

# Draft framework for formulating recommendations for the deployment of Ebola vaccines

SAGE Working Group on Ebola Vaccines and Vaccination, March 2015

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## **Abbreviations:**

ECBS	Expert Committee on Biological Standardization
EUAL	Emergency Use Assessment and Listing
EVD	Ebola Virus Disease
FLW	Front Line worker
HCW	Health Care Worker
SAGE	Strategic Advisory Group of Experts on Immunization
WG	Working Group
WHO	World Health Organization

## Background

In response to the ongoing widespread outbreak of Ebola Virus Disease (EVD) in West Africa, the World Health Organization (WHO) coordinated an effort to accelerate the development of vaccines against EVD for use in the current outbreak, as well as in response to future outbreaks.

In October 2014, the WHO Director General requested the Strategic Advisory Group of Experts (SAGE)<sup>1</sup> on Immunization to advise WHO on the large-scale use of the vaccine(s) in the context of one or more vaccines receiving regulatory or emergency authorization for use. In response to this request, the WHO SAGE secretariat established a Working Group with an urgent program of work to facilitate a SAGE review of the available and emerging evidence to inform the development of the recommendations for the use of Ebola vaccines (see Annex 1 for TOR of the SAGE WG).

The urgency of the task required that the SAGE Working Group process to review the available evidence and draft recommendations should proceed in parallel with the ongoing phase 1, phase 2 and phase 3 trials of candidate vaccines, before any substantive safety and efficacy data for the vaccines were available. Furthermore, the product characteristics of the vaccines most likely to be available for early deployment would pose a significant challenge to large scale deployment in countries with limited infrastructure, creating an additional dimension to consider when drafting recommendations for widespread use.

The lack of complete clarity on the requirements and timelines for the authorization for use of Ebola vaccines, including emergency authorization, represents an additional challenge for the Working Group. A consultation on draft guidelines on the scientific and regulatory considerations for the evaluation of vaccines for use in public health emergencies is ongoing prior to presentation to the WHO Expert Committee on Biological Standardization (ECBS).<sup>2</sup> Additionally, a public consultation on a process for Emergency Use Assessment and Listing (EUAL) of vaccines to be used during Public Health Emergencies of International Concern (PHEIC) is also underway.<sup>3</sup> The unprecedented urgency given to all these activities reflects the devastating impact of EVD, and the need to have recommendations for use, should a vaccine that satisfies the regulatory requirements for expanded use outside of clinical trials, whether approved or authorized for an emergency use only, become available and be needed based on the status of the outbreak.

The SAGE WG has held three teleconferences aimed at updating the members on the epidemiology of the current outbreak and the status of vaccine development. In order to draft a framework for formulating recommendations, the WG held its first face-to-face meeting on March 9-10, 2015, when it reviewed the latest available epidemiological data on the current outbreak, the status of vaccine development, including preliminary results from the phase 1 trials<sup>4 5</sup> and the status and

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<sup>1</sup> Strategic Advisory Group of Experts (SAGE) on Immunization-  
<http://www.who.int/immunization/policy/sage/en/>

<sup>2</sup> WHO Expert Committee on Biological Standardization.  
[http://www.who.int/biologicals/expert\\_committee/en/](http://www.who.int/biologicals/expert_committee/en/)

<sup>3</sup> Public consultation on emergency use assessment and listing procedures for medical products during public health emergencies: [http://www.who.int/medicines/news/public\\_consult\\_med\\_prods/en/](http://www.who.int/medicines/news/public_consult_med_prods/en/)

<sup>4</sup> Ledgerwood, J. E., et al. "Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report." *N.Engl.J.Med.* (2014)

plans for the phase 2 and 3 trials. The WG was also briefed on the preparations for supporting countries with the deployment of vaccines and for monitoring their safety and effectiveness post-introduction, the responses from local communities with regards to vaccine research, and on predictive mathematical models on the future course of the outbreak and the potential impact of different vaccination strategies for the different vaccine candidates. One of the key expected outcomes of the meeting was the development of a draft framework for drafting policy recommendation for vaccine use that SAGE could consider.

