:

1. Use of an adjusted dose is associated with potential risk that effectiveness may be reduced.
2. The more modest the adjustment in dose, the more modest the risk to effectiveness.
3. Tolerance for any risk to effectiveness should be informed by risks associated with other options and the number of vaccine doses projected to be needed (i.e., a critical factor in making decisions about potential vaccine dosage adjustment should be the number of vaccine doses needed and the projections for the availability of additional full-dose vaccine, see 4).
4. Weighing of risks associated with vaccine dosage adjustment should consider the likelihood of vaccine shortages and the potential public health benefits of having greater numbers of doses of vaccine available.
5. This analysis is restricted to animal and clinical data, so there may be other operational considerations in dosage adjustment. For example, adjustment of dosing may require use of different syringes than are used in the current protocol or modification of consent forms currently in use.