Update with the development of Ebola vaccines and implications of emerging evidence to inform future policy recommendations

1. Policy questions and overall conclusions

1.1. Are there remaining challenges that may prevent access to Ebola vaccines in future outbreaks, and, if yes, can SAGE make recommendations on how these might be addressed?

- Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases. Two vaccines were licensed nationally under emergency use provisions, eight vaccines have completed or are in trials up to Phase I stage, two vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. The Phase III trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP) was undertaken in Guinea and is the only study that has so far been able to demonstrate clinical efficacy and effectiveness for any candidate Ebola vaccine.
- The two licensed vaccines are a prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) and a monovalent candidate vaccine based on recombinant adenovirus type-5 vector (Ad5-EBOV).
- The rVSVΔG-ZEBOV-GP candidate vaccine with efficacy data was granted access to the Priority Medicine (PRIME) scheme by the European Medicines Agency (EMA) and Breakthrough Therapy Designation by the US Food and Drug Administration (FDA). This vaccine has also applied for the WHO Emergency Use Assessment and Listing (EUAL) procedure.
- The rVSVΔG-ZEBOV-GP candidate vaccine, a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) and the Ad5-EBOV candidate vaccine have submitted EUAL documentations to the WHO Secretariat. For all three vaccines, submissions were accepted and evaluated on a rolling basis and conclusions are expected to be available before the SAGE meeting.
- Potentially, various licensure options exist for candidate vaccines, e.g. animal rule (US), exceptional circumstances (EU), other provisions for licensure or deployment in emergencies.
- The WHO Secretariat is implementing the work plan of the Research and Development (R&D) Blueprint for Action to Prevent Epidemics, including experts' deliberations on future clinical trials for candidate Ebola vaccines. The Working Group recommended that there should be greater alignment of different initiatives (e.g. Coalition for Epidemic Preparedness Innovations [CEPI], and others) to support the development and licensure of Ebola vaccines and of other vaccines against epidemic-prone diseases, taking note of the mandates specific to each stakeholder.

1.2. Is the current evidence sufficient for SAGE to make recommendations regarding the use of Ebola vaccines in case of another Ebola outbreak (pre-licensure and/or post licensure)? If yes, which recommendations can be proposed? If not, what key data are missing?

- A single dose of rVSVΔG-ZEBOV-GP has shown 100% efficacy (95% confidence interval [CI]: 64%–100%) in a cluster randomized ring vaccination trial conducted in

Guinea (1). Ring vaccination with the same candidate vaccine was also carried out following the smaller flare-ups in 2016 in Guinea, Sierra Leone and Liberia and the most recent outbreak in the Democratic Republic of Congo (DRC).

- The duration of the immune responses elicited by the Ebola vaccines under development is currently documented for the observed follow-up periods of the trials. These periods remain short. As of July 2018, the information on the duration of protection for various candidate Ebola vaccines is up to 360 days post vaccination for the rVSVΔG-ZEBOV-GP (2), Ad26.ZEBOV/MVA-BN-Filo (3), and ChAd3-EBOZ vaccines (4). Although the understanding of the immune response to both natural infection and vaccination remains incomplete, it is expected that prime/boost vaccines offer better prospects of long-term protection to an Ebola virus infection than a single dose schedule. However, vaccines that elicit an earlier immune response after a single/first dose are likely to be more useful during outbreaks.
- Another uncertainty is whether vaccines protecting against Zaire Ebola virus species afford cross-protection against other species of Ebola virus and other filoviruses. Preliminary cross-protection data, assessed by enzyme-linked immunosorbent assays and virus neutralization assays results against other Ebola strains, was only reported for three candidate vaccines. There is no data on cross-protection against Marburg virus for any candidate vaccine.
- As no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee Expanded Access (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. Evidence from Phase I–III clinical trials and from the deployments during the 2018 outbreaks as well as modelling results comparing different vaccination strategies justify Expanded Access this candidate vaccine in a ring vaccination modality in outbreak responses. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries.
- In the event of an outbreak in the near future, doses of rVSVΔG-ZEBOV-GP would be available from different sources. Researchers in West Africa have a few thousand doses left from the trials, currently stored under Good Clinical Practices conditions. The manufacturer reported that there are a few thousand doses in stock that are owned by the US Biomedical Advanced Research and Development Authority. In addition, the manufacturer committed to produce 300,000 doses for GAVI Alliance through an Advance Procurement Commitment (APC).

2. Key findings

2.1. Epidemiology

From 1976 to Sep 2018, 42 filoviruses outbreaks have been documented (**Appendix 1**). Zaire ebolavirus caused 28 of these outbreaks (30,294 reported cases in total), Sudan ebolavirus seven (792), Bundibugyo ebolavirus two (206), Taï Forest one (1), and Marburg marburgvirus four (425). When the 2013–2016 West African epidemic is omitted, the range of reported cases for the 24 remaining Zaire ebolavirus outbreaks

was 1–318 (median=31). **Figure 1** illustrates the epidemic curve of such an outbreak (5). The 2013–2016 Zaire ebolavirus epidemic in West Africa was unprecedented in its geographical spread and total number of reported cases, but this epidemic lasted slightly longer than a Marburg virus outbreak that began in October 1998 in Angola (109 vs. 100 weeks) (6;7). When these two occurrences are omitted, the outbreaks have lasted between 1 and 42 weeks, with a median duration of 8.5 weeks. Other filoviruses known to infect humans are Reston ebolavirus (asymptomatic infections only in persons exposed to nonhuman primates and pigs from the Philippines) (8).

Since the 1995 Kikwit outbreak, the **principles for interrupting transmission of Ebola and Marburg viruses** are well characterized (9). These four principles are:

1. infection control in health-care facilities and protection of health-care workers;
2. detection, management and isolation of patients;
3. surveillance (inclusive of back and forward contact tracing) and fever surveillance with rapid diagnosis and isolation; and
4. community understanding with safe patient and body transport systems, safe burial and household/environmental decontamination.

While these principles were probably not implemented with sufficient rigor and in the proper order initially in the 2013–2016 epidemics of West Africa, they eventually led to transmission interruption.

In the 2013–2016 epidemics of West Africa, reported incidence in children and adolescents was lower than in adults (**Figure 2**) and **health-care workers (HCWs) were initially at increased risk** (**Figure 3**). As already observed in previous outbreaks, HCWs can play a role in amplifying an early, low-level transmission of Ebola viruses.

Although already postulated earlier, the 2013–2016 West African epidemic also showed the possibility of **late transmission via semen of Ebola virus disease survivors** as well as transmission via breast milk from a sub-symptomatic mother to her baby (10-14).

There have been two Ebola outbreaks in DRC in 2018 (by Sep 2018). An earlier outbreak occurred from April to August 2018 and a later one was started in August 2018 and is still on going in September 2018.

Figure 1. Epidemic curve of Ebola virus disease cases, by transmission mode – Yambuku, Democratic Republic of Congo, 1976 (5)

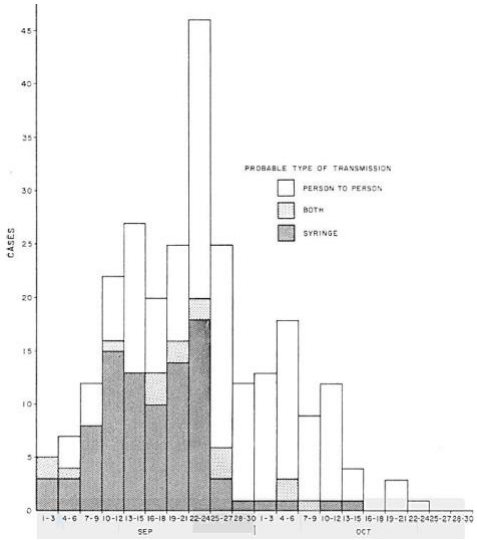


Figure 2. Age-specific cumulative incidence of confirmed and probable Ebola virus disease cases, by country – West Africa, 2013-2016 (15)

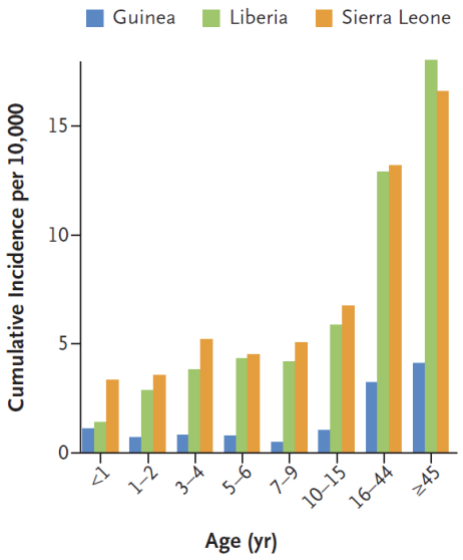
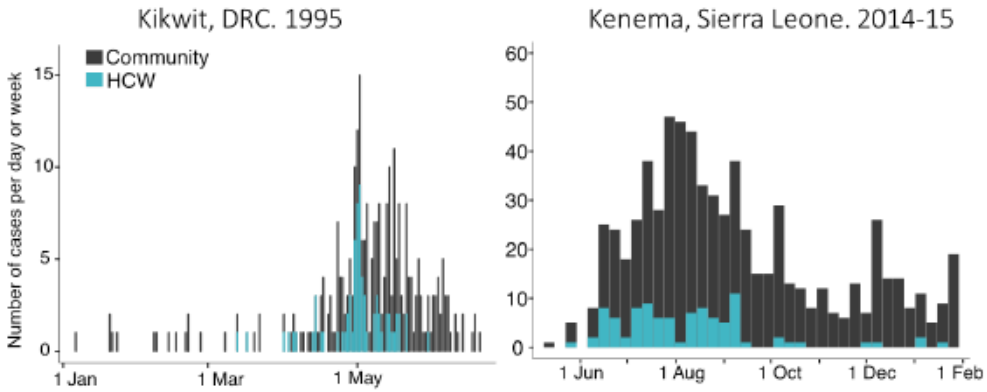


Figure 3. Epidemic curve of Ebola virus disease cases, by health-care workers (HCWs) and general population – Democratic Republic of Congo, 1995 and Sierra Leone, 2014-2015 (16;17)

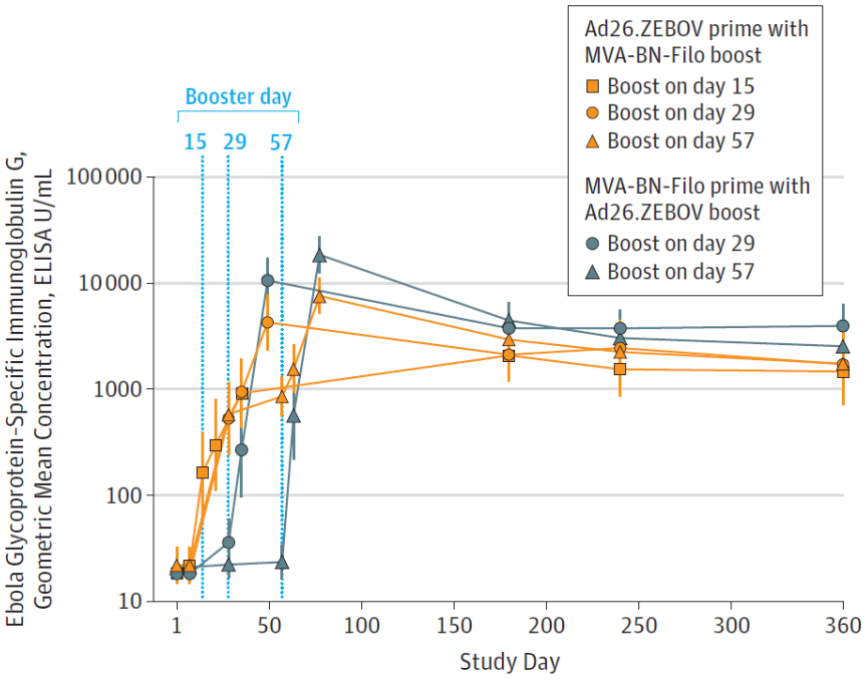


2.2. Vaccine development

Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases (**Table 1**). Two vaccines were licensed, eight vaccines have completed or are in trials up to Phase I stage, two vaccines up to or in Phase II stage, and one vaccine has completed Phase III stage. **Appendix 2** summarizes the published information on the clinical trials of all these vaccines or their combinations. Some vaccines are tested as single-dose regimen (Ad5-EBOV, ChAd3-EBOZ, rVSVΔG-ZEBOV-GP), while others include a priming and either homologous or heterologous boosting. When prime/boost regimens are tested, the interval between doses is at least 3–4 weeks.

Data on safety and immunogenicity are accumulating for all candidate vaccines under active clinical development (**Appendix 2**). Trials have not reported serious adverse events definitely linked to any candidate vaccine. However, **safety profile** is still being characterized and additional safety information is being generated for children and special populations. Limited systematic head-to-head comparisons are available. All vaccines show detectable humoral and cellular **immune responses** when measured after both priming and boosting (for instance, **Figure 4**). However, follow-up times over which maintenance of these immune responses are documented remain limited. As of July 2018, the longest available interval is 12 months, which refers to the Ad26.ZEBOV/MVA-BN-Filo, ChAd3-EBOV and rVSVΔG-ZEBOV-GP vaccines (2;3;18;19). Surrogates of protection are not defined yet.

