World Health Organization

SAGE Ebola Vaccines – Session 7
Overview of the evidence and recommendations

09 October 2019 - Geneva, Switzerland

R&DBlueprint

Powering research
to prevent epidemics

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Epidemiology

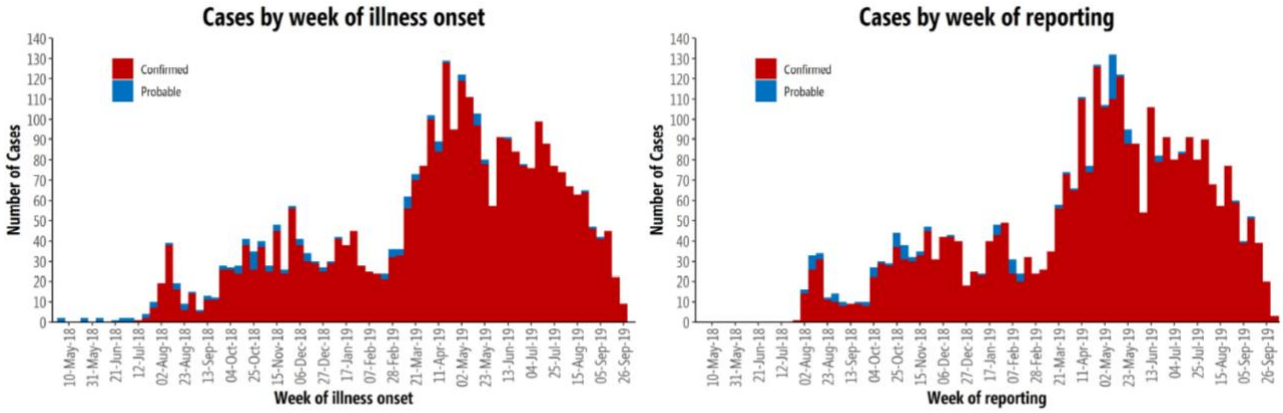
Summary as of 30 September 2019

A total of 3,197 cases (3,083 lab confirmed, 114 probable), have been reported in 29 HZs (13 HZs in the past 21 days). A total of 2,136 deaths have been reported with a case fatality rate of 67%. The number of cases has been steadily declining, with eight health zones (HZs) reporting 20 new confirmed cases the past week. There has recently been a shift in the hotspots of the outbreak from high density, urban areas (Butembo, Katwa, and Beni) to more rural areas with a lower population density (Mambasa, Mandima, Kalunguta). In the past week, three health areas reported 34% cases (Lwemba: HZ Mandima, Kabasha: HZ Kalunguta, Salama: HZ Mambasa).

The relatively low proportion of new cases who were known contacts under surveillance, the number of community deaths, the delay in detection and isolation in Ebola treatment centres (mean: 4 days), the existence of transmission chains linked to nosocomial infection, and in the timely reporting and response to probable cases continue to be ongoing challenges. Armed conflict and community resistance remain the main barriers to effective contact tracing and vaccination activities in Lwemba health areas (Mandima HZ) and Mambasa HZ. Mambasa and Mandima are less densely populated with difficult to access areas making response activities challenging.

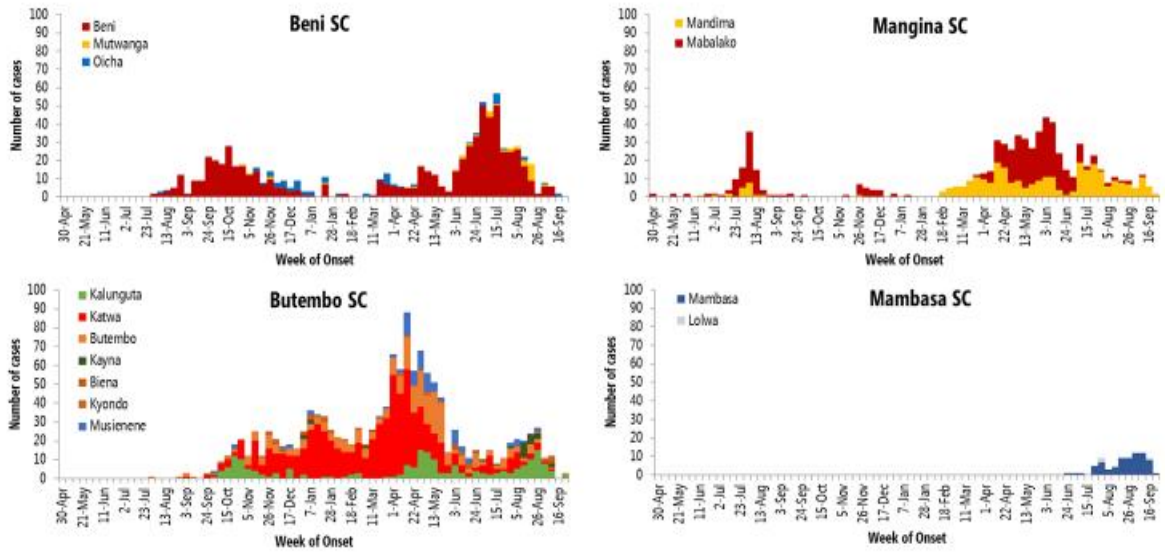
The rVSVΔG-ZEBOV-GP vaccine has been deployed in the Democratic Republic of the Congo (DRC) under the Expanded Access/Compassionate Use cohort protocol, with informed consent and in compliance with Good Clinical Practice since August 2018. The vaccination strategy is ring vaccination of contacts and contacts of contacts and when not possible targeted geographic vaccination.

Figure 1: Epidemic curves, Democratic Republic of the Congo, April 30-September 30, 2019



*Data in recent weeks are subject to delays in case confirmation and reporting, as well as ongoing data cleaning.

Figure 2: Epidemic curves by health zone, Democratic Republic of the Congo, April 30-September 30, 2019



*Data in recent weeks are subject to delays in case confirmation and reporting, as well as ongoing data cleaning.

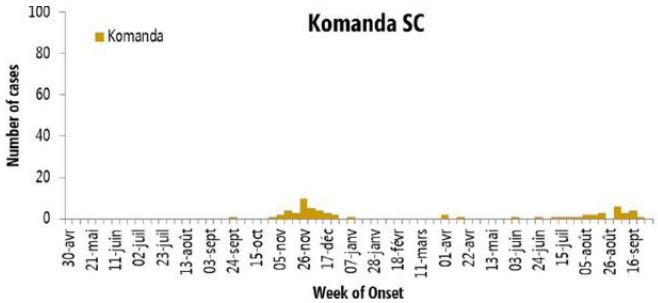


Table 1. Cumulative Cases by Health Zone, Confirmed and Probable, Democratic Republic of the Congo, August 2018 – September 30, 2019

