SAGE Interim Recommendations on Vaccination against Ebola Virus Disease (EVD)
February 20, 2019

Background

On August 1st, 2018, the Ministry of Health of the Democratic Republic of the Congo (DRC) declared a new outbreak of Ebola virus disease (EVD) in North Kivu Province. The Ministry of Health, WHO and partners are responding to this event, and working to establish the full extent of this outbreak. As of 16 February 2019, 838 cases of EVD have been reported including 773 confirmed cases and 65 probable cases. The number of deaths reported is 534, among these 469 confirmed and 65 probable. (https://www.who.int/ebola/situation-reports/drc-2018/en/).

The province of North Kivu of DRC, which is affected by the outbreak of EVD, is among the most populated provinces, with eight million inhabitants. The region has been experiencing intense insecurity and worsening humanitarian crisis, with over one million internally displaced people and a continuous efflux of refugees to the neighboring countries, including Uganda, Rwanda, Burundi and Tanzania.

The Strategic Advisory Group of Experts (SAGE) on Immunization currently recommends (as stated in the October 2018 SAGE report [1], and previous reports) a ring vaccination strategy and vaccination of health care workers (HCW) and other frontline workers (FLW) with rVSV-ZEBOV-GP vaccine for prevention of EVD. In exceptional circumstances, i.e. settings where because of serious security, social or epidemiological issues, ring vaccination (i.e. identification of contacts and contacts of contacts) cannot be adequately implemented, geographic targeted vaccination is recommended as an alternative strategy. The latter strategy includes vaccination of residents in the geographic area immediately around an Ebola case, such as a village or a neighborhood, that is most likely to include those individuals who were the contacts or contacts-of-contacts of the index case.

Despite the challenging context, by 4 February 2019, 695 rings and two geographic targeted zones were targeted for vaccination. In total 73,298 contacts of contacts have been vaccinated. Of those, 18,895 are contacts of confirmed EVD cases, 22,441 are HCW's and FLW's and 18,117 are children 1 to 17 years of age. In relation to neighboring countries, Uganda has vaccinated 2,642 eligible HCW/FLW in 101 health facilities and vaccination was initiated in South Sudan on January 28, 2019. Plans for vaccination of HCWs and FLWs are advanced in Rwanda and Burundi. All vaccinations are conducted using the experimental rVSV-ZEBOV-GP vaccine with informed consent and in compliance with Good Clinical Practice (GCP).

While the recommended vaccination strategies of the rVSV-ZEBOV-GP vaccine are highly effective, implementation can pose significant challenges. Therefore, consideration of alternative vaccination strategies and the assessment of other experimental vaccines needs regular consideration.

Notably, in this outbreak there have been a substantial number of cases with no a priori known contact with a confirmed Ebola case. Observations suggest that an important number of cases among these so called "unknown contacts" may be linked to nosocomial transmission, which could explain in part why there were no known contacts. Health-seeking behavior of patients with EVD symptoms may increase the risk of EVD transmission, as EVD cases have been typically found to have visited three or more health centers before getting access to care or to an Ebola Treatment Center. In addition, it is recognized that Infection Prevention Control standards can be suboptimal in the numerous health facilities located in areas at-risk of EVD transmission.

Given the continuing high case count and the risk of further spread, members of SAGE reviewed the epidemiological situation, progress in the development of different candidate Ebola vaccines, and modeling results of the potential impact of different Ebola vaccine delivery strategies.

As of 13 February, within the current outbreak in DRC, 57% of the confirmed and probable cases are females (n=472) of whom 61% (35% of total cases) are of childbearing age (15-49 years) using the denominator of overall confirmed and probable cases (n=829).

SAGE considered another vaccination strategy, suggested by the field workers and the DRC's Ministry of Health, called Ring +. This alternative strategy was debated as an option in exceptional circumstances and in settings where there is evidence of nosocomial transmission (and when the number of cases emerging from unknown contacts suggests that effective ring definition is not possible).

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[1] Report of the Strategic Advisory Group of Experts (SAGE) on Immunization. WHO WER. October 2018. https://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf?ua=1, accessed February 2019

The current empirical data from North Kivu indicates that in each ring (around each EVD case) 95% of the contacts and contacts of contacts are identified and vaccinated. However, it is also documented that the ring definition can be implemented for only a part, approximately 90% of cases. Therefore, the proportion of overall contacts and contacts of contacts identified and vaccinated will range from 60% to 85% (loosely considering as the proportion of identified cases that can be traced to a contact).

A modeling analysis based on the epidemiological situation and ring vaccination data is being performed by using a microsimulation model of Ebola transmission [2;3;4;5]. The model explicitly considers transmission in four settings, namely in households, extended families (i.e., a network of individuals with whom there are frequent interactions), community, and health care structures. For the Ring + strategy the modelers instead estimated that only 40% of the contacts and contacts of contacts are identified and vaccinated (nosocomial transmission contributing to occurrence of cases among unknown contacts) thus corresponding to an overall contact identification roughly in the range 10% to 35% (varying in time). In addition, the model explored various scenarios of intervals between onset of symptoms and identification/isolation of EVD cases. The model estimates the number of cases averted by each vaccination strategy, the number of doses required and the probability of extinction and size of the outbreak as a function of time if current control strategies are implemented. Preliminary model results also suggest that mass vaccination would not be nearly as effective as current strategies and will utilize most of the current rVSV-ZEBOV-GP vaccine supply.