Figure 4. Humoral immune response to Ad26.ZEBOV/MVA-BN-Filo vaccine in a Phase I trial (3)



Efficacy and effectiveness data are only available for rVSVΔG-ZEBOV-GP (1). In a Phase III trial mainly carried out in Guinea in 2015, this vaccine showed a 100% efficacy (95% CI: 64%–100%). **Table 2** details the efficacy and effectiveness results from this trial.

Table 1. Overview of candidate Ebola vaccines

Type of candidate vaccine	Strain(s) aimed to protect against	Current stage of clinical evaluation/regulatory status	Proposed vaccination schedule	Indication	Proposed target population	Storage	Current presentation
Candidate vaccines with updated data as of 5 June 2018							
Ad5-EBOV (monovalent) [1]	Monovalent Zaire (Makona)	- Phase II - Licensed based on Animal Rule by the Chinese Food and Drug Administration (FDA) - Submitting to WHO for Emergency Use Assessment and Listing (EUAL)	1 dose	Reactive	18 to 60 years	+2°C to +8°C for 12 months	2 vials of lyophilized powder + 1 vial of diluent
Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150) [2]	Multivalent: Zaire (Mayinga), Sudan, Tai Forest and Marburg	- Phase II completed in Europe, the United States and Africa - Ongoing Phase II in Africa, Phase III in Sierra Leone and Phase I/II/III in multi-countries - Submitted dossier to the US FDA to request licensure using the Animal Rule - Submitting to WHO for EUAL	2 doses (prime + boost on 28 or 56 days)	Preventive	≥ 18 years (possibly ≥ 1 year)	Ad26.ZEBOV: -20°C to -60°C for 48 months and +2 to +8°C for 12 months MVA-BN-Filo: 20°C to -60°C for 42 months and +2 to +8°C for 6 months	- Liquid frozen - Separate single-dose vials
ChAd3 (monovalent, ChAd3-EBO-Z) [3]	Monovalent Zaire (Mayinga)	Phase II	1 dose	Reactive	≥ 1 year	≤ 60°C for 24 months	- Liquid frozen - Single-dose vials
GamEvac-Combi and GamEvac-Lyo [4]	Monovalent Zaire (Makona)	- Phase IV completed in Russia - Ongoing Phase I/II in Russia and Phase III in Guinea (Kindia) - Licensed in Russia based on Phase I/II trial	2 doses (prime + boost on 21 days)	Preventive	18 to 55 years	-16°C to -20°C for 12 months	- Liquid frozen and Lyophilized - Single-dose vials
rVSVΔG-ZEBOV-GP [5]	Monovalent Zaire (Kikwit 1995)	- Phase III completed in Africa, the United States, Canada and Europe and expanded access protocol in Guinea Forestiere - Ongoing expanded access protocol in DRC - Ongoing Phase II in Canada and Africa - Granted Breakthrough Therapy	1 dose	Reactive	≥ 18 years	- 60°C to -80°C for 36 months	- Liquid frozen - 10-dose vials

Type of candidate vaccine	Strain(s) aimed to protect against	Current stage of clinical evaluation/regulatory status	Proposed vaccination schedule	Indication	Proposed target population	Storage	Current presentation
		Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) since 2016 - Submitting to WHO for EUAL					
DNA vaccine (INO-4212) [6]	Plasmid of the Guinea Makona strain	Phase I	2 doses	Reactive	≥ 18 years	+2°C to +8°C for 3 years and 25°C for 1 year	- Liquid - Separate single-dose vials
Candidate vaccines not having updated data (last update by Apr 2017)							
Ad5 (bivalent) [7]	Bivalent: Zaire (Mayinga), Sudan-Gulu	Phase I	1 dose	Preventive	18 to 50 years	-	Single-dose vials
ChAd3-EBOZ & MVA-BN-Filo (prime/boost) [8]	Multivalent: Zaire (Mayinga), Sudan, Tai Forest and Marburg	Phase I	2 doses	Preventive	18 to 50 years	-	- Liquid frozen - Separate single-dose vials
ChAd3 (bivalent) [9]	Bivalent: Zaire (Mayinga), Sudan-Gulu	Phase I	1 dose	Preventive	18 to 50 years	-	Single-dose vials
rVSV N4CT1 EBOVGP1 [10]	Trivalent: Zaire (Mayinga), Sudan (Boniface), Marburg (Angola)	Phase I	1 or 2 doses	Reactive and Preventive	≥ 1 year	<-70°C for more than 10 years	- Liquid frozen - Single-dose vials
Nanoparticle recombinant Ebola GP vaccine [11]	Monovalent Zaire (Makona)	Phase I	2 doses	Preventive	18 to 50 years	-	Separate single-dose vials
DNA plasmid vaccines [12]	Zaire (Mayinga), Marburg	Phase I	3 doses	Preventive	18 to 60 years	-	Separate single-dose vials
HPIV3-EbovZ GP [13]	Monovalent Zaire (Makona)	Phase I	2 doses	Preventive	18 to 50 years	-	Separate single-dose vials

Table 1 - Notes

[1] Ad5-EBOV (monovalent)

- Ad5-EBOV is a recombinant adenovirus type-5 vector-based Ebola vaccine which expresses envelope glycoprotein (GP) of Zaire Ebola virus species (Makona variant, monovalent).
- The formulation of Ad5-EBOV is lyophilized powder plus diluent; one dose with proposed 8 X 10^{10} vp per dose targeting adults aged 18 to 60 years.
- Two Phase I trials in China (120 and 61 healthy adults) (PMID: 25817373, 28017642, 2870962) and one phase II trial in Sierra Leone (500 healthy adults) (PMID: 28017399) 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).
- Ad5-EBOV has been licensed in China under the animal rule using data from 8 non-human primates challenged on day 28 (PMID: 27493239) and Phase II immunogenicity data for emergency use in the case of an outbreak (PMID: 28017399).
- EUAL application was submitted to WHO in July 2018, and is currently under review.
- WHO prequalification of Ad5-EBOV is planned in 2019-2020.

[2] Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150)

- Ad26.ZEBOV is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which expresses 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 expresses 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 a prime immunisation with Ad26.ZEBOV followed by a boost immunisation with MVA-BN-Filo 28 or 56 days later. The proposed doses of Ad26.ZEBOV and MVA-BN-Filo are 5 X 10^{10} and 1 X 10^{8} vp per dose respectively. The proposed target population includes adults, human immunodeficiency virus (HIV)-infected adults and possibly children aged ≥ 1 year.
- Four Phase I 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 II 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 III trials in the United States (144 and 329 healthy adults) (NCT02543567, NCT02543268) were completed. The investigators reported good safety (the most common AEs reported was injection site pain and no vaccine-related SAEs recorded) and immunogenicity profile (93% (95% CI: 68%-100%) and 100% (95% CI: 77%-100%) responder rates on 28 and 56 days after Ad26.ZEBOV prime respectively and the vaccine-induced T-cell responses persisted on 360 days in 62% (95% CI: 32%-86%) and 83% (95% CI: 52%-98%) participants receiving MVA-BN-Filo boost on 28 and 56 days after prime respectively) of Ad26.ZEBOV/MVA-BN-Filo (PMID: 27092831, 28291882).
- In addition, one Phase II trial on populations aged older than 1 year in African countries (NCT02876328) and one Phase I/II/III trial on healthy children and adults aged less than 71 years in multi-countries in the United States, Europe and Africa (NCT02661464) are ongoing. The planned Phase III study originally focused on a staged approach 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 and an effectiveness study in preventing cases of Ebola Virus Disease. Since designing this Phase III effectiveness study, the epidemic waned and it is currently infeasible to conduct an effectiveness evaluation as part of this study, so this component has been removed. 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).

- Ad26.ZEBOV/MVA-BN-Filo has not been licensed yet but a dossier has been submitted to the US FDA to request licensure using the animal rule.
- A rolling EUAL submission including CMC data, non-clinical and clinical Phase I data was submitted to WHO in July/September 2016 and is annually updated.
- No WHO prequalification has been obtained.

[3] ChAd3 (monovalent, ChAd3-EBO-Z)

- ChAd3-EBO-Z vaccine consists of a recombinant replication-defective chimpanzee adenovirus Type 3 vector (ChAd3) engineered to express the WT GP antigen from Ebola virus Zaire (Mayinga strain).
- The formulation of ChAd3-EBO-Z is liquid frozen; one dose with proposed 1 X 10^{11} particle units (pu) per dose targeting population older than 1 year of age.
- Two Phase I trials, one in Europe (120 healthy adults) (PMID: 26725450) and one in the United States (91 healthy adults) (PMID: 26546548), and two Phase II trials in Africa (3024 healthy adults and 600 healthy persons aged from 1 to 17 years) (NCT02485301, NTC02548078) were completed. The investigators reported an acceptable safety profile (the most common AEs reported included injection site pain and tenderness, fatigue and headache and no vaccine-related SAEs recorded) and immunogenicity profile (different dose levels showed 96% (95% CI: 86%-100%) and 96% (95% CI: 87%-100%) responder rates on 28 days after vaccination but the antibody response decreased by roughly half by 180 days following vaccination; GMT decreased from 51ug/mL (95% CI: 41-63) to 26ug/mL (95% CI: 21-32) in the high-dose group and from 45ug/mL (95% CI: 26-56) to 22ug/mL (95% CI: 19-29) in the low-dose group) of ChAd3-EBO-Z (PMID: 26725450).
- ChAd3-EBO-Z has not completed Phase III efficacy testing (PMID: 25629663). With the Ebola outbreak declared over, and no opportunity to establish the clinical benefit of the candidate vaccine, the developer has decided not to submit the monovalent Zaire Ebola vaccine candidate for licensure at this time. The clinical, non-clinical, and stability studies already initiated will be continued until completion and the manufacturing and regulatory dossiers will be completed accordingly.
- ChAd3-EBO-Z has not been licensed and the developer has decided not to submit this candidate vaccine for licensure at the time.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[4] 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 IV 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 III 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 I and 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 III GamEvac-Combi clinical trial in Guinea.

[5] 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.
- Eight Phase I trials 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 II trial in Africa (1000 healthy adults) (NCT02344407), one Phase II/III trial in Africa (8673 healthy adults) (PMID: 27387395, 29788345), and two Phase III 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 II trials 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 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.

[6] DNA vaccine (INO-4212)

- DNA vaccine (INO-4212) is a combination of INO-4201 and INO-4202. INO-4201 is a synthetic DNA plasmid construct expressing Ebola GP designed from consensus DNA sequences of Ebola outbreak strains from 1976-2006. INO-4202 is a DNA plasmid construct expressing Ebola GP from Ebola outbreak strain (Guinea) of 2014.
- The formulation of INO-4201 is liquid; two doses with proposed 2mg per dose in an interval of 4 weeks; targeting to adults aged over 18 years.
- One Phase I trial in the Unites States (75 healthy adults in the initial study) (NCT02464670) is ongoing. Interim analysis showed acceptable safety profile (the most common AEs reported included injection site pain, redness, swelling and itching and no vaccine-related SAEs recorded).

- Product currently in Phase I testing. Potential for application for licensure via Animal Rule by 2019/2020.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[7] Ad5 (bivalent)

- Ad5 is a recombinant adenovirus type-5 vaccine which expresses GP of Zaire strain of Ebola virus (Ad5.EBO.GP(Z).mt) and Gulu strain of Sudan Ebola virus species (Ad5.EBO.GP(S/G).mt).
- One dose of Ad5 (bivalent) is targeting adults aged 18 to 50 years.
- One Phase I trial of Ad5 (bivalent) in the United States (32 healthy adults) (21034824) was completed. The investigators reported acceptable safety profile (two of three AEs reported were asymptomatic prolongations in the activated partial-thromboplastin time in the 2 weeks following vaccination) of Ad5 (bivalent).
- Ad5 (bivalent) has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[8] ChAd3-EBOZ & MVA-BN-Filo (prime/boost)

- ChAd3-EBOZ vaccine consists of a recombinant replication-defective ChAd3 engineered to express the WT GP antigen from Ebola virus Zaire (Mayinga strain). MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which expresses 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 ChAd3-EBOZ/MVA-BN-Filo is liquid frozen. The vaccine regimen consists of a prime immunisation with ChAd3-EBOZ followed by a boost immunisation with MVA-BN-Filo 0, 7 or 14 days later. The target population is adults aged 18 to 50 years.
- Two Phase I trials of ChAd3-EBOZ/MVA-BN-Filo in the United Kingdom (60 healthy adults) (25629663) and in Mali (91 healthy adults) and the United States (20 healthy adults) (26546548) were completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain) of ChAd3-EBOZ/MVA-BN-Filo.
- ChAd3-EBOZ/MVA-BN-Filo has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[9] ChAd3 (bivalent)

- ChAd3 (bivalent) vaccine consists of cAd3-EBO glycoprotein Zaire and cAd3-EBO glycoprotein Sudan drug substances.
- One dose of ChAd3 (bivalent) is targeting adults aged 18 to 50 years.
- One Phase I trial of ChAd3 (bivalent) in the United States (20 healthy adults) (25426834) was completed. The investigators reported acceptable safety profile of ChAd3 (bivalent).
- ChAd3 (bivalent) has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[10] VSV N4CT1 EBOVGP1

- rVSV N4CT1 can be used individually or as a blended tri-valent vaccine. The monovalent vaccines are vectored by an attenuated replication competent rVSV vector. The Ebola vaccine (rVSV N4CT1 EBOVGP1) expresses the Mayinga strain GP of Zaire Ebola, the Sudan Ebola virus vaccine (rVSV N4CT1 SUDVGP1) expresses the GP from the Boniface strain and the Marburg vaccine (rVSV N4CT1 MARVGP1) expresses the GP from the Angola strain.
- The formulation of rVSV N4CT1 EBOVGP1 is liquid frozen; one dose of it is targeting adults aged 18 to 55 years.
- One Phase I trial of rVSV N4CT1 EBOVGP1 in the United States (39 healthy adults) (NCT02718469) was completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain) of rVSV N4CT1 EBOVGP1.