Province	Health zone	Confirmed		Probable	Confirmed + probable		Last confirmed case:		
		Cases	Deaths	(deceased)	Cases	Deaths (CFR)	Illness onset	Reported	Days elapsed
North Kivu	Alimbongo	5	2	0	5	2	13/Aug/19	20/Aug/19	41
	Beni	675	438	9	684	447	18/Aug/19	20/Sep/19	10
	Biena	18	12	2	20	14	15/Sep/19	16/Sep/19	14
	Butembo	283	349	3	286	352	25/Aug/19	28/Sep/19	2
	Goma	1	1	0	1	1	9/Jul/19	14/Jul/19	78
	Kalunguta	190	70	17	207	87	1/Sep/19	30/Sep/19	0
	Katwa	650	470	23	673	493	27/Aug/19	19/Sep/19	11
	Kayna	28	8	0	28	8	30/Aug/19	18/Sep/19	12
	Kyondo	25	15	4	29	19	10/Sep/19	12/Sep/19	18
	Lubero	31	4	2	33	6	19/Jul/19	25/Jul/19	67
	Mabalako	373	286	17	390	303	10/Sep/19	12/Sep/19	18
	Manguredjipa	18	12	0	18	12	9/Jul/19	16/Jul/19	76
	Masereka	50	17	6	56	23	14/Aug/19	21/Aug/19	40
	Musienene	84	33	1	85	34	26/Aug/19	31/Aug/19	30
	Mutwanga	32	12	0	32	12	2/Sep/19	4/Sep/19	26
	Nyiragongo	3	1	0	3	1	30/Jul/19	1/Aug/19	60
	Oicha	59	26	0	59	26	16/Aug/19	30/Sep/19	0
	Pinga	1	0	0	1	0	10/Aug/19	17/Aug/19	44
	Vuhovi	103	37	14	117	51	5/Aug/19	10/Aug/19	51
Ituri	Ariwara	1	1	0	1	1	#VALUE!	30/Jun/19	92
	Bunia	4	4	0	4	4	14/Jun/19	21/Jun/19	101
	Komanda	56	42	10	66	52	23/Sep/19	27/Sep/19	3
	Lolwa	4	1	0	4	1	21/Sep/19	26/Sep/19	4
	Mambasa	71	23	2	73	25	30/Aug/19	29/Sep/19	1
	Mandima	298	149	4	302	153	29/Aug/19	30/Sep/19	0
	Nyakunde	1	1	0	1	1	6/Dec/18	21/Dec/18	283
	Rwampara	8	3	0	8	3	20/Jun/19	26/Jun/19	96
	Tchomia	2	2	0	2	2	18/Sep/18	22/Sep/18	373
South Kivu	Mwenga	6	3	0	6	3	22/Aug/19	27/Aug/19	34
Total		**3080**	**2022**	**114**	**3194**	**2136 (67%)**	**29-Sep-19**	**30-Sep-19**	

Table 2. Key demographics, Democratic Republic of the Congo, August 2018-September 29, 2019

	Overall N = 3077		Last 21 days (9 Sep to 29 Sep) N = 110	
	N	%	N	%
Female	1731	56%	61	55%
Female, 15-49 years	1071	35%	40	36%
Pregnant/lactating**	90	3%	4	4%
Children < 18 years	836	27%	25	23%
Children < 1 year	146	5%	0	0%

**Age or sex missing for 118 confirmed cases overall and 1 in the last 21 days.*
***Pregnancy/breastfeeding status is not systematically captured for all cases, but derived from case narratives wherever reported; therefore, likely substantially underestimated.*

Update on status of Ebola candidate vaccines and ongoing efforts towards global vaccine security

Candidates vaccines

The table in Appendix 1 summarizes the information shared by the developers and manufacturers about their experimental vaccines.

Since the April 2019 SAGE meeting, DRC has approved a plan to introduce a second experimental Ebola vaccine (Ad26.ZEBOV & MVA-BN-Filo) in October 2019. The vaccine will be administered under approved protocols to the target populations. The open-label non-randomised design will aim to estimate the vaccine effectiveness and immunogenicity of the Ad26.ZEBOV & MVA-BN-Filo vaccine regimen. The number of participants vaccinated will be approximately 500,000.

The Ad26.ZEBOV & MVA-BN-Filo vaccine phase II trial started in August 2019 in Uganda. It is an open-label, single-arm study to provide additional information on immunogenicity and safety in 800 healthcare workers (HCWs) and frontline workers (FLWs).

Lastly, another candidate vaccine, EpiVacEbola was licensed for emergency use in Russia in 2018 based on a double blind, placebo-controlled and multicenter phase II-III trial in 240 volunteers.

Overview of SAGE recommendations for rVSVΔG-ZEBOV-GP in DRC and neighbouring countries

Table 2: Summary of SAGE recommendations

Date	SAGE recommendation	Reference - Full report
October 2014	SAGE confirmed that it would provide expert advice on the deployment of Ebola vaccines on an emergency basis, as needed, in response to requests from WHO. Subsequently SAGE was asked to immediately establish a SAGE working group on Ebola vaccines and vaccination.	https://www.who.int/wer/2014/wer8950.pdf?ua=1
April 2015	SAGE supported the proposed framework for making recommendations, but asked that it be made explicit that the identification and prioritization of target populations for vaccination will be based on a thorough assessment of risks and benefits. SAGE recommended that the further development of the Emergency Use Assessment and Listing procedure being developed by WHO, which would allow use of a vaccine in the context of a Public Health Emergency of International Concern. SAGE again noted the probability that efficacy data for any of the Ebola vaccines may not be available by the end of the outbreak, and therefore recommended that future use of unproven Ebola vaccines should be in the context of studies that would generate safety and effectiveness data.	https://www.who.int/wer/2015/wer9022.pdf?ua=1
October 2015	Vaccination during outbreaks should be part of an integrated strategy and complement other public health measures to interrupt transmission. The main objectives for vaccination are interruption of transmission and individual protection for those at high risk for infection during an outbreak. HCWs, as well as certain other categories of individuals with high likelihood of exposure to infectious body fluids, including informal health-care providers and those involved in funeral rites, are at higher risk for infection than the general population. Pregnant women and infants have very high case fatality rates (CFRs) and may benefit from the indirect effects of their close contacts being vaccinated. Careful planning should ensure readiness for vaccine introduction as soon as feasible.	https://www.who.int/wer/2015/wer9050.pdf?ua=1

SAGE Ebola Vaccines

April 2017	Should an Ebola disease outbreak occur before the candidate vaccine is licensed, SAGE recommended that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice. If the outbreak is caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species. Ring vaccination, as used in the Phase III study in Guinea, is the recommended delivery strategy. Include people at risk including but not limited to: (i) contacts and contacts of contacts; (ii) local and international HCWs and FLWs in the affected areas and (iii) HCWs and FLWs in areas at risk of expansion of the outbreak. SAGE considered that available evidence on candidate Ebola vaccines, especially duration of protection, is insufficient to formulate conclusive recommendations regarding mass vaccination of the general population or vaccination of HCWs in the absence of an outbreak.	https://apps.who.int/iris/bitstream/handle/10665/255611/WER9222.pdf?sequence=1
October 2018	SAGE reiterated that, should an Ebolavirus disease (EVD) outbreak due to the Zaire strain occurs before a candidate vaccine is licensed, rVSV-ZEBOV-GP vaccine should be promptly deployed. Ring vaccination remains the recommended strategy for delivery. A geographically targeted vaccination strategy may be considered in when it is impossible to identify the individuals who make up ring vaccination cohorts because of serious security, social or epidemiological issues. SAGE noted that (i) EVD in pregnancy is associated with very high risks of maternal and fetal loss; (ii) in outbreaks, with no vaccination, the risk for EVD of contacts and contacts of contacts of patients with EVD is moderately high; and (iii) the risk of unvaccinated people in a ring vaccination cohort with vaccination coverage of ≥50% is low. SAGE further noted that the risk of pregnant women for adverse effects after administration of the replicating live virus vaccine, rVSV-ZEBOV-GP, remains largely unknown, given the limited data. SAGE recognized that a decision on whether to offer rVSV-ZEBOV, a systemically replicating vaccine virus, to pregnant women is complex, with ethical, clinical, epidemiological and social considerations. Inclusion of pregnant women in an EVD vaccine research protocol depends on local national regulatory authorities and local ethics review committees.	https://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf?ua=1
Interim February 2019	As SAGE noted previously, 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. In view of the severity of the outbreak and aligned with SAGE's recommendation from October 2018, 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	https://www.who.int/immunization/interim_ebola_recommendations_feb_2019.pdf