This first draft of this framework is summarized below and provides an indication of the direction being taken by the Working Group. **The group consensus was that currently available data on any vaccines are too limited to allow any recommendations for use at this time.** Thus, the **framework should not be regarded as WG recommendations for immunization** with any Ebola vaccine now or future **but as a potential roadmap for further deliberations** and actual recommendations once data, and results of regulatory review, are available.

While developing the framework, the Working Group agreed that there were **a few overarching issues** that **needed to underpin the vaccine specific recommendations**. These include:

1. The need to stress the importance of the continued focus on other control measures that are known to be effective, even while deploying vaccines.
2. The need to continue efforts to re-establish routine childhood immunization in parallel to Ebola vaccine deployment, i.e. one should not be at the expense of the other.
3. Use the opportunity of Ebola vaccine deployment to strengthen health systems, e.g. disease and safety surveillance

## Draft framework for formulating policy recommendations

When developing the draft framework, the Working Group considered the following issues in sequence:

1. Defining a variety of epidemiological scenarios for framing the recommendations.
2. Establishing the objectives for immunization in each scenario.
3. Defining and prioritizing the target populations for vaccination under each scenario.
4. Defining additional considerations that need to be addressed when making recommendations.

## Epidemiological scenarios

The Working Group recognized that the risks and benefits of vaccination, particularly with a vaccine that has not had full regulatory licensure, will vary depending upon the status of the epidemic at the

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<sup>5</sup> Rampling, T., et al. "A Monovalent Chimpanzee Adenovirus Ebola Vaccine - Preliminary Report."

N.Engl.J.Med. (2015).

time vaccination is being considered for deployment. For example, potential benefits are likely to be higher, and uncertainties about safety and efficacy more acceptable, in considering recommended uses during a widespread outbreak that is not coming under control as compared with situations where cases are sporadic or declining. Recommendations were therefore organized according to different epidemiological scenarios to assess the different needs and respond most effectively under the circumstances. These were pitched to try to categorise different levels of public health emergency, as well as different patterns of spread. The initial categorization of the epidemiological scenarios for framing recommendations is summarized in Table 1.

In view of the fact that none of the vaccine candidates might reach full licensure, and, therefore, recommendations may have to be made for a vaccine authorized for emergency use only, the Working Group subdivided the recommendations for use under each epidemiological scenario into two subcategories: 1) if authorization was for emergency use only <sup>6 7 8</sup> and thus potentially only valid for a limited period of time or for a smaller set of indications, and subject to certain post-marketing conditions; and 2) if one or more fully licensed vaccines were available. In general, given that an emergency use process would, by definition, not provide conclusive information on efficacy and/or safety, and thus presents more uncertainty, the WG felt that use of a vaccine made available under such a provision is likely to be relatively more targeted and limited than use of a fully licensed vaccine.

Table 1. Epidemiologic scenarios for framing Ebola vaccine recommendations

Epidemiological scenarios		Authorization for use	
		Emergency	Full licensure
Widespread transmission of disease	Increasing disease trend		
	Flat trend		
	Declining trend		
Localized or limited transmission			
Countries/ communities with no reported cases but at high risk from an ongoing outbreak, e.g. neighbouring countries			
Future outbreaks	Reactive vaccination		
	Preventive vaccination		

<sup>6</sup> US FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>)

<sup>7</sup> European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Guideline on the scientific application and practical arrangements necessary to implement commission regulation (EC 507/2006) on the conditional marketing authorization for medicinal products for human use falling within the scope of regulation EC 726/2004. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500004908.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004908.pdf)

<sup>8</sup> Health Canada. Guidance document – submission and information requirements for extraordinary use of new drugs (EUNDS)

Four different epidemiological scenarios were considered. Three of the scenarios were in the context of the ongoing outbreak in West Africa. The fourth related to use of vaccine for responding to or preventing future outbreaks.