- rVSV N4CT1 EBOVGP1 has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[11] Nanoparticle recombinant Ebola GP vaccine

- Nanoparticle recombinant Ebola GP vaccine is an Ebola vaccine which expresses GP of Zaire Ebola virus species (Makona variant).
- Two doses of nanoparticle recombinant Ebola GP vaccine is targeting adults aged 18 to 50 years.
- One Phase I trial of nanoparticle recombinant Ebola GP vaccine in Australia (230 healthy adults) (NCT02370589) was completed. No published data on safety profile has been reported.
- Nanoparticle recombinant Ebola GP vaccine has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

[12] DNA plasmid vaccines

- The Ebola DNA plasmid vaccine is composed of 2 plasmids including GP from the Zaire and Sudan-Gulu species. The Marburg DNA plasmid vaccine consists of one plasmid expressing GP of the Marburg Angola strain.
- One dose of DNA plasmid vaccine is targeting adults aged 18 to 60 years.
- Three Phase I trials of DNA plasmid vaccines in the United States (27 (16988008) and 20 (25225676) healthy adults) and Uganda (108 healthy adults) (25540891) were completed. The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain and tenderness) of DNA plasmid vaccines.
    - DNA plasmid vaccines have not been licensed.
- No EUAL submission was initiated and no WHO prequalification have been obtained.

[13] HPIV3-EbovZ GP

- HPIV3-EbovZ GP vaccine is a live attenuated human parainfluenza virus type 3 vectored vaccine which expresses GP of Zaire Ebola virus species (Makona variant).
- Two doses of HPIV3-EbovZ GP vaccine is targeting adults aged 18 to 50 years.
- One Phase I trial of HPIV3-EbovZ GP vaccine in the United States (30 healthy adults) (NCT02564575) was completed and another Phase I trial in the United States (30 healthy adults) was started in March 2018 (NCT03462004). No published data on safety profile has been reported.
- HPIV3-EbovZ GP vaccine has not been licensed.
- No EUAL submission was initiated and no WHO prequalification has been obtained.

Table 2. Effect of rVSVΔG-ZEBOV-GP vaccine on cases of Ebola virus disease in different study populations – Guinea and Sierra Leone (2)

	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) *vs* all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) vs delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) *vs* all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed (group B)	All eligible in immediate (group A) *vs* all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) *vs* all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0·17%	0%	0%	0%	0·22%	0·22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0·43%	0·51%	0·49%	0·49%	0·7%	0·52%	0·52%	0·49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%, 95% CI)	100% (77·0 to 100·0)	100% (79·3 to 100·0)	70·1% (−4·9 to 91·5)	100% (−51·5 to 100·0)	100% (63·5 to 100·0)	100% (68·9 to 100·0)	64·6% (−46·5 to 91·4)	64·6% (−44·2 to 91·3)
p value§	0·0012	0·0033	0·2759	0·125	0·0471	0·0045	0·344	0·3761

2.3. Vaccine approval

To date, no vaccine has been WHO-prequalified or completed the WHO EUAL procedure. The rVSVΔG-ZEBOV-GP candidate vaccine, a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) and the Ad5-EBOV candidate vaccine have submitted EUAL documentations to the WHO Secretariat. For all three vaccines, submissions were accepted and evaluated on a rolling basis and conclusions are expected to be available before the SAGE meeting.

With regard to regulatory agencies, two candidate vaccines, GamEvac-Combi and Ad5-EBOV are licensed in the Russian Federation and China respectively, their countries of origin. Also, rVSVΔG-ZEBOV-GP vaccine was granted access to the PRIME scheme by the EMA and Breakthrough Therapy Designation by the US FDA.

2.4. Modelling of vaccination strategies

The following pre-emptive and reactive vaccination strategies were modeled to assess and compare their impact in controlling Ebola outbreaks:

1. **Pre-emptive vaccination**
   - Targeted vaccination: HCWs, front-line workers (FLWs) are not included because they are recruited after an outbreak is declared; and
   - Mass vaccination: random allocation among people living in areas at risk of Ebola.
2. **Reactive vaccination**
   - Ring vaccination: contacts and contacts of contacts (CCCs) of Ebola virus disease cases;
   - Targeted vaccination: HCWs and/or FLWs; and

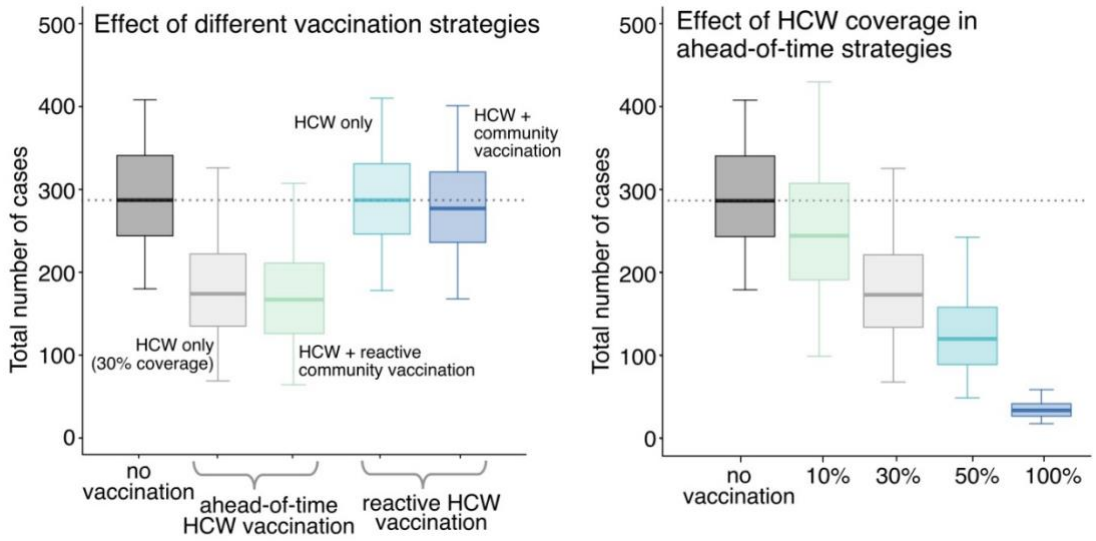
- Mass vaccination: random allocation among people living in areas reporting Ebola virus disease cases.

The strategies were assessed on both **localized outbreaks** similar to historical Ebola outbreaks (less than 300 cases and 6 months duration) as well as **widespread outbreaks**, similar to the 2013–16 West African outbreak (30,000 cases and 2-year duration).

Targeted vaccination

Figure 5 shows that the pre-emptive vaccination of HCWs, even at 30% coverage, can lead to a reduction around 40% of the total number of cases in a scenario similar to the one in Kikwit in 1995, where HCWs played an important role in amplifying the early spread of Ebola virus (see also **Figure 3**). By contrast, reactive vaccination targeting HCWs and/or mass-vaccination (70% coverage, 140,000 doses) has a negligible impact due to inherent implementation delays and the rapid control of the outbreak through classical control measures. And the total number of cases decreases by increasing the vaccination coverage in HCWs in ahead-of-time strategies.

Figure 5. Impacts of different vaccination strategies and health-care workers (HCWs) coverage in ahead-of-time strategies on the 1995 Ebola outbreak in Kikwit (Democratic Republic of Congo), while accounting for classical control measures implemented during the outbreak



Notes: Each boxplot represents the distribution of the total number of cases expected for a given vaccination strategy (left panel) and for a given vaccination coverage in HCWs (right panel), in comparison to the baseline scenario without vaccination (but with classical control measures). Variability arises from multiple stochastic simulations.
Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 5 June 2018.

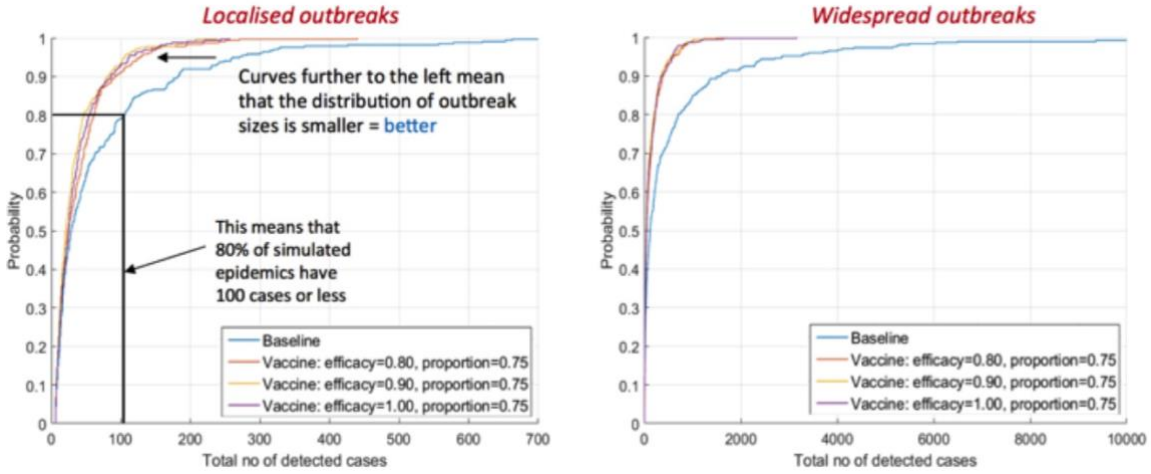
Ring vaccination

Figure 6 shows that ring vaccination of CCCs is an effective reactive strategy for preventing large outbreaks (>300 cases) when used in conjunction with classical control measures. For instance, in a scenario of localized outbreaks (up to 670 cases),

ring vaccination led to a reduction of the probability of observing a large outbreak from 4% to 1%. In a scenario of widespread transmission (up to 10,000 cases), the probability dropped from 33% to 12%, with 95% of the outbreaks having less than 600 cases.

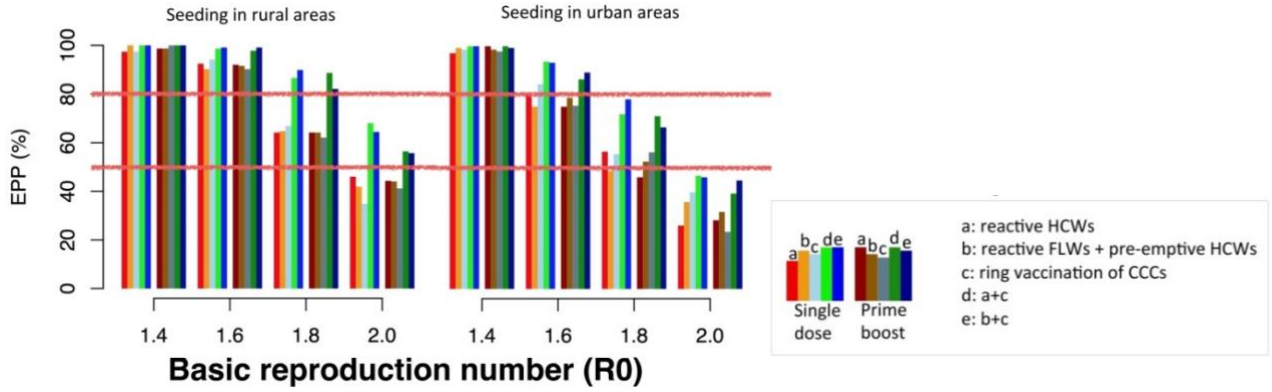
Figure 7 compares the impact of different combinations of pre-emptive and reactive strategies, including ring vaccination, for both single-dose and prime/boost vaccines in either rural or urban areas and for different intensity of transmission (as measured by the basic reproduction number R0). This model is gauged to a baseline with poor or zero initial infrastructures for classical control measures.

Figure 6. Cumulative probability distribution of the total number of cases with and without ring vaccination and for localized (left panel) and widespread (right panel) outbreaks



Notes: Classical control measures are also implemented in this model.
Source: Centre for Outbreak Analysis and Modelling, Imperial College London, presented to the SAGE Working Group on 5 June 2018.

Figure 7. Comparison of the epidemic prevention potential (EPP) for different vaccination strategies, urban Vs rural areas, single dose Vs prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreak (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 5 June 2018.