	recommended vaccination strategies, with the live-replicating rVSV-ZEBOV-GP vaccine with informed consent and in compliance with Good Clinical Practice. 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.	
April 2019	An examination of EVD cases in North Kivu found an attack rate of 1.3 cases per 100,000 persons in lactating women with a CFR of 63%, an attack rate of 23.5 cases per 100,000 in women of childbearing age (15–49 years old) with a CFR of 55%, and an attack rate of 30 cases per 100,000 persons in children under 1 year of age with a CFR of 70%. SAGE considered that the high rates of attack and fatality in these groups and the accumulating data on vaccine safety and efficacy for other groups justify inclusion in the ongoing ring vaccination in North Kivu of infants aged 6–12 months and lactating women. As data on the safety of the vaccine in infants aged 6–12 months accumulate, inclusion of infants from 6 weeks of age should be considered. Despite possible difficulties in follow-up, every effort should be made to monitor the safety of vaccination of lactating women, their infants and vaccinated children. SAGE previously recommended that consideration be given to urgent evaluation of new candidate vaccines. This recommendation remains to be implemented.	https://apps.who.int/iris/bitstream/handle/10665/325017/WER9422-23-en-fr.pdf?ua=1&ua=1
Interim May 2019	To ensure vaccine continues to be available and offered to individuals at the 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 (FDA). Administration 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 and 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 x 107 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.	https://www.who.int/immunization/policy/position_papers/interim_ebola_recommendations_may_2019.pdf

	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.	

Recommended Ebola Vaccines

Should an Ebola disease outbreak occur a, candidate vaccine is licensed, SAGE recommended that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practice.

The candidate vaccine rVSVΔG-ZEBOV-GP is a recombinant Vesicular Stomatitis Virus (VSV), pseudo-typed with the Ebola Zaire Glycoprotein. It is classed as a live, attenuated replication competent vector, administered intramuscularly. rVSVΔG-ZEBOV-GP is the only candidate Ebola vaccine that has undergone a Phase III clinical trial and has so far been able to demonstrate clinical efficacy and effectiveness. It has shown to be highly efficacious and has subsequently been deployed for emergency control of Ebola outbreaks in central Africa including the ongoing Ebola outbreak in North-Kivu in DRC. Results from the Phase I/II/III clinical trials, which so far engaged >18,000 participants, have demonstrated that the rVSVΔG-ZEBOV-GP candidate vaccine is safe, well tolerated, and highly immunogenic across a broad dose range.

In outbreak settings, SAGE currently recommends the use of rVSV-ZEBOV-GP vaccine. The vaccine should be administered using a ring vaccination strategy; that is to contacts and contacts of contacts (as stated in the October 2018 SAGE report, and several previous reports) in addition to the preventative vaccination of HCWs and FLWs. In circumstances, i.e., settings where there are serious security concerns or social or epidemiological issues that prevent accurate contact tracing (identification of contacts and contacts of contacts), targeted geographic 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, which is most likely to include those individuals who were the contacts or contacts-of-contacts of the index case.

SAGE previously recommended the need to assess the efficacy of other candidate vaccines, with particular consideration to the inclusion of pregnant and lactating women and pediatric populations. Sage reiterated that proposed studies should be scientifically and epidemiologically justified, have appropriate approvals, including from relevant African and other regulatory and ethics authorities, and have defined endpoints suitable for licensure. As randomized trials are the gold standard for the evaluation of vaccines, priority should be given to the implementation of the randomized trial among HCWs/FLWs at risk of exposure but who are not in the highest risk setting, as previously recommended by SAGE.

Recommended delivery strategies

Ring vaccination

Ring vaccination is currently the recommended strategy for vaccine delivery. The strategy was used to eradicate smallpox and was also used in the Phase III ca suffit trial in Guinea. The strategy includes the vaccination of individuals at highest risk of disease, including but not limited to contacts and contacts of contacts of an index Ebola case.

Healthcare worker and front line worker vaccination

Local and international HCWs and FLWs in the affected areas and HCWs and FLWs in areas at risk of expansion of the outbreak should also be vaccinated.

Pop up vaccination

Temporary 'pop-up' vaccination sites are set up, often at health posts or primary health facilities. This allows people to come to a fixed site for vaccination at a safe and more anonymous location away from the home of the confirmed case. In areas of ongoing conflict and insecurity, the "pop-up" site also protects the vaccination teams.

Targeted geographic vaccination

SAGE recommended that vaccination of broader geographic areas should remain a fallback strategy if contact tracing is not feasible and vaccine supplies are sufficient. This strategy should be considered when it is impossible to accurately identify the ring due to serious security, social or epidemiological issues and involves vaccinating everyone in the neighborhood, or village, rather than vaccinating only the known contacts and contacts of contacts. The geographical area immediately around a case of EVD, such as a village or a neighborhood, is most likely to include those individuals who were contacts or contacts of contacts of the index case.

Inclusion of pregnant women

In October 2018, SAGE noted that (i) EVD in pregnancy is associated with very high risks of maternal and fetal loss; (ii) in outbreaks, with no vaccination, the risk for EVD of contacts and contacts of contacts of patients with EVD is moderately high; and (iii) the risk of unvaccinated people in a ring vaccination cohort with vaccination coverage of ≥50% is low. Given the limited data, SAGE noted that the risk of adverse effects following administration of rVSVΔG-ZEBOV-GP to pregnant women remains largely unknown.

SAGE recognized that a decision on whether to offer rVSVΔG-ZEBOV to pregnant women is complex, with ethical, clinical, epidemiological and social considerations. Inclusion of pregnant women in an EVD vaccine research protocol depends on local national regulatory authorities and local ethics review committees.

Inclusion of lactating women and infants under 1-year old in ring vaccination

In April 2019, SAGE reviewed the risk–benefit analysis of vaccinating lactating women and infants <1 year of age with rVSVΔG-ZEBOV-GP as part of the ring vaccination strategy in North Kivu. The "compassionate use/expanded access protocol" in the DRC had previously excluded these groups, although the DRC Ethics Review Committee had authorized their inclusion. An examination of EVD cases in North Kivu found an attack rate of 1.3 cases per 100,000 persons in lactating women with a CFR of 63%, an attack rate of 23.5 cases per 100,000 in women of childbearing age (15–49 years old) with a CFR of 55%, and an attack rate of 30 cases per 100,000 persons in children under 1 year of age with a CFR of 70%. SAGE considered that the high rates of attack and fatality in these groups and the accumulating data on vaccine safety and efficacy justify the inclusion of infants aged 6–12 months and lactating women. As data on the safety of the vaccine in infants aged 6–12 months accumulate, inclusion of infants from 6 weeks of age should be considered. Despite possible difficulties in follow-up, every effort should be made to monitor the safety of vaccination of lactating women, their infants, and vaccinated children.

