Ebola Vaccines and Vaccination

Report of the SAGE Working Group on Ebola Vaccines and Vaccination with provisional recommendations for vaccination

September 30, 2015

SECTION C: CONCLUSIONS AND RECOMMENDATIONS

Conclusions of the Working Group and draft recommendations for consideration by SAGE

Conclusions:

General

- Based on the available data on the safety and immunogenicity of the leading vaccine candidates[1] and the preliminary data on the efficacy and effectiveness of the recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of *Zaire ebolavirus* (rVSV-ΔG-ZEBOV), the Working Group (WG) concluded **that vaccination is likely to provide added value in controlling outbreaks of Ebola Virus Disease (EVD) caused by the *Zaire ebolavirus* (ZEBOV) species**.

- Previous outbreaks had been curtailed using public health measures other than vaccination and transmission was interrupted in the recent outbreak in Liberia without the use of vaccines. Vaccination should be part of an integrated strategy and complement other public health measures in order to effectively interrupt transmission.

- Currently, there are no data to make any recommendations on vaccines against species of *Ebolavirus* other than ZEBOV. However, the WG took note that one of the leading candidate vaccines has a multivalent "boost" component (MVA) and that a bivalent ChAd3-vectored *Zaire-Sudan ebolavirus* vaccine is under development.

- The accelerated development of several candidate vaccines is unprecedented. Parallel processes to define the regulatory pathways, establish policy recommendations and prepare for introduction in the affected countries is a testament to the value of partnership, participatory approaches and co-ordination.

Vaccine safety

Adults

- Safety data from Phase 1 studies of both ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccines indicate an acceptable safety profile in healthy adults. Ongoing studies will provide additional experience in adults, and will allow more extensive assessment of safety. At the time of this recommendation, follow-up of human vaccine recipients did not exceed one year. The total number of recipients

[1] The four leading vaccine candidates reviewed by the SAGE WG are: (1) a chimeric, replication-competent vesicular stomatitis virus-based vaccine expressing surface glycoprotein of *Zaire ebolavirus* (rVSV-ΔG-ZEBOV); (2) a recombinant non-replicating chimpanzee adenovirus type 3-based vaccine expressing surface glycoprotein of *Zaire ebolavirus* (ChAd3-ZEBOV); (3) a heterologous prime boost approach based on 2 components, namely a non-replicating type 26 human adenoviral vector expressing *Zaire ebolavirus* surface glycoprotein (Ad26-ZEBOV) and a non-replicating modified vaccinia Ankara (MVA) vector expressing the *Zaire ebolavirus*, *Sudan ebolavirus* and Marburg virus glycoproteins and the *Tai Forest ebolavirus* nucleoprotein; and (4) A recombinant protein vaccine based *Zaire ebolavirus* glycoprotein adjuvanted with Matrix M

of any Ebola virus vaccine is not sufficient to detect potential adverse events that would occur in less than one in a few thousand vaccine doses.

- Arthritis and skin vesicular lesions have been reported in phase 1 studies with rVSV-ΔG-ZEBOV. High rates (24/102 recipients) were noted in one study, which might be associated with the higher median age of volunteers (41 years); while the symptoms subsided in most, 8 reported persistent joint stiffness, whereas 5 reported transient recurrence of joint pain and/or swelling. Vaccine RNA was detected in joint and vesicular fluid. In studies in African countries, reported rates of arthritis or arthralgia were low. Additional assessment of joint and skin events is planned in upcoming clinical studies.

Children

- Data on the safety of the rVSV-ΔG-ZEBOV vaccine are currently insufficient to make definitive recommendations for vaccination. Additional data on the safety of the rVSV-ΔG-ZEBOV in children over 6 years are expected from a trial in Gabon and from children (6-12 years of age) and adolescents (13-18 years of age) who are now eligible for vaccination in the Guinea ring vaccination trial. In addition, Phase 2 trials of the ChAd3-ZEBOV and the Ad26-ZEBOV/MVA vaccines in children are planned.

Special populations

- No data are currently available regarding the safety of the four leading candidate vaccines in subjects with underlying disease or medical conditions.

- There are currently no publicly available data on the safety of the available vaccine candidates in pregnant women. Pregnant women were inadvertently vaccinated in the ongoing phase 2/3 trials with rVSV-ΔG-ZEBOV and ChAd3-ZEBOV. Analysis of data from these individuals will provide preliminary data on safety and immunogenicity in this group.

- There are no publicly available data on the safety of the candidate vaccines among HIV infected individuals to permit recommendations for vaccination. Volunteers in the Liberia PREVAIL trial, which was a Phase 2/3 trial evaluating rVSV-ΔG-ZEBOV and ChAd3-ZEBOV vaccines, were screened for HIV but not excluded if positive. Analysis of data from the HIV-infected individuals in this trial will provide preliminary data on safety and immunogenicity in this group.