Mass vaccination

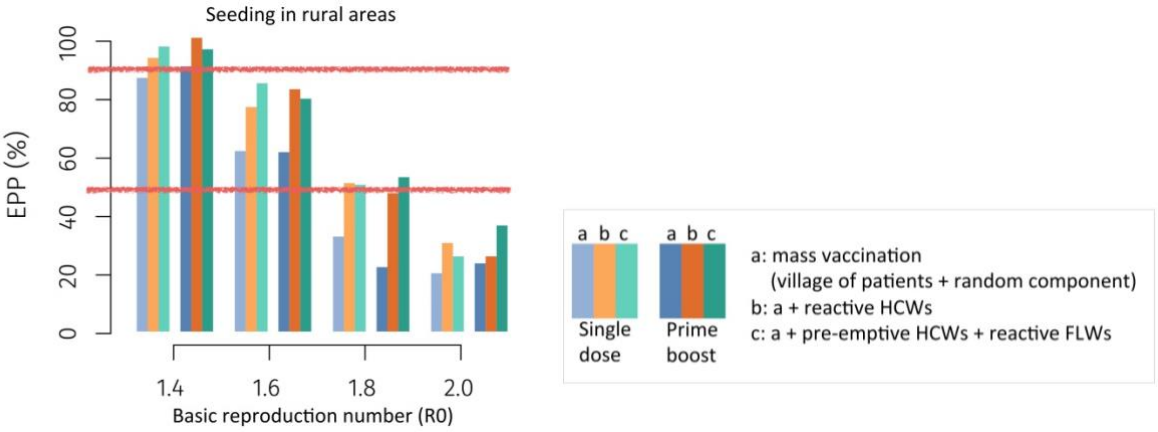
Figure 8 shows similar comparison for mass vaccination strategies.

Herd immunity to Ebola viruses is not a realistic target for current vaccination strategies (20). A 90% effective vaccine would require more than 80% coverage in the general population to establish herd immunity. This makes pre-emptive mass vaccination be an unrealistic strategy because of the resistance against vaccinations, financial/ logistical challenges, and a lack of vaccines that provide long-term protection against all human-pathogenic Ebola viruses.

Although the number of doses needed for pre-emptive vaccination of HCWs depends on the health system of each country, modelling can provide estimates of the number of doses required for the reactive vaccination strategies. Using a ring vaccination strategy, 10,000 doses were sufficient to contain simulated localized outbreaks, whereas 50,000 doses were sufficient to contain simulated widespread outbreaks. By contrast, mass vaccination required a tenfold number of doses.

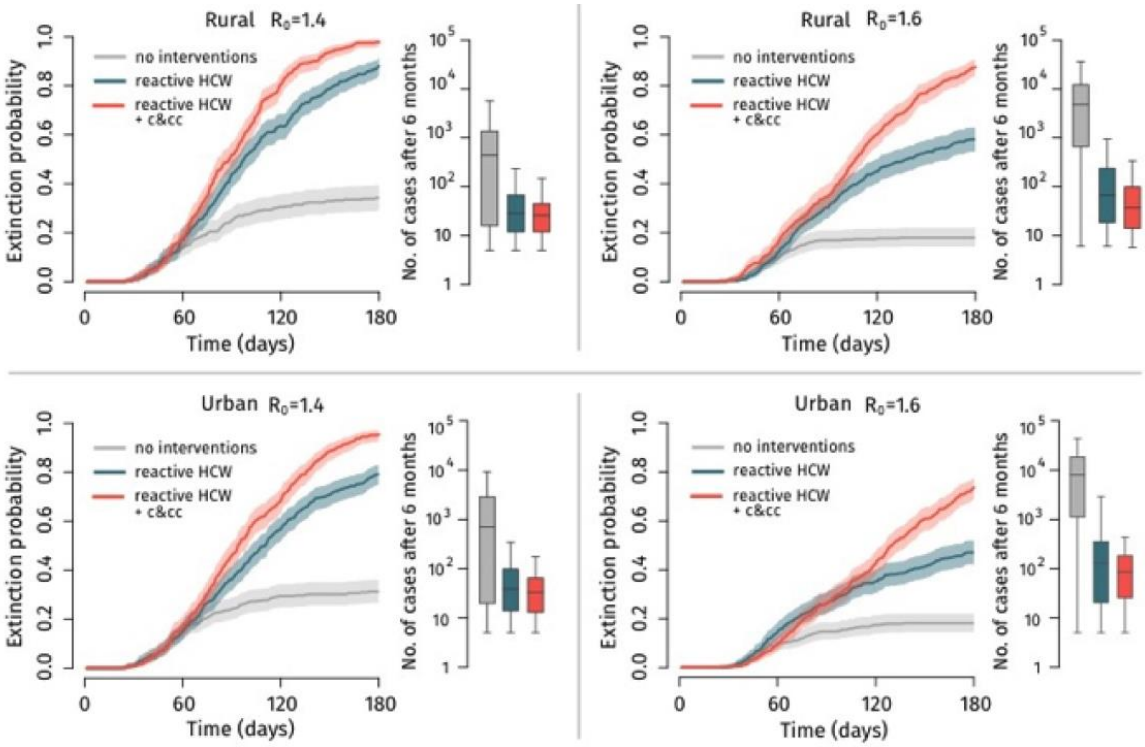
Overall, modelling suggests that pre-emptive vaccination of HCW combined with a reactive ring vaccination strategy is the most effective strategy to contain future Ebola outbreaks (**Figure 9**). Replacing ring vaccination by mass vaccination is less efficient as it reduces the chances of preventing large outbreaks (e.g. from 80% to 50% for R0 = 1.8, see **Figure 8**). This is because ring vaccination targets people at high risk of infection that mass vaccination might miss. It also appears that reducing the risk of large outbreaks is more difficult in urban than in rural areas, due to increased connectivity. Both single-dose and prime/boost (with boosting 28 days after priming) regimens with a similar vaccine efficacy of 90% lead to similar reduction of the risk of large outbreaks. Importantly, ring vaccination requires effective case detection and contact tracing, thus acting synergistically with classical control measure of Ebola virus transmission.

Figure 8. Comparison of the epidemic prevention potential (EPP) from a rural seeding, for different mass vaccination strategies, single dose Vs prime/boost and for different R0 values



Note: EPP is defined as the reduction of the risk of observing a large outbreak (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 5 June 2018.

Figure 9. Impact of ring vaccination and reactive vaccination in health-care workers (HCWs) for different vaccination strategies, urban Vs rural areas, and for different R0 values



Note: This model is gauged to a baseline with poor and zero initial infrastructure for classical control measures.
Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 5 June 2018.

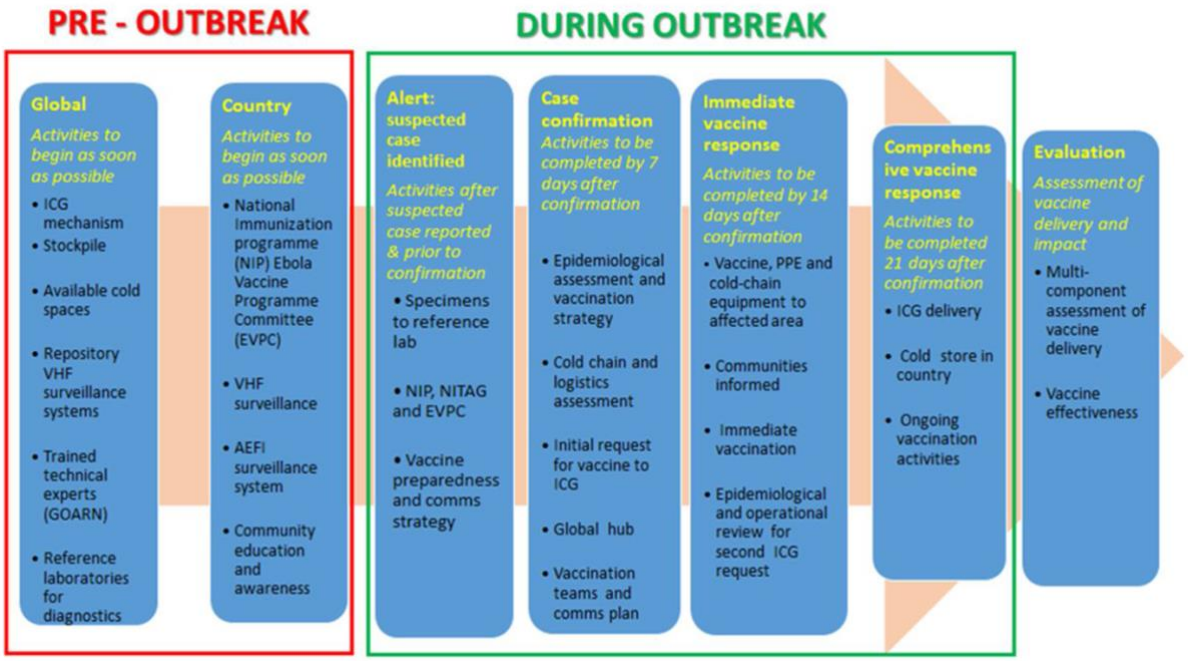
2.5. Emergency and post-licensure access

Because no candidate Ebola vaccine has received regulatory approval for use to date, discussions are ongoing jointly with 13 African Member States to guarantee **Expanded Access** (compassionate use, while safeguarding ethical and good clinical practice precautions) to rVSVΔG-ZEBOV-GP in the event of an outbreak. In addition to logistical arrangements, the preparation includes consultation and formal review of a protocol for an open-label, non-randomized, single arm study with the governments, national regulatory agencies and national ethics committees of the concerned 13 African countries. Under expanded access/ compassion use study protocols, the primary study objective is to measure the incidence of laboratory-confirmed EVD cases 84-days after vaccination; the secondary study objectives are to assess adverse events over 21 days after vaccination. Immunization is by ring vaccination of contacts and of contacts of those contacts around a confirmed case. Only persons who consented after information and who are eligible are vaccinated.

For post-licensure access, the **Global Ebola Vaccine Implementation Team (GEVIT)** has submitted into public consultation a practical guidance on the use of Ebola vaccines in an outbreak response. Its objectives are to improve understanding of the technical specificities of Ebola vaccines and the possible strategies for outbreak

response vaccination and to guide global partners and countries on preparedness plans to facilitate rapid vaccination response activities in the event of a future Ebola outbreak. The guide outlines phases that cover both preparation and implementation (**Figure 10**).

Figure 10. Outline of Ebola vaccination phases proposed by the Global Ebola Vaccine Implementation Team



3. Recommendations proposed by SAGE Working Group

Thirteen candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical evaluation at different trial phases. The Working Group reviewed the published data as well as the unpublished data submitted by the candidate vaccine developers (**Table 1**) and, together additional confidential data and information presented during closed meetings between the SAGE Working Group members and the individual developers.

Should an Ebola disease outbreak occur, the Working Group members reiterated that the current SAGE recommendation remains pertinent i.e. the rVSVΔG-ZEBOV-GP vaccine should be promptly deployed under the Expanded Access/Compassionate Use cohort protocol, with informed consent and in compliance with Good Clinical Practice. Ring vaccination remains the recommended delivery strategy. This should be adapted to the social and geographic conditions of the outbreak-affected areas and include people at risk including but not limited to: (i) contacts, and contacts of contacts; (ii) local and international health-care and FLWs in the affected areas; and (iii) health-care and FLWs in areas at significant risk of expansion of the outbreak. The implementation of a protocol using rVSVΔG-ZEBOV-GP and the ring vaccination strategy offers an important opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness, and long-term immunogenicity.

The modelling results on the effect of various preventive and reactive vaccination strategies (conducted by three independent groups and presented during the meeting) supports the above recommendations. Model results suggest that ring vaccination would have greater impact in reducing the duration of outbreak and the number of cases if implemented in conjunction with reactive vaccination of health-care and FLWs and, together with full implementation of other non-vaccine outbreak control measures. Under scenarios of poor case detection and contact tracing, model results suggest that ring vaccination may need to be adjusted to a more geographically targeted reactive vaccination approach. The Working Group encouraged modelers to consider including additional assumptions and parameters that could help better understand and predict the potential effect that sociocultural dynamics of affected communities have on the course of an outbreak.

The Working Group members noted that the rVSVΔG-ZEBOV-GP vaccine contains a replicating viral vector. A very limited number of pregnant women have received rVSVΔG-ZEBOV-GP vaccine, not aware they were pregnant at the time of vaccination, in previous randomized clinical trials or in the compassionate use/expanded access cohort study being implemented in the Democratic Republic of the Congo (DRC) (as recommended by the Ethics Review Committee in DRC). Therefore, the Working Group members emphasized the importance of maintaining a pregnancy registry to compile the safety data on vaccination during pregnancy including the data on women unaware of their pregnancy at the time of vaccination. This may inform future recommendations for the use of the vaccine in pregnant women. A similar registry approach is recommended for documenting vaccine safety in children.

In the context of the ongoing outbreak in the DRC and future outbreaks linked to the Zaire strain where a ring vaccination strategy is implemented using the rVSVΔG-ZEBOV-GP vaccine, consideration should be given to the potential for assessing the effect on disease outcomes of other Ebola candidate vaccines which target the Zaire strain. Access to other candidate vaccines might be relevant in terms of: manufacturing safety and stockpiling capacity, cold chain, multiple Ebola virus strain protection, cellular immunologic response or long-term protection. Target populations involved in such studies might include health-care and FLWs and other groups who may be at risk of further spread and who would not otherwise be eligible to receive the rVSVΔG-ZEBOV-GP vaccine under the current recommendations. To assess other candidate vaccines in such settings, given uncertainties of the direction of outbreak spread and likely low attack rates at the population level, consideration should be given to innovative randomized trial designs that have the potential to provide robust evidence on candidate vaccine efficacy and/or effectiveness and safety if the changing epidemiology of the disease would permit this. These trials should be designed to at least generate additional safety and immunogenicity data among populations at risk of Ebola.

