UPDATE WITH THE DEVELOPMENT OF EBOLA VACCINES AND IMPLICATIONS TO INFORM FUTURE POLICY RECOMMENDATIONS

1 | POLICY QUESTIONS AND OVERALL CONCLUSIONS

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?

- A dozen candidate vaccines (including monovalent, bivalent or multivalent candidates) underwent or are actively undergoing clinical development at different trial phases. Seven vaccines have completed or are in trials up to Phase I stage, 4 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 demonstrates clinical efficacy and effectiveness for any candidate Ebola vaccine.
- In addition, another prime/boost candidate vaccine based on rVSV- and Ad5-vectored components (GamEvac-Combi) is licensed in its country of origin. However, the full dossier has not been yet made available to the WHO Secretariat for review.
- The rVSVΔG-ZEBOV-GP candidate vaccine with efficacy data was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency and Breakthrough Therapy designation by the US Food and Drug Administration.
- To date, no vaccine has been WHO-prequalified or completed the WHO Emergency Use Assessment and Listing (EUAL) procedure. The rVSVΔG-ZEBOV-GP candidate vaccine and a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) have submitted EUAL documentation to the WHO Secretariat. For both vaccines, submissions were accepted and evaluated on a rolling basis and the formal EUAL review by an ad-hoc Committee for the Emergency Use of Vaccines is planned for the second or third quarter of 2017.
- Potentially, various licensure pathways exist for candidate vaccines. Developers are consulting individually with regulatory agencies to define the documentation and evidence that is needed. Requirements and procedures are thus being discussed one by one.
- The WHO Secretariat is implementing the work plan of the R&D Blueprint for Action to Prevent Epidemics, including experts' deliberations on future clinical trials for candidate Ebola vaccines. The WG recommended that there should be alignment of different initiatives (e.g. Coalition for Epidemic Preparedness Innovations [CEPI], and others) to support the development and licensure

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☒ **THIS SUMMARY DOES NOT INCLUDE**

The full extent of the evidence reviewed by the SAGE Working Group is not included.

of Ebola vaccines and of other vaccines against epidemic-prone diseases, taking note of the mandates specific to each stakeholder.

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: 64–100%) in a cluster randomised ring vaccination trial conducted in Guinea. Ring vaccination with the same candidate vaccine was also carried out following the smaller flare-ups in 2016 in Guinea, Sierra Leone and Liberia.
- 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 March 2017, the longest interval for which such data is available is 12 months (published and unpublished data on the prime/boost Ad26/MVA, rVSVΔG-ZEBOV-GP, and ChAd3-EBOZ vaccines). 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. At least five vaccines under development are also being tested clinically in bivalent or multivalent formulations that may protect against other species of Ebola virus or Marburg virus.
- 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. Evidence from Phase I–III clinical trials and from the deployments during the 2016 flare-ups 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 may 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 is producing 300,000 doses that have been purchased by GAVI Alliance.

2 | KEY FINDINGS

Epidemiology

From 1976 to March 2017, 25 filoviruses outbreaks with ≥4 reported human cases have been documented (see, **Appendix 1**). *Zaire ebolavirus* caused 13 of these outbreaks (30,101 reported cases in total), *Sudan ebolavirus* six (777), *Bundibugyo ebolavirus* two (185), and *Marburg marburgvirus* four (425). When the 2013–2016 West African epidemic is omitted, the range of reported cases for the 12 remaining *Zaire ebolavirus* outbreaks was 11–318 (median=64.5). **Figure 1** illustrates the epidemic curve of such an outbreak.(1) 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).(2, 3) When these two occurrences are omitted, the outbreaks have lasted between 1 and 42 weeks, with a median duration of 10 weeks. Other filoviruses known to infect humans are *Reston ebolavirus* (asymptomatic infections only in persons exposed to non-human primates and pigs from the Philippines) and *Taï Forest ebolavirus (*single case of a scientist who did an autopsy on a wild chimpanzee in Ivory Coast).(4, 5)

Since the 1995 Kikwit outbreak, the **principles for interrupting transmission of Ebola and Marburg viruses** are well characterized.(6) 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;
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 were initially at increased risk** (**Figure 3**). As already observed in previous outbreaks, health care workers 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.(7-11)

Vaccine development

A dozen candidate vaccines (including monovalent, bivalent or multivalent candidates) underwent or are actively undergoing **clinical development at different trial phases** (**Table 1**). Seven vaccines have completed or are in trials up to Phase I stage, four 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.