Immunogenicity, efficacy and effectiveness

- Both rVSV-ΔG-ZEBOV and ChAd3-ZEBOV vaccines are immunogenic when provided in a single dose (by both binding ELISA and neutralizing assay) at the chosen dose levels of $2x10^7$ *pfu* and 1 x 10^{11} *vp,* respectively. Three different two-dose schedules have also been evaluated in clinical trials for Ebola vaccines. Two of these are using two different vaccines for the two doses known as heterologous prime-boost approach. These are: (1) recombinant Ad26 and recombinant MVA used in either order; and (2) ChAd3 followed by MVA. There is also a more traditional two-dose schedule using a recombinant protein based approach. In all 3 cases there is good

immunogenicity after the two doses. While it is difficult to compare these with the one dose ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccine schedules because of differences in assays, immunogenicity after two doses (Ad26/MVA, ChAd3/MVA or protein/protein) appears similar or higher to that seen after one dose of ChAd3-ZEBOV or rVSV-ΔG-ZEBOV alone.

- An important question is comparability of immune responses between vaccine candidates. Unfortunately, there is limited information testing different vaccines using the same assay methodology and the same vaccine antigen vs test antigen matching, though an international partnership led by WHO made major efforts to allow for comparability. From data made available to WHO, the magnitude of the humoral immune response is similar for ChAd3-ZEBOV and rVSV-ΔG-ZEBOV vaccines at 1 x 10^{11} and 2 x 10^{7}dose levels, respectively, 28 days following vaccination.

- There are efficacy and effectiveness data from an interim analysis of a phase 3 trial of the rVSV-ΔG-ZEBOV vaccine in Guinea. The results of this interim analysis suggest that rVSV-ΔG-ZEBOV is efficacious (efficacy= 100%, 95% CL 74.7-100, p=0.0036), safe, and likely to be effective at the population level (effectiveness=75.1%, 95% CL -15.5 to 95, p=0.1791) when delivered during an EVD outbreak using a ring vaccination strategy.

- The WG takes note of the fact that the rVSV-ΔG-ZEBOV vaccine ring vaccination trial has been expanded from the Guinée Maritime to Sierra Leone. Randomization was stopped on 26 July, 2015 and all new rings, around newly confirmed index cases, are allocated to immediate vaccination aiming to collect additional safety and effectiveness data. In addition, given the preliminary efficacy results, it is anticipated that the ring vaccination strategy may contribute to preventing the spread of disease.

Vaccine development and registration

- Although data on the available candidate vaccines, including efficacy data for the rVSV-ΔG-ZEBOV, is accruing, current regulatory approvals are limited to the use of vaccine in a clinical trial setting.

Service delivery

- In a trial setting, it was possible to deliver vaccine at the community level while maintaining the stringent cold chain requirements (i.e. - 80◦ C). Studies are ongoing to evaluate the thermostability of different vaccines at temperatures more suitable for delivery of vaccine at the community level.

Draft Recommendations:

- Based on the review of current data on disease epidemiology, risk factors for infection and death from EVD, disease transmission patterns and projected impact of vaccination using different delivery strategies under different epidemiological scenarios, the WG proposes the following **provisional** recommendations for consideration by SAGE. These recommendations may need to be reviewed and revised in light of the emerging data on the different vaccines.

- The currently available evidence only allow for recommendations for reactive vaccination (i.e. in response to an outbreak). The evidence is insufficient to formulate recommendations for preventive vaccination (i.e. in the absence of any cases).

- While the rVSV-ΔG-ZEBOV vaccine and other candidate vaccines are currently being used in the context of a clinical trial, recommendations for use outside a trial setting will depend on the vaccines receiving regulatory approval (i.e. full licensure, conditional licensure or emergency use authorization outside a clinical trial setting).

- These draft recommendations are prepared on the basis of interim trial results suggesting high efficacy of the rVSV-ΔG-ZEBOV vaccine and immunogenicity data for the ChAd3-ZEBOV that suggest that it is comparable to rVSV-ΔG-ZEBOV. However, it is important to note that the recommendations do not apply to any specific vaccine. Vaccine-specific recommendations will be made once a vaccine is registered for use outside a trial setting. Meanwhile, it is important that the development and evaluation of other candidate Ebola vaccines continue, as there may be a need for alternative vaccines with different characteristics more suited for certain conditions or in specific target populations.

Recommendations for use of vaccine, provisional to regulatory authorization for use outside a trial setting

Objectives of vaccination: The main objectives for vaccination are interruption of transmission and individual protection for those at high risk for infection.