1. The first scenario included countries or communities with widespread transmission, e.g. the three most affected countries in the current outbreak in West Africa. Given the evolution of the epidemic in each country, it was felt that this scenario should be further divided into subcategories reflecting the status of the outbreak and the shifting risk-benefit balance of introducing vaccines with limited or varying levels of data on safety and efficacy.
2. The second scenario included countries (or communities) with one or more reported cases, but with limited or no further transmission (e.g. countries such as Senegal, Mali and Nigeria in the context of the current outbreak).
3. A third scenario included countries (or communities) with no reported cases, but at high risk of importation of cases (e.g. countries neighbouring the most affected countries in the context of the current outbreak and with significant cross-border population movement).
4. The fourth scenario included recommendations for the use of the vaccine in future outbreaks. This scenario was further divided into two subcategories. The first related to reactive vaccination in response to a future outbreak, including the creation of a vaccine stockpile with rapid release and deployment of vaccine in response to an outbreak. The second subcategory included preventive vaccination in individuals, communities or countries considered to be at high risk for acquiring EVD, for example countries with reported past outbreaks of EVD or with other risk factors that might lead to an outbreak.
5. Recommendations for use of the vaccine in each scenario would include vaccination of travellers to outbreak affected countries, especially all front line volunteer health care and laboratory workers and non-travellers who may be at increased risk, such as laboratory workers in unaffected countries, who may handle potentially infected materials.

### **Prioritization of the scenarios for drafting recommendations**

Given the tight timelines, the Working Group considered prioritizing the formulation of recommendations under each scenario and whether these could be sequenced. Given the status of the clinical trials, it was felt that any recommendations for early deployment would be preliminary and are likely to be implemented in the context of emergency use authorization, which was likely to only allow limited use of the vaccine accompanied by post-marketing conditions, with such use focused on individuals or communities at highest risk. However, it was understood that the regulatory pathways were still under discussion, that the situation might change and that this draft approach may need to be revisited.

Under the circumstances, and with the low likelihood that efficacy data would be available in the short term, the Working Group agreed to focus its effort on formulating recommendations on use of the vaccine in the context of the ongoing outbreak. Formulation of recommendations on future use of the vaccines could be deferred until additional data were available on the safety, immunogenicity and efficacy (either directly observed or inferred based on a correlate of protection), the regulatory processes were more clearly defined, and there were more data on the programmatic suitability of the different candidates.

## Objectives of vaccination

The Working Group considered the following objectives for use of vaccination:

1. Interruption of transmission, i.e. elimination of disease
2. Mortality reduction
3. Preservation of essential services (i.e. health, security, government)
4. Individual protection of the highest risk groups, e.g. front line health workers and lab personnel

The Working Group was of the opinion that any objective short of disease elimination (i.e. interruption of transmission) was unlikely to be acceptable in the context of the current epidemic given that all other EVD outbreaks have ended with disease elimination. In parallel to these primary objectives, individual protection would need to be considered as an objective in a scenario when vaccine supplies are limited and/or where the risk/benefit data on an EU vaccine may not be sufficient to support wider use in less at-risk populations and vaccine may be deployed mainly for the individual protection of the highest risk groups (e.g. front line workers). Individual protection may also be the main objective for laboratory personnel in non-endemic countries who may handle potentially infected specimens.

Based on these considerations, the Working Group proposed the following objectives for vaccination under all epidemiologic scenarios, within the context of the current outbreak:

**Primary objective:** Interruption of transmission leading to the complete control of an outbreak (i.e. elimination)

**Secondary objective:** Individual protection of high-risk individuals. This would be particularly relevant when vaccine supplies were limited or data to assess risks and benefits in population groups at lower risk were not available.