If the outbreak is caused by an Ebola virus species other than Zaire species, then robust randomized trial designs to assess candidate vaccines which target the relevant putative viral species should be implemented. Presently, one multivalent vaccine is currently in Phase II of clinical development (Ad26.ZEBOV/MVA-BN-Filo).

The Working Group members considered that available unpublished evidence on various candidate Ebola vaccines concerning duration of protection and cross-

protection are still insufficient to support policy recommendation(s) for routine preventive vaccination of the general population or vaccination of HCWs and/or FLWs in the absence of an outbreak. The current information on the duration of protection for various candidate Ebola vaccines is up to 360 days post vaccination for the rVSVΔG-ZEBOV-GP, Ad26.ZEBOV/MVA-BN-Filo and ChAd3-EBOZ vaccines. Preliminary reports for these 3 candidate vaccines suggest that Ebola antibody geometric mean titers (GMT) were initially high (with peaks at 56 or 84 days post vaccination and 21 and 14 days post boost respectively) and slightly decline over time, but a relatively high GMT was maintained at the end of these follow-up periods for each candidate vaccine. However, in the absence of a correlate of protection and given that different assays were used, it is challenging to interpret these data. Evidence on cross-protection against different Ebola virus species remains uncertain for all candidate vaccines. Preliminary cross-protection data, assessed by enzyme-linked immunosorbent assays and virus neutralization assays results against other Ebola strains, was only reported for three candidate vaccines (Ad26.ZEBOV/MVA-BN-Filo, GamEvac-Combi and INO-4212 DNA vaccines). There is no data on cross-protection against Marburg virus for any candidate vaccine. The Working Group encouraged developers and researchers to design studies that would generate additional information on long term immunogenicity and cross-protection with a view to contribute to potential market authorization for a preventive indication.

The Working Group recommended that the WHO Secretariat continue to encourage the dialogue between national regulatory authorities and developers and, to explore expedited regulatory processes by supporting national regulatory authorities to develop a consensus on the regulatory pathways for the evaluation and potential market authorization of candidate Ebola vaccines. The Working Group also recommends that manufacturers and sponsors seek proactive feed-back on generic protocols for efficacy/effectiveness trials and market authorization requirements from relevant regulatory authorities in affected countries.

The Working Group noted that there is an ongoing systematic review of vaccination acceptability in health-care workers. The review outcomes will provide additional evidence to inform future SAGE recommendations regarding health-care worker vaccination strategies. Additional safety data among other target populations such as children, HIV-positive individuals and pregnant women is required. Moreover, additional social behavioral research is essential to provide further insights into the context and determinants of expanding outbreaks, especially the dynamic responses of the communities involved, and how this might impact on future outbreak dynamics and response.

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5. Appendices

Appendix 1. Characteristics of Ebolavirus and Marburg virus outbreaks, 1976–2018 (1)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
1976	South Sudan	Sudan	5	20	284	151	53%	WHO/International Study Team, 1978 (2)
1976	Democratic Republic of Congo	Zaire	5	9	318	280	88%	Report of an International Commission, 1978 (3)
1977	Democratic Republic of Congo	Zaire	N/A	1	1	1	100%	
1979	South Sudan	Sudan	2	10	34	22	65%	Baron et al., 1983 (4)
1994	Gabon	Zaire	4	13	52	31	60%	Georges et al., 1999 (5)
1994	Côte d'Ivoire	Taï Forest	N/A	1	1	0	0%	
1995	Democratic Republic of Congo	Zaire	17	27	315	254	81%	Khan et al., 1999 (6)
1996 (Jan-Apr)	Gabon	Zaire	0	5	31	21	68%	Georges et al., 1999 (5)
1996 (Jul-Dec)	Gabon	Zaire	18	27	60	45	75%	Georges et al., 1999 (5)
1996	South Africa (ex-Gabon)	Zaire	N/A	1	1	1	100%	
1998	Democratic Republic of Congo	Marburg	13	100	154	125	81%	Bausch et al., 2006 (7)
2000	Uganda	Sudan	5	20	425	224	53%	Okware et al., 2002 (8)
2001-2002	Gabon	Zaire	6	21	65	53	82%	World Health Organization, 2003 (9) Nkoghe et al., 2005 (10)
2001-2002	Congo	Zaire	N/A	20	59	44	75%	Chippaux et al., 2014 (11)
2003 (Jan-Apr)	Congo	Zaire	N/A	19	143	128	90%	Formenty et al., 2003 (12)
2003 (Nov-Dec)	Congo	Zaire	5	7	35	29	83%	Boumandouki et al., 2005 (13)
2004	Angola	Marburg	24	42	252	227	90%	World Health Organization, 2005 (14, 15)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
								US CDC, 2005 (16) Towner et al., 2006 (17)
2004	Sudan	Sudan	1	10	17	7	41%	World Health Organization, 2005 (18)
2005	Congo	Zaire	N/A	6	12	10	83%	
2007	Democratic Republic of Congo	Zaire	13	15	264	187	71%	World Health Organization, 2007 (19) Leroy et al., 2009 (20) Grard et al., 2011 (21)
2007	Uganda	Marburg	N/A	13	4	1	25%	Adjemian et al., 2001 (22)
2007	Uganda	Bundibugyo	14	18	149	37	25%	MacNeil et al., 2011 (23)
2008	Democratic Republic of Congo	Zaire	3	5	32	14	44%	World Health Organization, 2009 (24) Rosello et al., 2015 (25)
2011	Uganda	Sudan	N/A	1	1	1	100%	
2012	Uganda	Marburg	N/A	3	15	4	27%	Albariño et al., 2013 (26)
2012	Uganda	Sudan	N/A	1	24	17	71%	Albariño et al., 2013 (26)
2012	Uganda	Sudan	N/A	1	7	4	57%	Albariño et al., 2013 (26)
2012	Democratic Republic of Congo	Bundibugyo	N/A	8	57	29	51%	Albariño et al., 2013 (26)
2014-2016	Guinea	Zaire	22	109	3811	2543	67%	WHO Ebola Response Team 2014, 2015 & 2016 (27-29) Boisen et al., 2016 (30)
2014-2016	Liberia	Zaire	10	92	10675	4809	45%	
2014-2016	Sierra Leone	Zaire	18	88	14124	3956	28%	
2014	Nigeria	Zaire	N/A	N/A	20	8	40%	
2014	Mali	Zaire	N/A	N/A	8	6	75%	
2014	Senegal	Zaire	N/A	1	1	0	0%	
2014	USA	Zaire	N/A	N/A	4	1	25%	
2014	UK	Zaire	N/A	1	1	0	0%	
2014	Spain	Zaire	N/A	1	1	0	0%	
2014	Democratic Republic of Congo	Zaire	4	10	66	49	74%	Maganga et al., 2014 (31)

Year	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Cases	Deaths	Case fatality rate (CFR) %	Reference
2015	Italy	Zaire	N/A	1	1	0	0%	
2017	Democratic Republic of Congo	Zaire	4	7	8	4	50%	World Health Organization, 2017 (32)
2018	Democratic Republic of Congo	Zaire	4	16	54	33	61%	World Health Organization, 2018 (33)
2018	Democratic Republic of Congo	Zaire	4	ongoing	142	97	68%	World Health Organization, 2018 (34)

* include suspect, probable and confirmed Ebola virus disease cases

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Appendix 2. Summary of published data on efficacy, immunogenicity and safety of candidate Ebola vaccines in clinical development (by 9 May 2018)

#	Candidate Ebola vaccine under clinical development	Developer	Published data available	Data updated
01	Ad5-EBOV (monovalent)	CanSino Biologics Inc. & Beijing Institute of Biotechnology, China	Yes	Yes
02	Ad5 (bivalent)	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
03	Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150)	Janssen Vaccines & Prevention B.V, The Netherlands	Yes	Yes
04	ChAd3 (monovalent, ChAd3-EBOZ)	GlaxoSmithKline, Belgium	Yes	Yes
05	ChAd3-EBOZ & MVA-BN-Filo (prime/boost)	University of Oxford, UK and National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
06	ChAd3 (bivalent)	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
07	GamEvac-Combi	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	Yes	Yes
09	rVSVΔG-ZEBOV-GP	Merck, USA	Yes	Yes
10	rVSV N4CT1 EBOVGP1	Profectus BioSciences, USA	Yes	
11	Nanoparticle recombinant Ebola GP vaccine	Novavax, USA	No	
12	DNA vaccine (INO-4212)	Inovio Pharmaceuticals, USA	No	
13	DNA plasmid vaccines	National Institute of Allergy and Infectious Diseases (NIAID), USA	Yes	
13	HPIV3-EbovZ GP	National Institute of Allergy and Infectious Diseases (NIAID), USA	No	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Ad5 expressing envelope GP of Zaire Ebola virus species (Makona variant, monovalent) with or without homologous boost							
Zhu et al., 2015 (1) Li et al., 2016 (2) (PMID: 25817373 and 28017642; NCT02326194 and NCT02533791)	1	China	120 healthy adults aged 18-60y; both men and women, but not pregnant or breast-feeding women. 60% participants had pre-existing Ad5 immunity (titres >1:200).	Randomised, placebo-controlled, double-blind trial; 1:1:1 randomisation to 1.6×1011, 4.0×1010 viral particles [vp], or placebo; follow-up to 168d (5.6m); unmasking after preliminary analysis. At 168d, 110 participants re-recruited and received 2nd dose of same intervention (the same vaccine & dose, or placebo; follow-up to 12m (18m after 1st dose). Enrolment 12/2014–1/2015.	After priming: Glycoprotein (GP) specific antibody titres were significantly increased at d14 and d28 in both vaccine groups; they peaked at d28 and persisted by d168. T-cell responses peaked at d14 in both vaccine groups. Immunogenicity was greater in high-dose than in low-dose vaccine group. After boosting: >20-fold increase in titres at d28 in both vaccine groups; titres persisted at m18. At lower dose, immunogenicity seemed more vulnerable to pre-existing Ad5	Mild and moderate solicited adverse reactions within 7d of vaccination reported at higher rate in both vaccine groups. No serious events recorded.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					immunity. Boosting provided greater antibody response, possibly with longer duration.		
Zhu et al., 2016 (3) (PMID: 28017399; PACTR201509001259869)	2	Sierra Leone	500 healthy adults aged 18-50y; both men and women, but not pregnant or breast-feeding women; HIV negative, no EVD history, no previous Ebola immunisation. 45% participants had pre-existing Ad5 immunity (titres >1:200).	Randomised, placebo-controlled, double-blind trial; 2:1:1 randomisation to 8.0x1010, 1.6x1011 vp, or placebo; safety follow-up at 7d, immunogenicity follow-up at d14, 28 and 168. Enrolment 10/2015.	GP-specific antibodies detected from d14, peaked at d28, and later declined by d168 (still approx. 40-fold greater than in placebo group). Although immunogenicity was greater in high-dose than in low-dose vaccine group, candidate vaccine was highly immunogenic at both dose levels in healthy Sierra Leonean adults. Lower dosage was chosen for further development also on basis of results from preclinical animal studies.	Rates of ≥1 adverse reaction within 7d of vaccination were similar in 3 groups; most reactions mild and self-limiting. Injection-site reactions were more frequent in vaccine groups. No serious events related to vaccine.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Wu, et al.2017(4), (PMID: 28708962; NCT02401373)	1b	China	61 healthy African aged 18-40y; both men and women, but not pregnant or breast-feeding women. HIV negative,64% participants had pre-existing Ad5 immunity (titres >1:200).	A dose-escalation, open-label trial, 31 participants receiving one shot intramuscular injection of 8.0x1010, and 30 participants receiving a double-shot regimen of 1.6x1011 vp. safety and immunogenicity follow-up at d14, 28. Enrolment 04/2015-08/2015.	Ebola glycoprotein-specific antibodies appeared in all 61 participants and antibodies titers peaked after 28 d of vaccination. The antibodies titers were similar between these 2 groups. The glycoprotein-specific T-cell responses rapidly peaked after 14 d of vaccination and then decreased, however, the percentage of subjects with responses were much higher in the high-dose group . Pre-existing Ad5 neutralizing antibodies could dampen the specific humoral immune response and cellular response to the	86.89% of participants reported at least one adverse reaction within 28 d of vaccination. The most common reaction was fever and the mild pain at injection site, and there were no significant difference between these 2 groups. No serious events recorded.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					vaccine		
Ad5 expressing envelope GP of Sudan and Zaire Ebola virus species (bivalent)							
Ledgerwood et al., 2010 (5) (PMID: 21034824; NCT00374309)	1	USA (Maryland)	31 healthy adults, both men and women; mean age 31y. Half of participants had a high level of pre-existing Ad5 immunity (titres >1:500)	Randomised, placebo-controlled, double-blind trial; 3: 1 randomisation to either 2×1011 or 2×1010 vp and placebo; follow-up for 48w. Enrolment 9/2006–11/2007.	Actual randomization 11:12:8, Sudan and Zaire GP-specific seropositivity peaked at 58% and 50% at w4 and was 42% and 33% at w48, respectively; response rates were higher in low-dose vaccine group, but magnitudes were non-statistically higher in high-dose group. Ad5-seronegative vaccinees had significantly higher response rates and magnitude of response than Ad5-seropositive vaccinees. Sudan and Zaire GP-specific T-cell responses were	Self-limited reactogenicity without sequelae was observed. Three adverse events related to vaccination (two cases of partial thromboplastin time, a case of Grade 3 fever with 24h).	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					present in both low- and high-dose vaccinees.		
Ad26 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, as prime) and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (MVA-BN-Filo, as boost)							
Milligan et al., 2016 (6) (PMID: 27092831; NCT02313077)	1	United Kingdom (Oxford)	87 healthy adults aged 18–50y (median age 38.5y); both men and women, but not pregnant or breast-feeding women; 67% participants were women. 3.4% participants had pre-existing Ad26 immunity 8tires threshold not defined).	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups: primed with either Ad26 5×1010 vp or MVA 1×108 infective dose and boosted with alternative vaccine at either d28 or d56; and primed with Ad26 and boosted by MVA at d14 (open-label). Follow-up for 8m after priming. Enrolment 12/2014–2/2015.	Seropositivity at d28 in 97% and 23% vaccinees primed with Ad26 and MVA, respectively; all vaccinees had detectable GP-specific IgG at d21 after boost and at 8m follow-up. Conclusion was that Ad26 priming induces immune response and MVA boosting sustained and specific immunity.	In randomised groups, 5% participants experienced fever after Ad26, none after MVA. In open-label group, 27% experienced fever. No vaccine-related serious adverse events occurred.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Enria et al., 2016 (7) (PMID: 27821112; NCT02509494)	3	Sierra Leone (Kambia)	*Stage 1:* 43 healthy adults aged ≥18y. *Stage 2:* 976 persons aged ≥1y.	Study denominated EBOVAC-Salon; reported as phase 3 trials, but stage description only reports safety/immunogenicity evaluation. *Stage 1:* open label, primed with Ad26 5×1010 vp and boosted with MVA 1×108 infective dose at d28; vaccinated from 10/2015. *Stage 2:* randomised, controlled, double-blind trial; randomization to same prime/boost regimen as stage 1 or MCV as control; allocation not detailed. 3rd dose for children aged <2 at 3m after boost. Follow-up for 56d (28d after boost), but for	N/A	N/A	Currently recruiting. Data collection for primary outcome measure finalized by 11/2019