SAGE also reviewed data on all Ebola candidate vaccines currently undergoing clinical evaluation. There are three candidate vaccines other than the rVSV-ZEBOV-GP vaccine, that are in advanced stages of clinical evaluation or have been licensed. Two of them are licensed in their country of origin (Ad5-EBOV, monovalent Zaire Makona, licensed in China; and GamEvac-Combi, monovalent Zaire Makona, licensed in Russia). A third vaccine candidate (Ad26.ZEBOV & MVA-BN-Filo, based on a prime/boost strategy using a multivalent, Zaire Mayinga, Sudan, Tai Forest and Marburg,) will be submitted for approval under the United States Food and Drug Administration (US FDA) Animal Rule.

Conclusions and recommendations

Based on the empirical data available from DRC North Kivu province, and the preliminary results of modeling, SAGE concluded that the currently recommended strategies for rVSV-ZEBOV-GP vaccine delivery, ring vaccination and geographic targeted vaccination, are effective. The Ring + strategy will likely have a less marked impact on the number of new cases than that of the current recommended strategies, and it requires the vaccination of a larger number of additional people, several of them probably at low or no risk of EVD. The Ring + approach would be unlikely to provide added benefit over existing strategies and is therefore not recommended.

As SAGE noted previously[1], it is important to advance the clinical evaluation of other vaccines against EVD and to accrue additional information on their immunogenicity, safety and efficacy if possible. Noting the available data, SAGE recommends that consideration is given to the use of any of these three above mentioned new vaccines to vaccinate HCWs and FLWs in the *neighboring areas* where there is a possibility of spread. Such vaccination should be implemented as part of a randomised clinical trial and in compliance with GCP and informed consent. Since these three new candidate vaccines are non-replicating or replication deficient, pregnant and lactating women should be included into the clinical trial protocols. The protocols must include provisions for safety monitoring and for documentation of EVD cases among vaccinees, including follow-up of pregnant women and their offspring. Choice of vaccine should be undertaken by national authorities based on a transparent and evidence-based process. The WHO R&D Blueprint expert group on vaccine trials is asked to provide guidance on the design of such trials.

If a confirmed case of Ebola (Zaire strain) is observed among the HCWs or FLWs vaccinated with one of these three candidate vaccine regimens, SAGE reiterated that the control of such an outbreak must include the use of rVSV-ZEBOV-GP using the ring vaccination, or the geographic targeted approach if necessary, as previously recommended by SAGE, in preference to these new candidate vaccines.
SAGE stressed that in outbreak affected areas, HCWs and FLWs should continue to be offered the rVSV-ZEBOV-GP vaccine. Similarly, peacekeeping forces deployed to such areas should be offered the vaccine.

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[2] Merler, S., Ajelli, M., Fumanelli, L., Parlamento, S., Pastore y Piontti, A., Dean, N.E., Putoto, G., Carraro, D., Longini Jr, I.M., Halloran, M.E. and Vespignani, A., 2016. Containing Ebola at the source with ring vaccination. PLoS neglected tropical diseases, 10(11), p.e0005093.

[3] Ajelli,M., Merler S. , Fumanelli, L., Pastore y Piontti,A., Dean, N.E., Longini Jr., I.M., Halloran, M.E. and Vespignani A., 2016. Spatiotemporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modeling analysis BMC Medicine 14:130.

[4] Merler, S., Ajelli, M., Fumanelli, L., Gomes, M.F., y Piontti, A.P., Rossi, L., Chao, D.L., Longini Jr, I.M., Halloran, M.E. and Vespignani, A., 2015. Spatiotemporal spread of the 2014 outbreak of Ebola virus disease in Liberia and the effectiveness of non-pharmaceutical interventions: a computational modelling analysis. The Lancet Infectious Diseases, 15(2), pp.204-211.

[5] WHO Ebola Response Team. West African Ebola epidemic after one year—slowing but not yet under control. New England Journal of Medicine. 2015 Feb 5;372(6):584-7.

In view of the severity of the outbreak and aligned with SAGE's recommendation from October 2018 [1], SAGE welcomes and supports the recent recommendation of the ethics committee of DRC to also authorize the vaccination of pregnant women in outbreak affected areas, using the currently recommended vaccination strategies, with the live-replicating rVSV-ZEBOV-GP vaccine with informed consent and in compliance with GCP. As recommended by the ethics committee, every effort must be made to collect data on the safety of the vaccine in these populations, including a documentation of the pregnancy outcomes. SAGE advises that the use of rVSV-ZEBOV-GP vaccine in pregnant women currently remains limited to the EVD outbreak affected areas in DRC and should be continuously evaluated based on the emerging data on the safety and efficacy of the vaccine in this target population. This careful review of the emerging safety data is needed to inform vaccine recommendations for future outbreaks.

SAGE acknowledges the decision of the ethics committee of DRC to also proceed with vaccination of lactating women and children under 1 year of age given the ongoing outbreak and population risk. SAGE is now reviewing the data, including modelling, in relation to the use of the vaccine in these populations and will provide an updated assessment as soon as is feasible.