## Target populations for vaccination

Based on the information reviewed during the meeting, the Working Group initiated the process of defining target populations to be prioritized for vaccination. **It was, however, recognized that this list must be considered provisional and illustrative at this time and will need to be revisited as new evidence that might influence this prioritisation becomes available on the vaccine candidates, the status of the epidemic, on the risk of disease in different population groups, and on the social contexts that affect the balance of risks and benefits.** A review of these recommendations will be undertaken by the WG before final presentation to SAGE.

Available evidence presented at the meeting suggested that health workers (medical doctors, nurses, midwives and laboratory workers) were 20-40 times more likely to get infected than non-health workers. While the attack rates in this group have declined, they remain at substantially higher risk of disease than those not in these fields of work. This group is essential to providing ongoing care of other affected individuals while they are exposing themselves to increased risk while providing this care. The principle of reciprocity thus provides ethical support to this approach. Hence, this group was considered as the highest priority for vaccination under all scenarios.

In the context of widespread transmission of virus a similar priority may be given to other front line workers involved in the Ebola response (burial teams, contact tracers, community workers etc.). Further data on the magnitude of risk in this category of workers is being sought to make informed recommendation.

**Additional analysis of the data will be required to determine the different categories of workers to be included among “health care workers” and “other front line workers” and the relative risk of disease in each category of workers in order to assess the risks and benefits of vaccination and prioritize them accordingly.**

Next in priority were adults 15 years and older (the exact age range to be defined based on additional analysis of the epidemiologic data), who have been shown to have a much higher incidence of disease than children and appear to be more likely to transmit disease as compared to children. Mathematical models indicate that vaccinating adults would have a higher impact on preventing disease in children and that the additional vaccination of children would have relatively little incremental benefit. **However, updated data from the models that are periodically updated would need to be considered in prioritizing target groups when actually framing recommendations.** Nevertheless, social and community considerations might require the vaccination of children for individual protection, should a safe and effective vaccine become available for this age group. Whether the use of vaccine in this adult priority group would be targeted (e.g. ring vaccination, in high risk districts) or universal would depend on the nature of the epidemic and the availability of vaccine, with targeted vaccination likely to enjoy higher priority than universal vaccination.

The tentative definition and prioritization of target groups for vaccination under each scenario are summarised in Table 2. However, it may be stressed once again that **these are meant to be illustrative and intended to provide SAGE with a sense of the direction being taken. This prioritization will need to be reviewed and refined, based on a more comprehensive review, compilation of the data, and GRADE-ing of the evidence (where appropriate).** Prioritization was only considered, albeit very briefly, for target groups within the context of the current outbreak.



**Table 2.** Illustration of the definition and prioritization of target populations under each scenario (actual recommendations will be based on available evidence at time of consideration of use of an emergency use or licensed vaccine)

Epidemiological scenarios		Target population (ILLUSTRATIVE ONLY)	
		Emergency Authorization	Full licensure
Widespread transmission of disease	Increasing disease trend	FLW	FLW
		Adults (targeted)	Adults (targeted)
			Universal
	Flat trend	FLW	FLW
		Adults (targeted)	Adults (targeted)
	Declining trend	FLW	FLW
		Adults (targeted)	
Localized or limited transmission		HCW	HCW
		Adults (targeted)	Adults (targeted)
Countries/ communities with no reported cases but at high risk from an ongoing outbreak		None	HCW

HCW= Health care workers ( e.g. doctors, nurses, laboratory workers, cleaners in Ebola Treatment Units)

FLW=Front Line Workers= HCW + burial teams, contact tracers, community care givers, etc.<sup>9</sup>

The vaccination of the adult population was further subdivided into:

1. Targeted vaccination, i.e. vaccination targeted by geography (most affected communities) or by chain of transmission (e.g. ring vaccination – vaccination of contacts and potential contacts of contacts).
2. Universal vaccination of all eligible individuals throughout the country.