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				serious adverse events for 36/12m for stage 1/2, respectively. Additional stages are being consulted with national and international stakeholders.			
Vandebosch et al., 2016 (8) (PMID:26768568)	3 (design)	Not applicable	Not appplicable	This manuscript aims to present the statistical and modeling considerations, design rationale and challenges encountered due to the emergent, epidemic setting that led to the selection of a cluster-randomized phase 3 study design under field conditions.	Not applicable	Not applicable	Not applicable
Shukarev, G et al., 2017 (9) (PMID: 27925844)	Overall program and Phase I, 1001, durability 8 months (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)	Not applicable (Commentary)

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Camacho A, et al. 2017 (10) (PMID: 28024952)	3 (design)	3 Regions in Sierra Leone	Not applicable (modelling)	In real-time, we fitted, forecasted, and simulated a proposed phase 3 cluster-randomized vaccine trial for a prime-boost EVD vaccine in three candidate regions in Sierra Leone. The aim was to forecast trial feasibility in these areas through time and guide study design planning.	Not applicable	Not applicable	Not applicable
Winslow RL et al. 2017 (11) (PMID: 28291882)	1 (Durability)	United Kingdom (Oxford)	87 healthy adults aged 18–50y (median age 38.5y); both men and women, but not pregnant or breast-feeding women; 67% participants were women. 3.4% participants had pre-existing Ad26 immunity 8tires threshold not	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups: primed with either Ad26 5×1010 vp or MVA 1×108 infective dose and boosted with alternative vaccine at either	All of the active vaccine recipientsmaintained Ebola virus–specific immunoglobulin G responses at day 360. Vaccine-induced T-cell responses persisted in 60% to 83% of participants receiving	No serious adverse events were recorded from day 240 through day 360.	completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			defined). Of 75 active vaccine recipients, 64 attended follow-up at day 360 (median age, 39 years; women, 66%). Eleven participants withdrew (1-3 per group) and missing data were not imputed	d28 or d56; and primed with Ad26 and boosted by MVA at d14 (open-label). Follow-up at 1 year. Enrolment 12/2014–2/2015.	Ad26.ZEBOV first followed by MVA-BN-Filo as a booster compared with 69% to 100% of those receiving the reverse regimen.		
ChAd3 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, monovalent)							
De Santis et al., 2016 (13) (PMID: 26725450; NCT02289027)	1/2a	Switzerland (Lausanne)	120 healthy adults aged 18–65y. Also, individual potentially deployable to areas with ongoing transmission.	Randomised, placebo-controlled, double-blind, dose-finding trial; 2:2:1 randomisation to ChAd3-EBOZ 2.5×1010 pu (low dose), 5×1010 pu (high dose) or placebo. Allocation not concealed for deployable participants. Follow-up for	GP-specific antibody response rate in vaccinees was 96% (5% in placebo). Ab-level peaked at d28 and halved by d180. CD4/8 cell responses were 60–70%. ChAd3-EBO-Z was safe and well tolerated, although mild/ moderate systemic adverse events were common. No	>75% vaccinees reported local adverse events. Fatigue or malaise was most reported systemic event (60%) and 25–30% vaccinees reported fever within 24h after vaccination. No serious vaccine-related adverse events reported.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				180d.	significant differences related to two dosages.		
Tapia et al., 2016 (14) (PMID: 26546548; NCT02231866)	1	USA (Maryland), Mali	In total 91 healthy participants aged 18–65y: ChAd3-EBOZ at 1×1010 pu (N=10), at 2.5×1010 pu (N=35), at 5×1010 pu (N=35) and at 1×1011 pu (N=11). Malian subjects were invited to participate to a nested, placebo-controlled MVA booster extension.	Randomized, open-label and double-blind trial.	Anti-GP ELISA response observed in 83 to 100% of vaccinees at d28 after ChAd3-EBO-Z vaccination. Titres were higher in the 1×1011 pu group. Antibody and	Local pain and tenderness, fatigue and headache were most frequently reported adverse events. No serious safety concerns identified.	Completed
Ewer et al., 2016 (15) (PMID: 25629663; NCT02240875)	1	UK	In total 76 healthy participants aged 18–50y: ChAd3-EBOZ at 1×1010 pu (N=20), at 2.5×1010 pu (N=36), at 5×1010 pu (N=20). Subjects were invited to	Randomized, open-label	Induction of anti-GP ELISA (standardized glycoprotein and whole-virion assays) responses 28 days after ChAd3-EBO-Z vaccination. Low levels of	The majority of adverse events were self-limited and mild. Local pain was the most common local event. Moderate systemic adverse events were fever, myalgia,	Active, not recruiting