Recommendation on adjusting the dose to the dose used in the Guinea trial (Ebola Ca suffit) 2 x 10_7 pfu/mL

To increase the supply of the rVSVΔG-ZEBOV-GP candidate vaccine and provide broader vaccination coverage to at risk individuals SAGE reviewed manufacturing data, animal protection data, and immunogenicity data from Phase I and II clinical trials conducted in various subpopulations.

Manufacturing data

Potency data for the currently available vaccine lots could support a 2-fold dose adjustment, while on average approximating the Guinea Ebola ca suffit dose (referred to as the "Guinea dose"). Of note, this calculation may be subject to revisions, pending the release of potency data of future rVSVΔG-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 the four smaller studies, two had results consistent with a difference in immune response. In two of these studies, a dose response relationship was not observed and vaccination at a lower dose resulted in higher immune responses compared to vaccination with higher doses. In the two larger studies, no major difference in immune responses induced by the “Guinea dose” and the 6.7-fold adjusted lower dose were observed.

The kinetics and time to immunity are especially important in outbreak response. The trend (albeit with overlapping confidence intervals) towards higher geometric mean titres (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. At 28 days or more post vaccination, human immunogenicity data from these small studies suggest a modest to negligible reduction with a lower dose.

While the relationship between immunogenicity and vaccine effectiveness is not established in humans or animals, data from non-human primate challenge protection studies are generally consistent with immunogenicity data. Moreover, protection for other replicating live-virus vaccines is usually considerably less sensitive to the immunizing dose than it is for other types of vaccines. Together, the clinical immunogenicity and non-human primate challenge study data could support a 2 to 5-fold adjustment in the immunizing dose. However, with the limited clinical data, there remains some uncertainty 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 available data. 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, a 2-fold

reduction of the current DRC dose (so it is comparable to the “Guinea dose”) could be used for ring vaccination. 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, a 5-fold reduction (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 a potential risk that effectiveness may be reduced.
2. The more modest the adjustment in dose, the more modest the risk to effectiveness.
3. Any risk for decreased vaccine effectiveness should be weighed by the risks and benefits associated with other options and the number of vaccine doses projected to be needed (see 4).
4. A vaccine dosage adjustment should also 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.

In May 2019, SAGE recommended that currently available rVSVΔG-ZEBOV-GP vaccine lots be given with adjusted dosing, based on an analysis undertaken by the U.S. FDA. This recommendation was made to ensure that vaccine continues to be available and offered to individuals at the greatest risk of EVD during this outbreak.

(i) For those at higher risk of Ebola including contacts and contacts of contacts and 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 x 107 pfu).

(ii) For those potentially involved in a tertiary generation of cases (e.g., 3rd level of contacts), a 5-fold dose adjustment compared with the current dosing of the vaccine was recommended. 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 doses could be readily implemented by injection of 0.5 mL and 0.2 mL, respectively.

Implementation of SAGE recommendations

List of major amendments in the compassionate use protocol

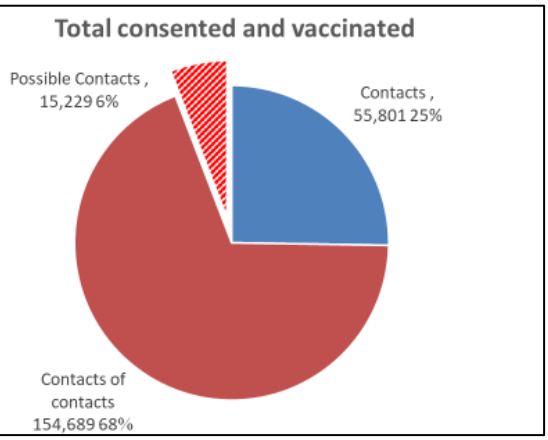
1. Inclusion criteria: inclusion of children >1 year old
2. Vaccination strategy: addition of geographical vaccination
3. Inclusion criteria: inclusion of pregnant (after 3 months pregnancy) and breastfeeding women and children >6 months old
4. Serious adverse events follow-up visits: follow-up of all vaccinated for 30 minutes remains in the protocol, children >6 months are follow-up for 21 days; pregnant women are followed until the birth of the child.
5. Dosage: the dose was adjusted to $2x10_7$ pfu/mL = 0,5 mL = Guinea dose ca suffit trial

Ring vaccination

More than 220,000 people in the DRC outbreak have received rVSVΔG-ZEBOV-GP vaccine using the ring vaccination approach: the vaccine is offered to contacts of confirmed case, their contacts, and HCWs/FLWs. Ring vaccination has been hindered by security concerns and community resistance, despite these challenges, 85% of the confirmed cases have a completed ring.

Figure 3. Vaccinated individuals, Democratic Republic of the Congo, August 2018-September 29, 2019

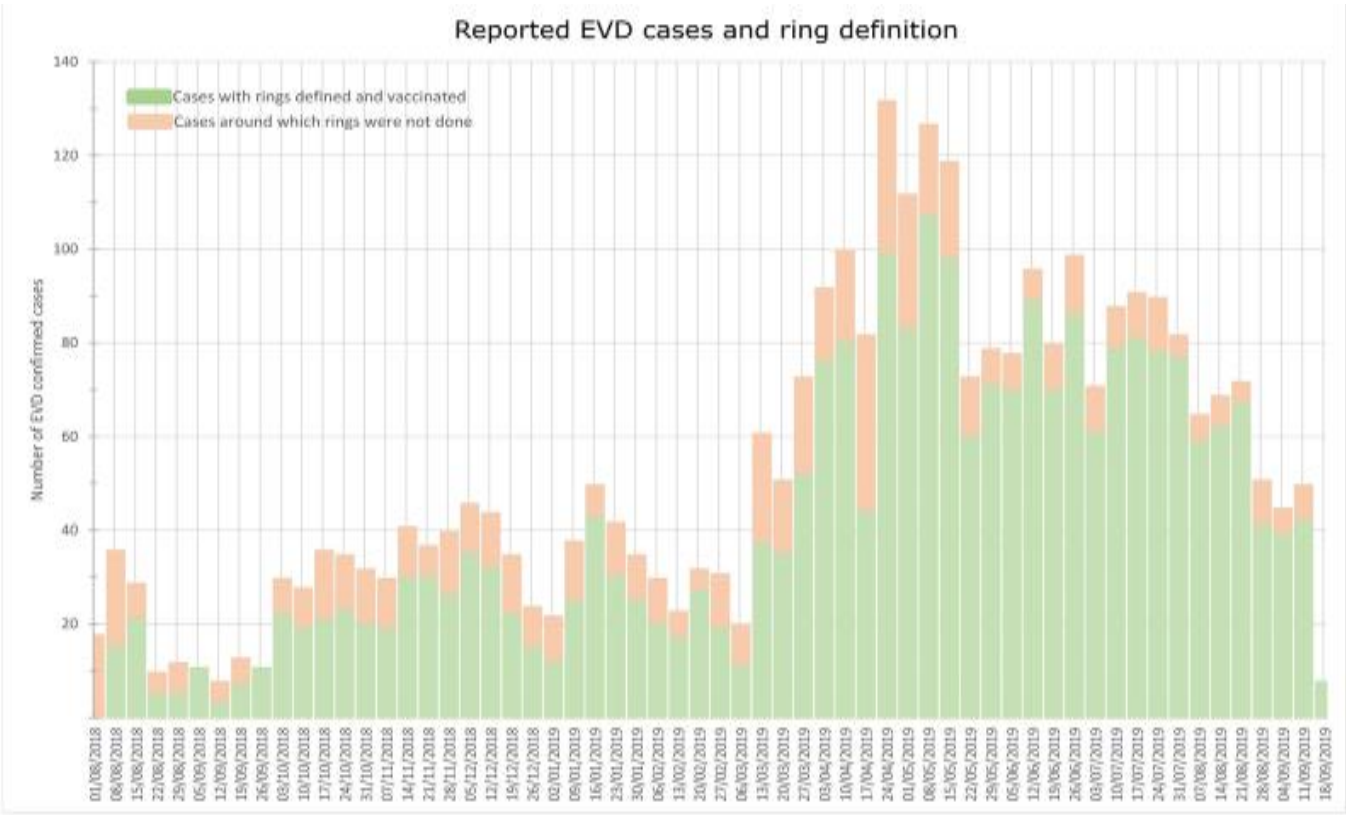
	Number	%
Total consented and vaccinated	**229'336**	
Contacts	56' 089	24.6%
Contacts of contacts	157'121	68%
Possible Contacts	16'151	6.8%
Those vaccinated included the following populations:		
HCWs/FLWS	48'505	21%
Children 6-11 months	2'064	0.9%
Children 1-17 year old	73'613	32%
Pregnant women	878	> 0.1%
Breastfeeding Women	4'360	1.8%