## Additional considerations while formulating recommendations

There was consensus within the working group that additional issues needed to be taken into consideration, in particular stressing the importance of continued focus on the non-vaccination prevention and control strategies. In the absence of vaccine effectiveness data, it is particularly important to ensure that these measures continue to be prioritized and implemented as effectively as possible and that there is no relaxation of these efforts despite the potential for deployment of vaccines. Conversely, It was pointed out that based on the evolution of the epidemic in Liberia, it is possible to stop this epidemic without vaccine and that if an investigational vaccine had been used in Liberia, many would have erroneously concluded that it worked and stopped the epidemic.

These considerations, as was the case with the definition and prioritization of targets groups, were not discussed in detail at the meeting and would be the subject of future teleconferences and meetings of the Working Group.

<sup>9</sup> The categories of workers classified as FLW may evolve based on further analyses of epidemiological data

The following issues have been tentatively listed for the consideration of the Working Group:

1. Recommendations on disease and safety surveillance to accompany deployment of vaccines.
2. Recommendations on managing febrile episodes following vaccination (especially when vaccination targets potential contacts of cases as part of a ring vaccination strategy).
3. Recommendations on community engagement and risk communications to improve the uptake of vaccines by the target populations.
4. The potential trade-offs and how should they be addressed, for example:
  - a. Between vaccines or schedules that rapidly induce protection versus those that provide longer duration of protection?
  - b. Between efficacy and programmatic feasibility, e.g. choosing between the vaccine with highest efficacy versus one that is programmatically more easily deployed but has lower efficacy?
5. The non-vaccination control measures that needed to be stressed.
6. Considerations for vaccine deployment in the face of ongoing enrolment in phase 3 vaccine trials.
7. The need for continued focus for re-establishing routine childhood immunization in parallel deploying Ebola vaccines

## Geographical aspects

The importance of prioritizing vaccination in specific settings affected by the disease was highlighted in the meeting. Widespread vaccination campaigns would be difficult to implement, could be limited by the total number of doses needed and cold chain requirements, and might not respond to the geographical distribution of EVD cases. Cluster (ring) or locally targeted vaccination might be an asset if EVD outbreaks are in small clusters or affect only certain regions and not widespread, thereby preventing more cases in specific communities and neighbouring populations. The thermostability and the presentation and packaging of the currently available candidates may limit the ability to deploy them widely in countries with limited infrastructure. Ring or targeted vaccination would help overcome some of the infrastructural barriers by limiting vaccination to specific settings where they are likely to have the biggest impact.

## Next steps

1. Further develop and refine the framework based on feedback from SAGE, through on-going discussions of the WG during teleconferences, and a second face-to-face meeting if required. These discussions will be informed by additional analysis of the epidemiological data, the further

evolution of the current outbreak, and further clarity on the scope and timelines for the regulatory processes. It will also be essential that complete and detailed information is made available from the vaccine trials, in particular how the study designs and primary outcome measures of the phase 3 trials are being adapted to the changing epidemiology and how they will provide the evidence of safety and immunogenicity/efficacy critical to inform Public Health decision making..

2. Develop timelines for having a first draft set of recommendations for presentation to SAGE (which will most likely focus on use in the context of current epidemic) either at its next meeting in October 2015, or, if required, at an extraordinary meeting specifically to discuss the Ebola Vaccination recommendations.

## **Request to SAGE**

SAGE is requested to consider the proposed framework for drafting recommendations for use for Ebola vaccines and provide its input for the further development and refinement of this framework.