Target populations: While all eligible individuals should be vaccinated as per the chosen vaccination strategy, certain high-risk groups merit special consideration. Individuals who come into direct contact with patients or infectious body fluids from patients with EVD are at highest risk of infection. The data from the three worst affected countries in the current outbreak in West Africa indicates that among the frontline workers, health care workers (doctors, registered nurses, and laboratory workers) are at highest risk for infection. Limited data suggest that other categories of health workers (mid-wives, surveillance staff, radiographers, cleaners and laundry workers) may also be at high risk. While hard evidence is not available, certain other categories of individuals have a greater likelihood of exposure to infectious body fluids. They include informal health care providers (e.g. traditional healers, herbalists etc.), and those involved in funeral rites (elders, religious leaders, senior members of secret societies, and traditional washers). The categories of front-line workers and other risk groups may vary from one community to the other and may need to be defined locally.

These high-risk categories, including first responders, should be given priority consideration in any vaccination strategy.

Vaccination delivery strategy: The vaccination delivery strategy of choice will depend on the extent of the spread of disease, the number of cases being confirmed per week at the time when vaccination is initiated, the status of implementation of other public health measures, the effectiveness of contact tracing and the available supply of vaccine. Regular reviews of the epidemiological data should be used to inform adjustments to the delivery strategies throughout the outbreak. Potential strategies include ring vaccination, geographic targeting of an area (mass vaccination) and front line worker vaccination. When more data are available, it may be possible to provide more precise recommendations on the choice of vaccination strategy.

Other considerations for improving acceptability or impact of vaccination

- The absolute and per capita case incidence of EVD among children younger than 16 years of age has been significantly and consistently much lower than the incidence among adults in all three countries. This pattern is similar to that observed in past EVD outbreaks. The case fatality rate (CFR) was lowest among children between 10 and 15 years of age. Pregnant women and infants have very high CFR. They may be protected by indirect protection if others in the community are vaccinated. Inclusion of pregnant women as a means to indirectly protect their infants and young children might need consideration in the future.

- A communication strategy tailored for the affected communities should be considered, including:
    - Public vaccination of community leaders (e.g. religious leaders, members of Parliament, chiefs, etc.).
    - Information provided on an anticipatory, iterative and responsive basis to address rumors, anxieties and resistance. Appropriate media including m-Health messaging, should be utilized in in the affected communities if pertinent.
    - Engaging survivor networks for advocacy to enhance the acceptability of vaccination.

- Introduction of Ebola vaccination will require specific preparation and will need to be closely integrated as part of EVD outbreak control measures. Therefore, careful planning should be promoted to ensure readiness for introduction as soon as feasible. The work of the Global Ebola Vaccine Implementation Team (GEVIT) to develop tools and generic deployment plans is critical to ensure the timely and successful deployment of any vaccine(s) and should be completed as soon as possible.

Recommendations on further research

- The WG requests researchers to share data from pregnant women and immunocompromised subjects vaccinated during the ongoing trials once they become available. All future trials should consider collecting data on the safety and immunogenicity of the respective vaccine candidates in children and adolescents, pregnant and lactating women, and immunocompromised individuals.

- Noting that relatively large outbreaks have occurred with Sudan, Bundibugyo and Marburg viruses, the WG recommends continued efforts to develop and evaluate vaccines against filoviruses other than ZEBOV, such as Sudan, Bundibugyo and Marburg. Multi-valent filo virus vaccines are desirable. The WG is encouraged by efforts to develop a bivalent *Zaire-Sudan ebolavirus* vaccine.

- Should the data on safety, immunogenicity or efficacy result in pregnant women being precluded from vaccination, then alternate strategies should be evaluated, recognizing the high case fatality. Alternative or complementary approaches might include the effect of cocoon vaccination approach (i.e. vaccination of possible contacts of pregnant women).

- All trials should carefully document adverse events using standard definitions, including duration, severity and sequelae. In particular, for rVSV-ΔG-ZEBOV vaccine, safety monitoring should document and clearly distinguish arthritis from arthralgia.

- Future studies should evaluate the feasibility and effectiveness of the delivery approaches, duration of protection, and measures that ensure high levels of community acceptance.

- Future research should implement community-based participatory approaches to engage participants in all stages of clinical trials, including design, monitoring and evaluations.

- The WG acknowledges the ongoing work to improve the thermostability of the candidate vaccines and encourages optimization of thermostability to meet the WHO criteria for programmatic suitability for prequalification.

- Pre-approved and pre-positioned protocols and local research capacity strengthening in countries at risk for future outbreaks should be put in place now to facilitate rapid implementation of relevant studies including assessment of newer vaccine products, in the event of future outbreaks. Such protocols are included in the blueprint for conducting research during public health emergencies, which is currently being developed under the leadership of WHO.

- The ongoing efforts to model the impact of different Ebola vaccination strategies on preventing disease and transmission should be pursued and expanded to further inform the understanding of their respective value in controlling an outbreak.