Pop-up vaccination and targeted geographic vaccination

The main vaccination strategy used with the rVSVΔG-ZEBOV-GP vaccine is a ring strategy where all people who had contact with a confirmed EVD case are offered vaccine. Where people are stigmatized or feel threatened, temporary 'pop-up', vaccination sites are set up, often at health posts, rather than near the homes of individuals infected with Ebola. This allows people to receive the vaccine at a safe, more anonymous site, but also increases protection for vaccinators in areas where there is ongoing conflict and insecurity. Another vaccination approach is 'targeted geographic vaccination'. This strategy involves vaccinating everyone in the neighborhood, or village, rather than vaccinating only the known contacts and contacts of contacts.

Figure 4: Reported EVD cases with a defined ring, Democratic Republic of the Congo, August 2018-September 29, 2019



Inclusion of other groups

The compassionate use protocol was amended and approved by the DRC local ethics committee. Since 13 June 2019, pregnant and lactating women, as well as children 6 – 11 months of age have been offered rVSVΔG-ZEBOV-GP vaccine. As of 29 September 2019, 878 pregnant women, 4,360 breastfeeding women, and 2,064 children 6-11 months old have been vaccinated in DRC.

Preventive vaccination of high risk groups, HCWs and FLWs in neighboring countries (South Soudan, Uganda, Rwanda and Burundi)

WHO supported the Ministries of Health of Uganda, South Sudan, Rwanda and Burundi to implement the SAGE recommendation of preventative vaccination of HCWs and FLWs in areas at risk of outbreak expansion. Between 7 November 2018 and October 2019, Uganda, South Sudan, Rwanda and Burundi implemented the recommendation and vaccinated 14,075 HCWs and FLWs in 35 districts and 405 health care centers.

Uganda

In Uganda, preventative vaccination of HCW/FLW took place from 7 November 2018 to 7 March 2019 in 13 high-risk districts with 4420 HCWs vaccinated. Since June 2019, there have been three rounds of ring vaccination in Kasese District in response to confirmed EVD cases in Uganda, or in transit through Uganda continued to provide preventive vaccination in health facilities in Kasese to HCWs and FLWs that did not accept vaccination previously and to response team members in addition to vaccinating contacts and contacts of contacts. In the first ring, 682 HCW/FLW were vaccinated. In the second ring, an additional 85 HCWs/FLWs were preventively vaccinated and four HCWs/ FLWs were vaccinated in the third ring. In addition, pre-emptive HCW vaccination was conducted in Arua, in response to a confirmed EVD case in Ariwara, DRC on 3 July 2019. In Arua, 1,504 HCWs/ FLWs were vaccinated from 5 to 13 July 2019. Following an EVD case detected at the Mpwonde point of entry on 28 August 2019, 60 additional HCWs and FLWs were vaccinated.

South Sudan

In South Sudan, HCW vaccination began on 25 January 2019 and ended on 28 May 2019 in Juba with 2,793 HCWs and FLWs vaccinated. When a case was confirmed in Ariwara, DRC near the South Sudan border (50 km from Morobo, in Yei River state), an additional 180 HCW were vaccinated at health facilities that had been missed.

Rwanda

In Rwanda, 2,813 (2,565 HCWs and 309 FLWs) were vaccinated in 60 health facilities in eight districts. There are current plans vaccinate an additional 500 HCWs and FLWs.

Burundi

In Burundi, HCW/FLW vaccination is ongoing. As of 1 October 2019, 2,924 HCWs and FLWs were vaccinated in 32 health facilities in eight districts/health zones and 6 point of entries (including the international airport).

Preliminary observations regarding effect of rVSVΔG-ZEBOV-GP vaccination in DRC

DRC's national research institute, the Institute National pour la Recherche Biomedicale (INRB), and WHO conducted a preliminary analysis of vaccine effectiveness between 1 May 2018 and 25 March 2019. A more detailed analysis is being prepared and will be available in a peer-reviewed journal at a later date.[1]

Key public health messages arising from this information

1. The results confirm previous observations of high efficacy of rVSVΔG-ZEBOV-GP candidate vaccine against EVD. While this is an observational study with the inherent methodological limitations, the ring vaccination strategy works because of rapid protection after a single dose, and high coverage achieved in the rings.
2. No deaths were reported among vaccines who developed Ebola with onset 10 or more days after vaccination. Moreover, the overall CFR was reduced among all vaccines who developed Ebola. Therefore, the vaccine is protective against death.
3. Vaccination of HCWs/FLWs in the affected areas have provided information on the efficacy of this vaccine in preventing EVD and EVD mortality among HCWs/FLWs.
4. The ring vaccination strategy is a highly efficient delivery strategy for Ebola vaccines during outbreaks. Only two contacts of contacts developed EVD suggesting ring vaccination is effective in preventing tertiary generation of cases. This concept, which is based on smallpox eradication strategies, considers the fact that Ebola transmits mainly through human-to-human contact, has a relatively long serial interval (i.e., 2 weeks), and that the people at risk of contracting the disease can be identified

[1] https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf?ua=1

(contacts and contacts of contacts). It is also efficient for teams operating in an insecure context and is a dose sparing vaccination strategy.

5. Integration of research into the outbreak response has facilitated the further assessment of this candidate Ebola vaccine, while contributing to the control of the outbreak. It is feasible to rapidly and effectively implement ring vaccination using a yet to be licensed Ebola vaccine in an outbreak setting and, to integrate this innovative strategy with the more traditional Ebola control measures. The fact that a protocol was already available, teams were already trained, and equipment could be promptly deployed, meant that ring vaccination was initiated only 7 days after the declaration of the outbreak.

Ebola Vaccines: Towards global vaccine security

As of 27 September 2019, 245,600 doses of rVSVΔG-ZEBOV-GP have been deployed for vaccination in DRC, South Sudan, Uganda, Rwanda and Burundi.