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			participate to an MVA booster extension.		neutralizing antibody titers to live Zaire Ebola (Mayinga) strain, as well as Polyfunctional EBOV-specific CD4+ and CD8+ T-cell responses also observed at Day 30. All vaccine responses boosted by the MVA.	arthralgia, headache, fatigue, nausea, and malaise. No severe systemic solicited adverse events were reported. No fever persisted for more than 24 hours.	
EBOLA Z CHAD3-005 (NCT02485301)	2	Senegal, Mali, Nigeria, Cameroon	Healthy adults aged 18 years and above (N=3000)	Single vaccination with ChAd3-EBO-Z. Randomized 1:1 ChAd3-EBO-Z 1×1011 pu vs. placebo. Observer-blind (until D30); single-blind (until M6); open label (until M12).	Approximately 25% of the subjects were seropositive for anti-GP-EBOV ELISA antibodies on Day 0 before vaccination. Anti-GP EBOV ELISA antibodies were induced at 30 days after vaccination and persisted until the end of the study follow-up (Month 12). Polyfunctional EBOV-specific CD4+ and CD8+ T-	The ChAd3-EBO-Z vaccine candidate was generally well tolerated in the subjects. Vaccination with ChAd3-EBO-Z was mainly associated with transient and non-severe local pain, headache and fatigue. No SAEs were considered related to the study vaccination by the Investigator. Drops from baseline platelet levels, the	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					cell responses were observed at Day 30 in the EBO-Z group. A ChAd3 neutralizing antibody response above the threshold of positivity was observed in 58.3% subjects in the EBO-Z group and 27.2% subjects in the Placebo/ EBO-Z group at Day 30. At Month 6, it was observed in 35% of subjects of the EBO-Z group and 24.5% of subjects of the Placebo/ EBO-Z groups. The GMC value was just above the threshold of positivity at Day 30 in the EBO-Z group and below the threshold in the Placebo/ EBO-Z group. At Month	majority of them occurring within the normal range, were observed in both the EBO-Z and the Placebo/ EBO-Z groups without notable differences between both groups, and no clinical signs of thrombocytopenia (AESI) were reported within the first 7 days post-vaccination in either of the groups. No other clinically significant laboratory abnormalities related to the vaccination were noted.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					6, GMC values were below the threshold of positivity in the two groups.		
EBOLA Z CHAD3-004 (NCT02548078)	2	Senegal, Mali	Children aged 1 to 17 years (13-17y [N=200], 6-12y [N=200], 1-5y [N=200])	Randomized 1:1 ChAd3-EBO-Z 1×1011 pu vs. MenACWY. Observer-blind (until D30); single-blind (until M12).	Approximately 17% of the subjects were seropositive for anti-GP-EBOV ELISA antibodies on Day 0 before vaccination. Anti-GP EBOV ELISA antibodies were induced at 30 days after vaccination with ChAd3-EBO-Z and persisted until the end of the study follow-up (Month 12). Poly-functional EBOV CD4+ and CD8+ T-cell responses were observed at 30 days post ChAd3-EBO-Z vaccination. A ChAd3 neutralising antibody response	The ChAd3-EBO-Z vaccine candidate was generally well tolerated in the subjects. Vaccination with ChAd3-EBO-Z was mainly associated with transient and non-severe local pain (except Grade 3 pain for one subject aged 6 to 12 years and three subjects aged 1 to 5 years), fever, headache and fatigue. No SAEs were considered related to the study vaccination by the Investigator. Drops from baseline platelet levels, the majority of them occurring within	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					above the threshold of positivity was observed in 57% subjects in the EBO-Z/ MENACWY-TT group and 14.6% subjects in the MENACWY-TT/ EBO-Z group at Day 30. At Month 6, it was observed in 41.2% of subjects of the EBO-Z/ MENACWY-TT group and 20.5% of subjects of the MENACWY-TT/ EBO-Z groups. The GMC value was 304 at Day 30 in the EBO-Z/ MENACWY-TT group and below the threshold in the MENACWY-TT/ EBO-Z group. At Month 6, GMC values were below the threshold of	the normal range, were observed in both the EBO-Z/ MENACWY-TT and the MENACWY-TT/ EBO-Z groups without notable differences between both groups, and no clinical signs of thrombocytopenia (AESI) were reported within the first 7 days post-vaccination in either of the groups. No clinically significant laboratory abnormalities were related to vaccination.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					positivity in the two groups.		
ChAd3 (monvalent) boosted with MVA-BN-Filo							
Tapia et al., 2016 (14) (PMID: 26546548; NCT02267109)	1b	Mali	91 adults aged 18–50y (52 participants boosted with either MVA-BN-Filo [27] or saline [25]). Males & females not breast-feeding, not pregnant & not planning to become pregnant.	Open-label and double-blind, dose-escalation trial (ChAd3 prime); nested, randomised, placebo-controlled and double-blind trial (MVA boost). 1:3:3:1 randomisation to ChAd3 1×1010, 2.5×1010, 5×1010 or 1×1011 vp. 52 participants were further 1:1 randomised to boost MVA 2×108 pfu or placebo. Follow up for 180d after primary or booster vaccination. Enrolment 11/2014 (prime) and 2/2015 (boost).	83–100% vaccinees showed humoral response after ChAd3 at d28, unrelated to dose level. 100% vaccinees showed humoral response after MVA boost at both d7 and d28. T-cell responses after ChAd3 priming were of small magnitude, but stable at time of boosting. In contrast, cellular response was high-magnitude in 85% after boosting. Results suggest use of 1×1011 ChAd3 dose for reactive vaccination and MVA boosting for conferring long-	Most adverse events were mild. Predominant solicited adverse event was fever (10/11 episodes resolved within 24h). Only one serious event observed in a Malian participant, but deemed unrelated to vaccine.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					lived protection.		
Ewer et al., 2016 (15) (PMID: 25629663; NCT02240875)	1	UK (Oxford)	76 healthy adults aged 18–50y.	Open-label trial. *Priming:* 20:36:20 participants each received ChAd3 at 1×1010, 2.5×1010 and 5×1010 vp. *Boosting:* 46 participants in total boosted with MVA. At w1–2, 16 participants of ChAd3 2.5×1010 dose boosted with MVA 1.5×108 plaque forming units (pfu). At w3–10, 10 participants of 3 ChAd3 dose groups boosted at either MVA 1.5×108 (18 participants) or 3x108 (12), stratified per priming dose group. Follow-up for 29d (primed only) or 180d (if boosted). Also, comparison of neutralizing	After MVA boost, GP-specific antibody response increased by d7 compared to pre-boost level, peaked at d14, and remained higher at d180 days. At w4, MVA boosting also increased virus-specific (12-fold) and neutralizing antibodies titres and CD8 cell response (5-fold). At d180, 100% boosted and less than half primed-only vaccinees remained positive for GP-specific antibodies; titres in boosted were 4-fold greater. ChAd3 boosted with MVA elicited humoral and cellular immune responses that	Majority of adverse events were self-limited and mild. Moderate systemic adverse events included fever, myalgia, arthralgia, headache, fatigue, nausea and malaise. No severe systemic solicited adverse reported. No safety concerns were identified at any of the dose levels studied.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				antibody activity with that observed in ph1 trial of rVSV-ZEBOV. Enrolment in late 2014.	were superior to those induced by ChAd3 alone		
ChAd3 expressing envelope GP of Zaire (Mayinga variant) and Sudan Ebola virus species (bivalent)							
Ledgerwood et al., 2014 & 2017 (16, 17) (PMID: 25426834; NCT02231866)	1	USA (Maryland)	20 healthy participants aged 18–50, both sexes (55% women)	Open-label, dose-escalation trial. Participants sequentially enrolled in groups of 10 to receive ChAd3 (bivalent) at doses 2×1010 and 2×1011 vp. Followed-up for 48w. Enrolment 9/2014.	At w4, 90/100%, 90/90% & 70/80% vaccinees showed Zaire/Mayinga, Zaire/Makona & Sudan GP-specific humoral response (low/high dose), respectively. At w48, Zaire/Mayinga titres remained eleveated. T-cell responses were dose-dependent (20-80% at w4 & 10-50% at w8). Pre-existing ChAd3 & Ad5 antibodies had no correlation with immune responses.	No safety concerns were identified. Fever reported in 2 participants in higher dose group. No serious adverse events were reported.	Completed
GamEvac-Combi and GamEvac-Lyo (rVSV & Ad5, prime & heterologous boost) expressing Zaire Ebola virus species (Makona variant)							
Dolzhikova et al., 2017 (15) (PMID:	1/2	Russia	84 healthy volunteers aged	Open-label, dose-escalation trial.	100% prime-boost vaccinees of both	Pain at the injection site was	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
28152326; zakupki.gov.ru no. 0373100043 215000055)			18–55y, both sexes (76% men)	GamEvac-Combi (rVSV prime & heterologous Ad5 boost), each component alone or in combination at full (rVSV 2.5×107 pfu & Ad5 2.5×1011 vp) or half dose. For safety evaluation, an initial group was assigned to receive either rVSV (12 participants) or Ad5 (12) at half dose. For safety and immunogenicity evaluation, a second group of 60 participants received rVSV followed by Ad5 at d21 at either full or half dose. Followed up for 42d. Enrolment 9–11/2015.	dose groups showed GP-specific immune response at d42. Titres were 1.25-fold greater in full-dose vaccinees at d42 compared to half-dose vaccinees. In full-dose vaccinees, titres were 5-fold lower in rVSV only vaccinees compared to prime-boost vaccinees. Preexisting neutralizing Ad5 antibodies adversely influenced GP-specific response in half-dose group, but not in full-dose group. 93% prime-boost vaccinees in full-dose group showed neutralizing Mayinga, taken as indication of	most frequently reported adverse event. No serious adverse event were reported.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					crossreactive immunogenicity from Makona. 59–83% prime-boost vaccinees of both dose groups showed Tcell responses at d28, with lower percentages at d42. Vaccine showed high immunogenicity and had good safety profile. Accordingly, it was registered in Russia in 12/2015.		
Only information from clinical trial registry entry (N.F. Gamaleya FRCEM, Russia) (PMID: N/A; NCT02911415)	4	Russia	60 healthy volunteers aged 18–56y, both sexes. (NCT02911415)	Open Study of the Duration of Immunity After Vaccination With Medicinal Product GamEvac-Combi - Combined Vector-Based Vaccine Against Ebola Virus Disease, 0.5 ml+0.5 ml/Dose Observational, prospective cohort study to evaluate	100% prime-boost vaccinees of both dose groups showed GP-specific immune response at 12 months. Average titers were 1.29-fold greater in full-dose vaccinees at 12 month compared to half-dose vaccinees.	No serious adverse events were reported.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				duration of immunity after earlier vaccination (that occurred 10–11/2015) at two dose levels. Follow-up visits at 12, 18 & 24m after vaccination. Enrolment from 10/2016.	The GP-specific antibody titre was detected in 96% of volunteers in full-dose group and in 93% of volunteers in half-dose group at 18 month. Average titers were 1,5-fold greater in full-dose vaccinees at 18 month compared to half-dose vaccinees. The GP-specific antibody titer was detected in 89% of volunteers in full-dose group and 53% of volunteers in half-dose group at 24 months. Average titers were 8-fold greater in full-dose vaccinees at 24 month compared to half-dose vaccinees.		
Russian Federation	3	Guinea (Kindia)	2,000 healthy	GamEvac-Combi:	in progress	The data obtained	Recruiting.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
MOH briefing at WHO Executive Board meeting of 2/2016 (PMID: N/A; NCT03072030 & PACTR201702002053400)			volunteers aged 18–60y, both sexes	rVSV prime, 2.5x107 pfu; Ad5 boost at d21, 2.5x1011 vp. Randomized, placebo-controlled, double-blind trial. 19:1 randomization to either prime/boost (1,900 participants) or placebo (100). According to epidemiological situation, option for ring vaccination around confirmed EVD cases. Follow-up for 12m.		during the clinical trial about adverse events after administration of the vaccine correspond to the available safety information specified in the official instructions for medical use, approved by the Ministry of health of the Russian Federation, and in Investigators Brochure. No serious adverse events were reported. In the structure of adverse events, systemic reactions were mainly represented by temperature increase, fever, which in a number of volunteers was accompanied by concomitant symptoms of	Actual study started at 8/2017; data collection for primary analysis will be obtained up to 12/2019.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
						intoxication. Local reactions were noted in the form of hyperemia and edema at the site of the vaccine injection. Clinical manifestations of allergic reactions (urticaria, rash, anaphylactic reactions) associated with vaccine administration, were not recorded.	
Only information from clinical trial registry entry (N.F. Gamaleya FRCEM, Russia) ClinicalTrials.gov Identifier: NCT03333538	1/2	Smorodintsev research Institute of Influenza Sankt-Peterburg, Russian Federation	220 healthy volunteers aged 18–55y, both sexes	A Double-blind Randomized Placebo-controlled Study of Safety and Immunogenicity of Medicinal Product GamEvac-Lyo, Vector-Based Vaccine Against Ebola Virus Disease, Lyophilisate for Preparation of Solution for	in progress	During the first stage of the study, mild adverse events (temperature increase, fever, headache, malaise, pain at the injection site) were recorded. All reported adverse events were resolved within 1-2 days without the use of	Recruiting. Actual study started at 11/2017; data collection for primary outcome measure will be finaled to 12/2018. Currently, the investigation of immunogenicity of the drug "GamEvac-Lyo" with 200

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				Intramuscular Injection. This clinical trial is designed as a double blind randomized placebo-controlled study to evaluate immunogenicity of medicinal product GamEvac-Lyo-Vector-Based Vaccine against Ebola Virus Disease The study consist of two stages At the first stage were studied the safety and tolerability of one dose of component A and B vaccine against Ebola in 20 healthy volunteers: 10 for component A and 10 to component B. In the first stage, the placebo will not be used. The duration of		symptomatic therapy. The frequency and nature of the adverse events recorded after the administration of the vaccine, are corresponding to the available safety information for the vaccine-analog "GamEvac-Combi".	volunteers, which will be determined by the tension of humoral and T-cellular immunity in response to vaccination is ongoing

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				screening up to 10 days. After interim analysis of safety data was obtained permission of the local ethics Committee of the Research Centre about the possibility of further studies of the drug. the second phase of the study was started, which, along with continued security research, provides the definition of the parameters of immunogenicity of the study drug. The second phase of the study will includ 200 participants, including 150 people will receive the vaccine and 50 will get a placebo.			
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSVΔG-ZEBOV-GP) with or without homologous boost							
Huttner et al.,	1	Switzerland	115 healthy adults	Randomized,	Huttner 2015	Mild, early-onset	Completed and

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
2015 (19) (PMID: 26248510; NCT02287480) Huttner et al., 2018 (20) (PMID: 29627147)		(Geneva)	aged 18–65 years	placebo-controlled, double-blind trial (deployable subjects not randomized to placebo) of rVSV doses ranging from $3x10^5$ –$5x10^7$ pfu; Follow-up for 28d (safety) and 180d (immunogenicity).	interim results reported seropositivity rates were similar (>90%), but GP-specific and neutralising Ab titres were 3 times lower in low-dose versus high-dose vaccinees. Lowering rVSV dose improved early tolerability, but also lowered antibody responses and did not prevent vaccine-induced arthritis, dermatitis, or vasculitis. Huttner 2018 reported sustained GP-ELISA responses and decreased PsVNA responses at 2 years	reactogenicity reported in 88%, 98% and 15% of low-, high-dose and placebo participants, respectively. 25% vaccinees at dose $1x10^7$ pfu w/ had objective fever. 25% low-dose vaccinees experienced oligoarthritis with median onset d10, associated with increasing age. No serious adverse events reported. Huttner 2018 reported vaccine related arthritis is associated with increased IgG GMCs beyond 6 months.	published
Agnandji et al., 2016 (21) (PMID: 25830326; NCT02283099,	1	Africa (Lambaréné, Gabon; Kilifi, Kenya) and Europe (Hamburg,	*Gabon, Kenya, Germany:* 185 healthy adults aged 18–55y, both	*Gabon, Kenya, Germany:* Open-label, uncontrolled,	All vaccinees showed GP-specific antibody responses; similar	Within 1st day, mild-to-moderate adverse events, with fever being	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
NCT02287480, NCT02296983, and PACTR201411000919191) Agnandji et al., 2017 (22) (PMID: 28985239)		Germany; Geneva, Switzerland) Data from Switzerland captured in prior row	sexes (75% men). 40 children aged 6-17 y.	dose-escalation trials of single rVSV dose ranging from $3x10^3$–$2x10^7$ pfu.	titres for different doses that were sustained at 180d. Most vaccinees showed neutralizing antibodies, with higher titres at higher doses.	most frequent (up to 30% vaccinees). Two (3%) vaccinees experienced arthritis. No serious vaccine-related adverse events reported. Vaccine viremia higher in children than adults and higher proportion of children than adults with PCR positive saliva through day 7 (latest timepoint tested).	
Regules et al., 2015 & 2017 (23, 24) (PMID: 25830322; NCT02269423 and NCT02280408)	1	USA (Maryland)	78 healthy adults aged 18–50y, both sexes (71% men)	Placebo-controlled, double-blind, dose-escalation trials. Consecutive enrolment to $3x10^6$, $2x10^7$ and $1x10^8$ pfu (60 participants) or placebo (18). In one of two studies, participants	100% vaccinees seroconverted for GP-specific antibodies by d28. Higher titres in vaccinees with two higher dose levels. 2nd dose at d28 increased titres by d56, but titres were diminished at 6m. Results support	Injection-site pain, fatigue, myalgia, and headache were reported most frequently. Rates of adverse events were lower after 2nd dose. No serious adverse events observed.	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				received 2nd dose at d28. Follow-up for 28d (after either 1st or 2nd injection).	further evaluation of rVSV at dose $2x10^7$ pfu and indicate that 2nd dose boosts antibody responses.		
El Sherif et al., 2018 (25) (PMID: 28630358)	1	Canada	40 healthy adults aged 18–65y, both sexes (43% men)	Randomized, Single-Center, Double-Blind, Placebo Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of $1x10^5$, $5x10^5$ and $3x10^6$ pfu (30 participants) or placebo (10)	ZEBOV rGP ELISA seroconversions Day 28 were 70% in participants who received the 1×10^5 pfu or 5×10^5 pfu dose and 100% in participants who received the 3×10^6 pfu dose.	Solicited AEs were primarily characterized as mild to moderate, with only 3 severe events (headache and diarrhea in the 5×10^5 pfu group; fatigue in the 3×10^6 pfu group). Arthralgia during the first 14 days postvaccination was infrequent and not severe. Arthritis was not reported.	Completed and published
Heppner et al., 2017 (26) (PMID: 28606591)	1b	USA	512 healthy eligible subjects between the ages of 18 and 61 years received vaccine or placebo	Randomized, multi-center, double-blind, placebo controlled, dose-ranging study to evaluate the	On day 28 at the 2×10^7 PFU dose, the geometric mean IgG ELISA endpoint titre was 1624 (95% CI 1146–	At the 2×10^7 PFU dose the most common local adverse events versus placebo within the first 14 days were arm	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				safety and immunogenicity of a broad dose range from $3x10^3$ to $1x10^8$ pfu	2302) and seroconversion was 95·7% (95% CI 85·5–98·8); the geometric mean neutralising antibody titre by $PRNT_{60}$ was 250 (176–355) and seroconversion was 95·7% (85·5–98·8)	pain and local tenderness. The most common systemic adverse events were headache, fatigue, myalgia, subjective fever, shivering or chills, sweats, joint pain, objective fever, and joint tenderness or swelling. Self-limited, post-vaccination arthritis occurred in 4.5% of vaccinees. Post-vaccination dermatitis occurred in 5.7% of vaccinees.	
Halperin et al., 2017 (27) (PMID: 28549145) Simon et al., 2017 (28)	3	USA, Canada, Spain	1,197 Healthy eligible subjects between the ages of 18 and 65 years	Randomized, double-blind, placebo-controlled study to evaluate safety and lot consistency of $2x10^7$ pfu standard dose and $1x10^8$ pfu high dose	Using validated assays day 28 geometric mean titer comparisons among subjects randomized to the 3 lots of standard dose vaccine demonstrated lot-	Fever (≥38.0°C) was observed in 20.2% of combined lots, 32.2% of high-dose, and 0.8% of placebo recipients. Incidences of AEs of interest (days	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					to-lot consistency. Seroconversion defined as ≥ 2-fold increase in antibody over baseline and ≥200 EU/ml was achieved by more than 94% of subjects who received any standard dose and 98% of subjects who received the high dose. At Month 6, more than 95% of subjects who received any standard dose and 96% of subjects who received the high dose met these criteria. Geometric mean titers increased by more than 58-fold from baseline by Day 28 and were increased by more than 52 fold from baseline at Month	1–42) were arthralgia (17.1% combined lots, 20.4% high-dose, 3.0% placebo), arthritis (5.1% combined lots, 4.2% high-dose, 0.0% placebo), and rash (3.8% combined lots, 3.8% high-dose, 1.5% placebo). Twenty-one SAEs and 2 deaths were reported, all assessed by investigators as unrelated to vaccine.	