# ANNEX

## SAGE Working Group on Ebola Vaccines and Vaccination (established November 2014)

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### Terms of reference of the Working Group

The Strategic Advisory Group of Experts (SAGE) on Immunization Working Group is exceptionally established with an urgent program of work to facilitate a SAGE review of available evidence and advice to WHO on the potential post-licensure use of the Ebola vaccines in order to mitigate the public health impact of the disease and possibly curtail the ongoing epidemic, as well as to prevent or reduce the risk of spread of disease in the future. The Working Group will consult with the Task Force for Immunization for the African region to get their inputs into the operationalization of immunization delivery and consolidate the feedback into a report to SAGE with recommendations on potential strategies for the deployment of vaccines.

In order to facilitate the review, the Working Group will provide technical advice and support to the WHO secretariat by:

- Reviewing the essential evidence required for making policy recommendations and on strategies for deployment of vaccines.
- Reviewing the available epidemiological data to define the risk of disease and mortality in different population groups in order to allow prioritization of vaccination.
- Reviewing the evidence, as it becomes available, on the safety, and efficacy of candidate vaccines, including the optimal vaccination schedules to be used for each vaccine.
- Reviewing the data on the projected impact of different vaccination strategies generated by mathematical models.
- Reviewing the synthesis of the above data for presentation to SAGE and in drafting recommendations for consideration by SAGE.
- Reviewing the projections of vaccine supply to inform recommendations on the deployment of vaccines.

### Composition

- Rees, Helen (Co-Chair, Chair of the African Task Force on Immunization (TFI)); Executive Director - Reproductive Health Research Unit, University of Witwatersrand, South Africa; Chair South Africa Medicines Control Council.
- Tomori, Oyewale (Co-Chair, Member of SAGE); Professor of Virology, Redeemer's University, Nigeria.
- Andrews, Nick; Deputy Head of Statistics Unit, Public Health England, UK.
- Bonsu, George; Immunization program manager Ghana, Ghana.
- Durrheim, David; Hunter New England Area Health Service and Professor of Public Health, Australia
- Goodman, Jesse; Professor of Medicine, Georgetown University, USA

- Jemmy, Jean-Paul; Medical Coordinator of Operations, Médecins San Frontières, Belgium
- Kelly, Ann; Senior Lecturer in Anthropology, Department of Philosophy, Sociology, and Anthropology, University of Exeter, UK.
- Moodley, Keymanthri; Director, Centre for Medical Ethics and Law, Department of Medicine, Stellenbosch University, South Africa.
- Ndack, Diop: Lecturer in Socio-Anthropology & Methodology of research in social science. University Cheikh Anta Diop, Dakar, Senegal
- O'Brien, Kate (Member of SAGE); Professor, Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA.
- Ockenhouse, Chris; Director, Medical and Clinical Operations, Malaria Vaccine initiative, PATH, USA.
- Velasco Muñoz, Cesar; Preventive Medicine and Epidemiology Unit, Hospital Clínic- Universitat de Barcelona-Barcelona Centre for International Health Research, Barcelona, Catalonia, Spain. /Surveillance and Response Support, European Center for Disease Control, Sweden.
- Were, Fred (Member of SAGE and member of TFI); Executive Director - Professor, Department of Paediatrics and Child Health, University of Nairobi, Kenya
- Wiysonge, Charles (Member of TFI); Professor in Community Health Stellenbosch University; Deputy Director Centre for Evidence-based Health Care Stellenbosch University, South Africa

### Ex-Officio members

- Breiman, Robert; (Chair of WHO Immunization and vaccines related implementation research advisory committee (IVIR-AC))
- Griffiths, Elwyn; (Chair of WHO Expert Committee on Biological Standardization (ECBS))
- Morgan, Chris; (Chair of WHO Immunization Practices Advisory Committee (IPAC))
- Wharton, Melinda; (Chair of WHO Global Advisory Committee on Vaccine Safety (GACVS))

### WHO Secretariat

- Focal point: Cherian, Thomas

Link to the website: [http://www.who.int/immunization/policy/sage/sage\\_wgEbola\\_nov14/en/](http://www.who.int/immunization/policy/sage/sage_wgEbola_nov14/en/)