The manufacturer currently has 194,620 doses that are ready for shipment. The number of doses in stock and ready to ship, change weekly depending on the DRC consumption, which is currently about 1,000 doses per day. The current 6-18 month production plan is 650,000 doses: 170,000 doses in Jan/Feb 2020, 30,000 doses in Apr/May 2020 and 450,000 doses in Jun-Dec 2020.

WHO and GAVI are working to estimate the size of a stockpile for reactive and eventually preventive use of the vaccine if recommended. Prior preliminary estimations for a global stockpile were estimated at 300,000 to 500,000 doses. In addition, there will be expectations for national stockpiles in some industrialized countries. The baseline demand would be around 1 million doses for stockpiles/outbreak response.

The FDA has accepted an application for approval of rVSVΔG-ZEBOV-GP vaccine. FDA would approve rVSVΔG-ZEBOV-GP in the beginning of 2020. Its current production capacity is 300,000 doses/year, which can be increased up to 500,000 doses/year in a 3-year timeframe.

The manufacturer of Ad26.ZEBOV & MVA-BN-Filo vaccine anticipated that their vaccine would be licensed by 2021, with a production capacity of 500,000 doses per year. There are three vaccines licensed in their country of origin: two in Russia, EpivacEbola and GamEvac-Lyo; and one in China, Ad5-EBOV. These vaccines have been licensed for emergency use in their respective countries based on immunogenicity data phase II/III.

SAGE Ebola Vaccines

WHO has developed a DRAFT Global Vaccine Security plan with a goal to ensure ethical and timely access to Ebola vaccines. The plan outlines a mechanism to ensure that there are sufficient quantities of vaccine to respond to current and future EVD outbreaks. The document describes a series of strategies

and activities that will be implemented in 2019-2020 with the expectation that rVSVΔG-ZEBOV-GP vaccine will be licensed and available in the market.

Appendix 1: Summary of data of all candidate vaccines

Nine candidate Ebola vaccines have undergone or are currently undergoing clinical evaluation in different phases. Three vaccines were licensed, three vaccines have completed or are in trials up to Phase I development, two vaccines have completed or are in Phase II development, and one vaccine has completed Phase III development.

OVERVIEW OF CANDIDATE EBOLA VACCINE

Type of candidate vaccine	Developer	Strain(s) aimed to protect against	Current stage of clinical evaluation Number of subjects with data analysed to date Regulatory status	Proposed vaccination schedule	Proposed indication	Proposed target population for the label indication	Current storage specifications*	Current formulation and presentation (doses per vial)	Number of clinical research grade does available	Forecasted production capacity
PROPOSED INDICATION: REACTIVE USE DURING OUTBREAKS										
Licensed in country of origin										
Ad5-EBOV (monovalent)[1]	CanSino Biologics Inc. & Beijing Institute of Biotechnology, China	Zaire ebolavirus (Makona)	a. Phase 1 in China and Phase 2 in Sierra Leone b. >681 people enrolled c. Licensed obtained from CFDA in October 2017 to use under national reserves by National Medical Products Administration (NMPA), China in the event of Ebola outbreak Submitted to WHO for Emergency Use Assessment and Listing (EUAL) in July 2018.	1 dose	Reactive	18 to 60 years	+2°C to +8°C for 12 months	Final Formulation: Lyophilized Presentation: Single dose vial + diluent	20,000 doses	Can produce 150 000 doses per year and potentially scale-up to 500 000 doses/year.
Granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016										
rVSVΔG-ZEBOV-GP[2]	Merck, USA	Monovalent Zaire (Kikwit 1995)	a. Phase 3 completed in Guinea (2016). b. >200,000 people Over 18,000 people enrolled in clinical trials. Ongoing expanded access protocol in DRC with over 200,000 people vaccinated in affected areas in DRC c. Granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016 Submitting rolling BLA to US FDA and rolling MAA to EMA for licensure Submitting to WHO for EUAL.	1 dose	Reactive	Active immunization (reactive use) of at-risk subjects ≥ 18 years of age to protect against disease caused by *Zaire ebolavirus*. [When the required paediatric data are available, will seek an indication for use in subjects ≥ 1 year of age].	60°C to -80°C for 36 months And, 2°C – 8°C for 14 days	Final Formulation: Liquid frozen Presentation: 10 dose vials. After licensure single dose vials	380,000 doses currently available for dossing recommended by SAGE = 2x10^7 pfu/mL (Guinea dose) (Corresponds to – 190,000 doses available for dosing proposed for licensure)	For 2020, planned replenishments targets are set to be (display as Guinea dose (2x10^{7}pfu/mL): Jan 2020: Approx. 340000 additional doses April/May: Approx 60000 June-Dec: Approx 900 000 additional doses Total: Approx. 1300 000
Ongoing clinical evaluation										
INO-4201 (DNA vaccine)[3]	Inovio Pharmaceuticals, USA	Plasmid of Ebola outbreak strains from 1976-2006	a. Phase 1 b. >230 people enrolled	2 doses	Reactive	≥ 18 years	+2°C to +8°C for 3 years 25°C for 1 year 37°C for 1 month	Final Formulation: Liquid Presentation: Single-dose vials	Potentially have 10,000 doses in bulk remaining of INO-4201.	No information available

SAGE Ebola Vaccines

Type of candidate vaccine	Developer	Strain(s) aimed to protect against	Current stage of clinical evaluation Number of subjects with data analysed to date Regulatory status	Proposed vaccination schedule	Proposed indication	Proposed target population for the label indication	Current storage specifications*	Current formulation and presentation (doses per vial)	Number of clinical research grade does available	Forecasted production capacity
							60°C for several days			
ChAd3 (monovalent Zaire)[4]	Sabin Vaccines Institute / National Institute of Allergy and Infectious Diseases (NIAID), USA	Monovalent: Zaire (Mayinga)	a. Phase 2 in Cameroon, Senegal, Mali, Liberia, Nigeria b. >5,600 people enrolled c. GSK has sublicensed the investigational product to Sabin (press release).	1 dose	Reactive	Adults and Children		Final Formulation: Unknown Presentation: Single dose vials	450,000 doses	No data
PROPOSED INDICATION: PREVENTIVE USE										
Licensed in country of origin										
EpivacEbola[5]	FBRI SRC VB VECTOR, Rospotrebnadzor, Russia	Monovalent Zaire (Makona)	a. Phase 1 and 2/3 in Russia b. >300 people enrolled a. Licensed in Russia since 2016	2 doses (prime + boost on 28 days)	Preventive	18 to 55 years	2-8°C for 1 year Can extend shelf-life to 2 years	Final Formulation: Liquid Presentation: Single dose vial	20 000 doses currently available	Can produce 1,000,000 doses in a few weeks, no additional data
GamEvac-Combi and GamEvac-Lyo[6] rVSV-GP rAd5-GP	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	Monovalent Zaire (Makona)	a. Ongoing Phase 1/2 in Russia and Phase 3 in Guinea (Kindia) Phase 4 reported in Russia b. >2,000 people enrolled b. Licensed in Russia for emergency use in the event of an EVD outbreak	2 doses (prime + boost on 21 days) 1st dose: rVSV-GP 2nd dose: rAd5-GP	Preventive	18 to 55 years	16°C to -20°C for 12 months 4°C for lyophilized formulation	Final Formulation: Liquid frozen and Lyophilized Presentation: Single-dose vials	**No information available**	Can produce 20 000 doses per year and potentially scale-up to 100 000 doses/year.
Currently submitting o US FDA to seek licensure under the Animal Rule and/or to European Medicines Agency										
Ad26.ZEBOV & MVA-BN-Filo (2-dose regimen, VAC52150)[7]	Janssen Vaccines & Prevention B.V, The Netherlands	Zaire ebolavirus (Mayinga)	a. Phase 1: Four studies completed in Europe, the United States and Africa Phase 2/3: Six Phase 2/3 studies in Europe, USA and Africa (partially) unblinded; two Phase 2/3 studies in Africa ongoing b. >6,500 people enrolled c. Negotiating with the US FDA to obtain licensure using the Animal Rule Filing at EMA under conditional approval or approval under exceptional circumstances Collaborative review with WHO (PQ) and African NRAs planned d. Submitted file to WHO for EUAL. Received request for additional evidence.	2 doses 1st dose: Ad26.ZEBOV (EBOV GP) 2nd dose on day 56: MVA-BN-Filo (EBOV/SUDV/MARV GP, TAFV NP)	Preventive	Adults and children ≥ 1 year of age	Ad26.ZEBOV: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 12 months MVA-BN-Filo: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 6 months	Final Formulation: Liquid frozen Presentation: Single-dose vials	50,000 labelled regimens ready to be used. 1.5 million regimens in vials, QC-released, need to be labelled. Depending on urgency 45,000 or more additional regimens available each month	500,000 per year depending on the demand
Nanoparticle recombinant Ebola GP vaccine[8]	Novavax, USA	Monovalent Zaire (Makona)	a. Phase 1 b. >182 people enrolled	2 doses with planned boosts for HCW in potential epidemic areas	Preventive	≥ 18 years	N.A.	Final Formulation: Liquid Matrix-M1 Adjuvant Presentation: Separate single-dose vials	N.A.	