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					6 in subjects that received standard dose or high dose of vaccine.		
Ebola ça suffit ring vaccination trial consortium, 2015 (29) Henao-Restrepo et al., 2015 & 2017 (30, 31) Soumah et al., 2016 (32) (PMID: 26215666, 26248676 & 28017403; PACTR201503001057193)	3	Guinea, Sierra Leone	5837 vaccinated participants out of 11, 841 people enumerated in 117 clusters total in communities with confirmed EVD. Initially aged ≥18y and not pregnant, breastfeeding, or severely ill; later age lowered to ≥6y. Both sexes (60% women). 2,016 healthy adults, front-line workers aged ≥18y. Both sexes (75% men)	*Cluster-randomized trial:* Ebola Ça Suffit! trial. Cluster-randomized (ring) trial; single rVSV dose of $2x10^7$ pfu; randomization by cluster into immediate or 21d delayed vaccination. No immunological testing. Follow up for 84d. Following DSMB recommendation randomization stopped and children down to 6 years enrolled. Enrolled 3/2015–1/2016. *Front-line worker trial:* non-randomized, open-label trial for safety and	*Cluster-randomized trial:* Vaccine efficacy was 100.0% (95% CI: 68.9–100.0%). *Front-line worker trial:* Only preliminary results are available. 29% and 70% of participants were whole virion ELISA positive at d0 and 28, respectively; 0% and 8% showed cellular response at d0 and 28, respectively.	*Cluster-randomized trial:* 54% of participants reported at ≥1 adverse event in 14d after vaccination; 88% of all adverse events were mild; 80 serious adverse events were identified, of which two were judged to be related to vaccination. *Front-line worker trial:* 70% participants reported adverse events. Headache and fatigue were most frequently reported. No serious adverse event was vaccine-related.	*Cluster-randomized trial:* completed and published Front-line *worker trial:* completed but not yet published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				immunogenicity; subgroup w/ immunological assessment (112 participants): 5 blood drawings (at inclusion and w2, 4, 12, 24). Follow-up for 24w. Enrolled 4–8/2015.			
Widdowson et al., 2016 (33) Goldstein et al., 2016 (34) Samai et al., 2018 (35) (PMID: 27387395 & N/A; NCT02378753)	2/3	Sierra Leone	8,673 clinical and nonclinical workers and other Ebola front-line workers (e.g., surveillance, burial, and ambulance personnel) enrolled and randomized; 8651 with valid consent	STRIVE trial (Sierra Leone Trial to Introduce a Vaccine against Ebola). Single rVSV dose of $2x10^7$ pfu. Initially planned as modified stepped-wedge trial: facilities randomized to receive vaccine at a specified time over a 6m period. Implemented as individually randomized trial of workers assigned to receive vaccine immediately or	8,651 vaccinees in 5 districts, of whom 4,319 (50%) immediately vaccinated. 44 participants became EVD suspect, but no cases were laboratory confirmed.	No serious vaccine-related adverse events or deaths report among vaccinees. 91.2% reported systemic adverse events within 7 days of vaccination.	Completed and published

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				delayed by 18–24w. Follow-up monthly for 6m. 436 participants in safety sub-study.			
Günther et al., 2011 (35) (PMID: 21987751; N/A)	N/A	USA	1 (post -exposure vaccination of biosafety level 4 laboratory worker)	Case report related to emergency vaccination of BL4 worker who got a needlestick injury with syringe containing Zaire Ebola virus species; single dose of rVSV $5.3x10^7$ pfu 48h after accident.	Person remained healthy. Except for the glycoprotein gene expressed in the vaccine, Ebola virus was never detected in serum and peripheral blood mononuclear cells during 3w observation period.	Patient developed fever and myalgia 3d after accident (1d after vaccination).	N/A
Lai et al., 2015 (36) (PMID: 25742465; N/A)	N/A	USA	1 (post -exposure vaccination of HCW)	Case report related to emergency vaccination of a physician who got a needlestick injury while working in an Ebola treatment unit in Sierra Leone in 9/2014. Vaccine administered 43h after accident	Ebola virus glycoprotein gene (included in the vaccine), Cytokine secretion and T lymphocyte and plasmablast activation were detected shortly after vaccination. Later, GP- specific antibodies and T cells were detected, but not	Fever and moderate to severe symptoms observed 12h after vaccination and lasted 3-4d.	N/A

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					antibodies against Ebola viral matrix protein 40 (not generated from vaccine). PCR was consistently negative for Ebola virus nucleoprotein gene (not in the vaccine).		
Wong et al., 2016 (37) (PMID: 27118786; N/A)	N/A	USA	5 (post-exposure vaccination of healthcare workers)	Case report related to emergency vaccination of HCWs who had potential exposures while working in Ebola treatment units in West Africa. Vaccine administered 24h to 3 days post-exposure	No subjects had RT-PCR evidence of Ebola infection	Fever, headache, and nausea were the most common AEs reported. 1 or 2 subjects reported diarrhea, vomiting, rash, arthralgia, or pain at injection site	N/A
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSV N4CT1 EBOVGP1)							
Matassov et al., 2016 (38) (PMID: N/A; NCT02718469)	1	USA	39 healthy adults, aged 18–55, both sexes	Randomized, placebo-controlled, double-blind, truncated dose escalation trial.	Preliminary results are from still blinded groups. GP-specific antibody responses	Adverse events across all dose groups were generally mild. Most frequently reported events	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				10:3 randomization in 3 groups to either vaccine (at doses 2.5x104, 2.5x105 & 2.0x106 pfu for each group) or placebo. Second dose administered at 28d interval. Follow-up for 26w (4m). Enrolment early 2016.	detected in 10/13, 9/12 & 10/13 participants in low-, mid- and high-dose groups, respectively. Similarly, T cell responses detected in 8/13, 8/12 & 9/13 participants.	were pain at injection (13/39) and fatigue (5/39).	
DNA plasmid vaccines							
Martin et al., 2006 (39) (PMID: 16988008; NCT00072605)	1		27 healthy adults aged 18–44 years	1st generation DNA vaccine, protocol VRC 204. Three-plasmid DNA vaccine encoding GP from Zaire and Sudan/Gulu species and nucleoprotein (VRC-EBODNA012-00-VP). Randomized, controlled, double-blind trial. 5:8:8:6 randomization to three injections	100% vaccinees showed GP-specific humoral and cellular responses detected at 4w after 3rd dose. Responses were also detectable after 2nd dose. Results of cellular responses also reported. Candidate DNA vaccine was immunogenic.	Vaccine was well-tolerated, with no significant adverse events.	Completed in 8/2005

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				(d0, d28, d56) of vaccine at doses 2, 4, 8mg or placebo. Followed for 12m. Enrolment in 11/2003–7/2004.			
Kibuuka et al., 2015 (40) (PMID: 25540891; NCT00997607)	1b	Uganda (Kampala)	108 healthy adults aged 18–50y	Two DNA plasmid vaccines: one encoding Zaire and Sudan Ebola virus species GP (EBO, VRC-EBODNA023-00-VP) and one Marburg virus (MAR, VRC-MARDNA025-00-VP). Randomised, placebo-controlled, double-blind trial. 5:1 randomization to 3 injections of vaccine or placebo at d0, w4 and w8, with vaccine allocations divided equally b/w EBO only, MAR only, and both. Follow-up for 2y. Enrolled 11/2009–4/2010.	GP-specific humoral and T-cell immune responses were similar between separate and concomitant use of two vaccines at w4 after 3rd dose (humoral: approx. 50% EBO and 25% MAR; cellular: 30–60% EBO and 40–50% MAR). Both vaccines given alone or jointly elicited antigen immune responses. Responses were not cross-reactive between EBO and MAR vaccines.	Vaccines were well tolerated. No significant differences in local or systemic reactions observed between groups.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Sarwar et al., 2015 (41) (PMID: 25225676; NCT00605514)	1	USA (Maryland)	20 healthy adults aged 18–60 y	Same vaccine as previous trial. Open-label trial. Vaccination at d0, w4and w8, with optional homologous boost at ≥w32. Follow-up for 32/44w (w/o or w/ boost). Enrolled 6/2008–6/2009.	80% vaccinees showed GP-specific humoral response at w4 after 3rd dose. Titres peaked at w4 and were decreased at w24. Cellular responses observed at less frequently (CD4+ T-cell 13–30% at w4 after 3rd dose). 4th dose boosted humoral response to near peak levels and T-cell responses slightly.	Vaccines were well tolerated and no serious adverse events were reported.	Completed
Multiple vaccines (Ad26, ChAd3, MVA [MVA-BN-Filo], rVSV [rVSVΔG-ZEBOV-GP])							
Kennedy et al., 2016 (42) Bolay, 2016 (43) (PMID: 26768572 & N/A; NCT02344407)	2	Liberia	1,500 healthy adults aged ≥18y; not pregnant or breastfeeding or EDV history (median age 30y, 37% female)	PREVAIL-I, as part of Partnership for Research on Ebola Vaccines in Liberia. Originally also intended as Phase 3 trial (w/ enrolment of 28,000 participants). Randomisation 1:1:1 to ChAd3 and rVSV, and	At 1m post-vaccination, ChAd3 and rVSV immunogenic for 87% and 94% participants, respectively. At enrolment, 6.3% of participants had Ebola virus antibodies, but no reported EVD. 98.6% completed	Both vaccines well-tolerated; differences in report of adverse events between 2 vaccine and placebo groups after 1w, but not after 1m.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				placebo; follow-up 8–12m. Enrolment 2–4/2015.	follow-up, which ended in 4/2016.		
Published reference N/A (PMID: N/A; NCT02876328)	2/3	Guinea & Liberia	4,900 healthy persons aged ≥1y; not pregnant, breast-feeding, EDV history, Ebola vaccination or HIV-positive	PREVAC (Partnership for Research on Ebola VACcinations). Randomization to Ad26, MVA, rVSV (single or boost at 56d), placebo. Follow-up for 12m and possibly 5y.	Primary outcome measures relate to immunogenicity. Study start in 1/2017, final data collection for primary outcome measure by 9/2018.	N/A	Not yet recruiting; data collection for primary outcome measure finalized by 9/2018.
Kennedy et al., 2017 (44) (PMID: 29020589; NCT02344407)	2	Liberia	1500 adults aged 18 years and above were randomized 1:1:1 between ChAd3-EBO-Z 1×1011 pu, rVSV and placebo. Follow-up of 12 months.	Randomized, double-blind, placebo-controlled study of 2x107 pfu dose rVSV, 1x1011 particles ChAd3-EBO-Z, or placebo	Induction of anti-GP ELISA responses in 71% of ChAd3-EBO-Z recipients one month after vaccination. Responses persisted in 63.5% of ChAd3-EBO-Z recipients until Month 12. By 1 month, an antibody response developed in 83.7% of subjects in the rVSV	Symptoms most commonly reported were headache, muscle pain, feverishness, and fatigue. Adverse events occurred significantly more often with the active vaccine than with placebo and included injection-site reactions in 30.9%, headache in 31.9%, muscle	Completed and published; long term follow-up continuing

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					vaccine group, as compared with 2.8% of those in the placebo group	pain in 26.9%, feverishness in 30.5%, and fatigue in 15.4% of subjects at 1 week. Serious adverse events within 12 months after injection were seen in 9.4% in the vaccinated group and 11.8% of the placebo group.	

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