Notes

1 Ad5-EBOV (monovalent)

- Ad5-EBOV is a replication-defective recombinant human type 5 adenovirus expressing Zaire (Makona, 2014) Ebola virus envelope glycoprotein.
- After re-constitution, each dose includes two vials (0.5ml/vial) with a total volume of 1ml, containing $8\times10_{10}$ 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 Ia clinical trial of 120 Chinese subjects, an open Phase Ib clinical trial of 61 Africans in China (PMID: 25817373, 28017642, 2870962) and a Phase 2clinical trial of 500 Africans in West Africa (PMID: 28017399). Total 156 subjects were inoculated according to the registration specification ($8\times10_{10}$ VP/dose), 78 subjects were inoculated by $4\times10_{10}$ VP/dose and 355 subjects were inoculated by $1.6\times10_{11}$ VP/dose.
- Two Phase 1trials in China (120 and 61 healthy adults) and one Phase 2trial in Sierra Leone (500 healthy adults) were completed. The investigators reported good safety (the most common adverse events (AEs) reported included fever and mild injection site pain and no vaccine-related serious adverse events (SAEs) recorded) and immunogenicity profile (the geometric mean titre (GMT) of anti GP antibody peaked around 28 days after vaccination with a responder rate of 96% (95% CI: 91%-99%) but the vaccine-elicited antibody responses decreased on 168 days with a responder rate of 76% (95% CI: 67%-83%)) of Ad5-EBOV (PMID: 28017399).
- 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 Ebola virus (Zaire).
- EUAL application was submitted to WHO in July 2018 and is currently under review.

2 rVSVΔG-ZEBOV-GP

- rVSVΔG-ZEBOV-GP consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire Ebola virus (Kikwit 1995 strain).
- The formulation of rVSVΔG-ZEBOV-GP is liquid frozen; one dose with proposed 1ml per dose targeting adults. In the context of the ongoing outbreak in DRC, SAGE recommended to administer 0.5 mL per dose to increase the number of doses available.
- Eight Phase 1trials in Europe and Africa (115 and 185 healthy adults and 40 healthy children aged 6 to 17 years) (PMID: 26248510, 29627147, 25830326, 28985239), Canada (40 healthy adults) (PMID: 28630358), and the United States (78 and 512 healthy adults) (PMID: 25830322, 28606591), one Phase 2trial in Africa (1000 healthy adults) (NCT02344407), one Phase II/III trial in Africa (8673 healthy adults) (PMID: 27387395, 29788345), and two Phase 3 trials in Africa (5837 healthy adults) (PMID: 26215666, 26248676, 28017403), and in the United States, Canada and Europe (1197 healthy adults) (PMID: 28549145). The investigators reported acceptable safety profile (the most common AEs reported included injection site pain, headache, pyrexia, fatigue, myalgia and chills and few vaccine-related SAEs recorded) and 100% (95% CI: 69%-100%) efficacy (PMID: 28017403)of rVSVΔG-ZEBOV-GP in the ring-vaccination Guinea trial. The GMT were sustained with minimal change through 360 days after vaccination (PMID: 28606591) .
- Two Phase 2trials on populations aged from 13 to 65 years in Africa and Canada (NCT03031912) and older than 1 year in Africa (NCT02876328) are ongoing.
- Granted Breakthrough Therapy Designation from FPA and PRIME status from EMA since 2016.

- The developer submitted an application for licensure to the US FDA and the EMA; the expected timeline to obtain regulatory approval is early 2020. There is ongoing discussion with both regulatory authorities to shorten the timelines.
- EUAL application was submitted to WHO in 2015, and is currently under review.
- No WHO prequalification has been obtained.

3 INO-4201 (DNA vaccine)

- DNA vaccine INO-4201 is a synthetic DNA plasmid construct expressing Ebola GP designed from consensus DNA sequences of Ebola outbreak strains from 1976-2006.
- The formulation of INO-4201 is liquid; two doses with proposed 2mg per dose intradermally administered in an interval of 4 weeks; targeting to adults aged over 18 years.
- One Phase 1 trial in the Unites States (75 healthy adults in the initial study) (NCT02464670) was completed. Final analysis (JID) showed acceptable safety profile (the most common AEs reported included injection site pain, redness, swelling and itching and no vaccine-related SAEs recorded). Humoral and cellular levels were similar to the rVSV vaccine (Tebas *et al*, JID 2019)
- No EUAL submission was initiated and no WHO prequalification has been obtained.

4 ChAd3 (monovalent Zaire)

- ChAd3 (monovalent Zaire) vaccine consists of ChAd3-EBOZ glycoprotein Zaire drug substance
- ChAd3 (monovalent Zaire) has been administered to over 5000 adults and children
- A Phase 1 trial was conducted in Mali (91 healthy adults) (NCT02267109). A Phase 1/1b trial has been completed in 143 adults in the U.S. (NCT02231866). A Phase Ib trial has been completed in 90 adults in Uganda (NCT02354404). The investigators reported acceptable safety profile of ChAd3 (monovalent Zaire)
- A Phase 1/2 trial was conducted in 120 healthy adults in Switzerland (NCT02289027)
- Three Phase 2 trials were conducted and completed in Cameroon, Nigeria, Senegal, Mali (3013 adults and 600 children), and Liberia (1500 adults) (NCT02485301; NCT02548078; NCT02344407). The investigators reported acceptable safety profile of ChAd3 (monovalent Zaire)
- ChAd3 (monovalent Zaire) has been licensed to GSK and sublicensed to Sabin Vaccine Institute (press release).
- No EUAL submission was initiated and no WHO prequalification has been obtained.

5 EpiVacEbola

- EpiVacEbola is a polyepitope vaccine, for the prevention of Ebola fever, based on peptide antigens conjugated to a carrier protein and adsorbed to an aluminium-containing adjuvant.
- The vaccine contributes to the development of protective immunity against the Zaire strain of Ebola virus following two subcutaneous administrations, spaced 21 to 28 days apart.
- A Phase 1 trial was conducted in Russian (60 healthy adults). A Phase 2-3 trial has been completed in 240 healthy adults in Russia.
- Two subcutaneous 100-µg doses (0.5 mL) given 28 days apart are well tolerated by adults aged 18-60. Low frequency of local and systemic reactions suggests good tolerance and low reactogenicity of the vaccine. Physical examinations as well as clinical and biochemical assays of blood and urine demonstrated no pathologic changes, which suggest a high safety profile of the vaccine. The vaccine induced Ebola-specific antibodies and virus-neutralizing antibodies in 78% and 71% of cases, respectively.

6 GamEvac-Combi and GamEvac-Lyo

- 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 but 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 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) (PMID: 28152326) and one Phase 4 trial in Russia (60 healthy adults) (NCT02911415) were completed for GamEvac-Combi. The investigators reported good safety (the most common AE reported was injection site pain and no vaccine-related SAEs recorded) and immunogenicity profile (antigen-specific response was detected in 93% (half dose) and 100% (full dose) on 28 days after vaccination, and 100% on 42 days) of GamEvac-Combi (PMID: 28152326).
- There is one Phase 3 trial of GamEvac-Combi in Guinea, Africa (2000 healthy adults) (NCT03072030) and one Phase I/II trial of GamEvac-Lyo in Russia (220 healthy adults) (NCT03333538) on-going.
- GamEvac-Combi has been licensed by the Ministry of Health of the Russian Federation for emergency use in the territory of the Russian Federation in December 2015 (registration number: LP-003390). The emergency license was based on Phase 1and II clinical data of safety and immunogenicity (PMID: 28152326).
- No EUAL submission was initiated.
- Regarding WHO prequalification the company stated that a decision to submit will be made after completion of the Phase 3 GamEvac-Combi clinical trial in Guinea.

7 Ad26.ZEBOV & MVA-BN-Filo (2-dose regimen, VAC52150)

- Ad26.ZEBOV is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which encodes the full-length GP of the EBOV Mayinga variant, and is produced in the human PER.C6®cell line. MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which encodes 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). It is manufactured in chicken embryo fibroblast cells derived from specific pathogen-free eggs.
- The formulation of Ad26.ZEBOV, MVA-BN-Filo is liquid frozen. The vaccine regimen consists of an immunization with Ad26.ZEBOV (5×10^{10} vp) as the first dose, followed by MVA-BN-Filo (1×10^{8} Inf U) as a second dose 56 days later. The proposed target population includes adults and children aged ≥ 1 year.
- Efficacy of the vaccine was demonstrated in an EBOV animal model where vaccination with the clinical dose provided 100% protection. Partial protection was observed when the doses of the vaccines were reduced. A shorter interval between doses as well as an inverted dose-order were also associated with lower protective efficacy rates.
- Four Phase 1 trials were completed: 87 healthy adults in Europe (PMID: 27092831, 28291882), 164 healthy adults in the United States (NCT02325050) and 72 and 72 healthy adults in Africa (NCT02376426, NCT02376400). Three Phase 2 trials were completed: 423 healthy adults in Europe (NCT02416453), 200 healthy adults and 200 HIV-infected adults in the United States and Africa (NCT02598388), and 669

healthy adults, 142 HIV-infected adults, 132 healthy adolescents and 132 healthy children in African countries (NCT02564523). Two Phase 3 trials in the United States (144 and 329 healthy adults) (NCT02543567, NCT02543268) were completed. One Phase 3 study in an Ebola-affected region (Sierra Leone) (445 healthy adults, 192 healthy adolescents and 193 healthy children) (PMID: 27821112) with the aim of establishing safety and immunogenicity in adults, followed by an expanded safety and immunogenicity study in adults and children was partially unblinded. In addition, one Phase 1/2/3 trial on healthy children and adults aged less than 71 years in multi-countries in the United States, Europe and Africa (NCT02661464) are ongoing. One additional trial was started in 2017, PREVAC (in partnership with NIAID, INSERM, LSHTM) (NCT02876328), to evaluate the safety and immunogenicity of the vaccine regimen in previously affected countries (Guinea, Liberia, and potentially Sierra Leone). Finally, in August 2018, a safety and immunogenicity trial in health care and frontline workers was started in Uganda (NCT04028349).

- To date more than 6,500 people have been enrolled. The available (partially) unblinded and analyzed clinical studies (4 Phase 1, 3 Phase 2, and 3 Phase 3) evaluating the 2-dose Ad26.ZEBOV, MVA-BN-Filo regimen in different intervals (14 to 84 days) in adults did not reveal any safety concerns. An unblinded safety review on pooled data from 1932 adults (of which 118 HIV+) revealed only mild to moderate AEs of short duration with no sequelae. Unblinded pediatric safety data are available for 649 children aged ≥1 year receiving active vaccination (253 adolescents 12-17 years old; 252 children 4-11 years old and 144 toddlers 1-3 years old) and 189 children receiving at least one dose of placebo/control. Overall, the safety profile consists of mild to moderate AEs of short duration with no sequelae, with no relevant differences compared with adult participants. No safety signals were identified.
- Following phase 1 vaccine development, phase 2 and 3 studies confirm the robust immunogenicity of the vaccine regimen, including long term persistence of the immune response up to at least two years. The vaccine has been demonstrated to be immunogenic in all populations evaluated.
- In the absence of clinical efficacy data, and as agreed with regulatory agencies EMA and FDA, the likelihood of protection of the Ad26.ZEBOV, MVA-BN-Filo 0, 56 vaccine regimen is inferred by immunobridging. For this, human immunogenicity is assessed against an animal model that describes the relationship between immunogenicity and survival after a challenge with Ebola virus.
- Ad26.ZEBOV/MVA-BN-Filo has not been licensed yet. Agreements on the approach to demonstrate the protective effect of the vaccine were achieved with FDA (licensure under Animal Rule) and EMA (conditional approval or licensure under exceptional circumstances). WHO PQ and African country registrations are planned to be achieved via parallel review with EMA.
- A file in support of WHO EUAL was submitted to WHO in a rolling manner including CMC, non-clinical and clinical Phase 1/2/3 data in July/September 2016 and in subsequent annual updates.

8 Nanoparticle recombinant Ebola GP vaccine

- The nanoparticle vaccine is based on purified recombinant full-length and unmodified 2014 Guinea EBOV GP trimers that self-assemble into distinct nanoparticle structures of approximately 30 to 40 nm diameter. The baculovirus/Sf9 insect cell system was used to clone and express the recombinant EBOV GP protein.
- A Phase 1, randomized, observer-blinded, dose-ranging study to evaluate the immunogenicity and safety of EBOV GP Vaccine with or without Matrix-M1 adjuvant in healthy subjects (≥ 18 to < 50 years of age) was conducted in Australia and completed through 1 year follow-up in April 2016 (NCT02370589). This study demonstrated the safety of single (Day 0) and repeat doses (Days 0 and 21) of the EBOV GP Vaccine (antigen doses of 6.5, 13, 25, or 50 µg) administered IM alone or in combination with Matrix-M1 adjuvant (50 µg) in healthy volunteers.

- No EUAL submission was initiated and no WHO prequalification has been obtained.