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

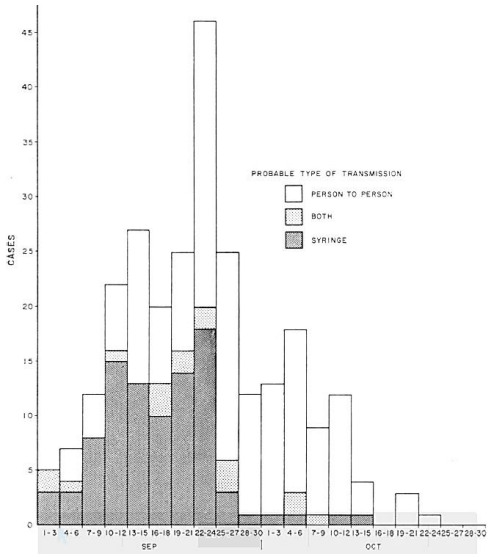


Figure 2. Age-specific cumulative incidence of confirmed and probable Ebola virus disease cases, by country—West Africa, 2013–2016 (12)

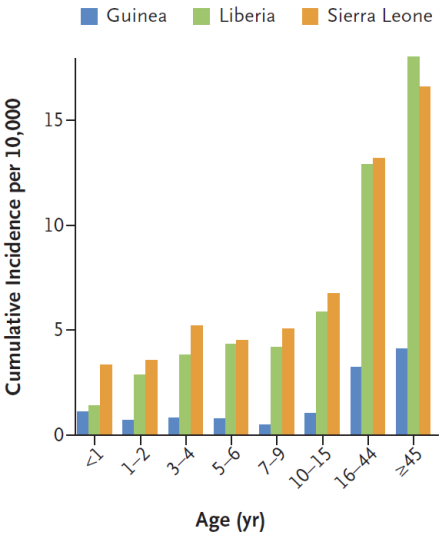


Figure 3. Epidemic curve of Ebola virus disease cases, by health care workers (HCW) and general population—DRC, 1995, and Sierra Leone 2014–2015 (13, 14)

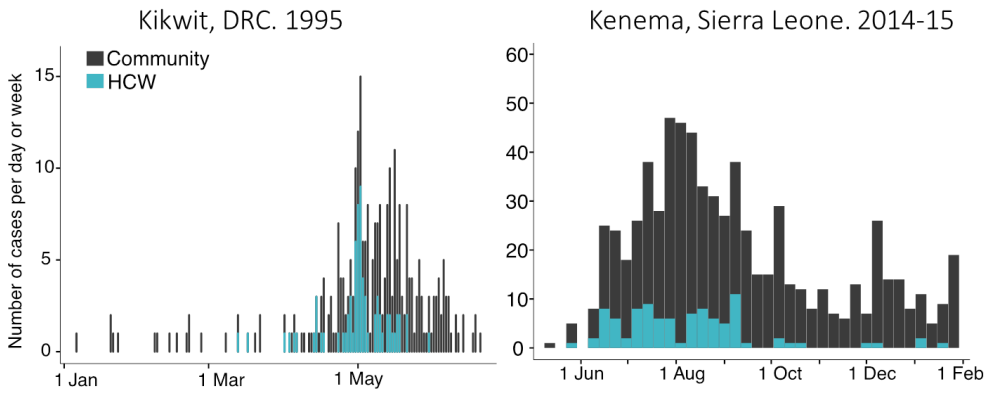
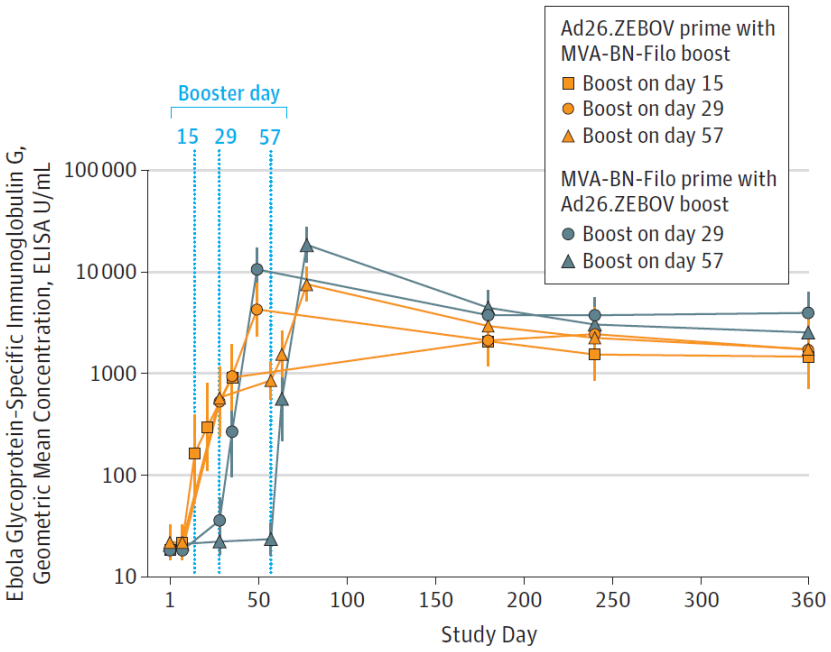


Table 1. Description of candidate Ebola vaccines under clinical development

Candidate vaccine (manufacturer/developer)	**Short description of vaccine**	**Clinical stages**
Ad5-EBOV (monovalent) (CanSino Biologics & Beijing Institute of Biotechnology, China)	Non-replicative, recombinant human adenovirus serotype 5 expressing envelope GP of Zaire (Makona strain) Ebola virus species	1 & 2
Ad5 (bivalent) (National Institute of Allergy and Infectious Diseases, USA)	Non-replicative, recombinant human adenovirus serotype 5 expressing envelope GP of Zaire and Sudan Ebola virus species	1 (inactive)
Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150) (Janssen Vaccines & Prevention B.V, The Netherlands)	Non-replicative, recombinant adenovirus serotype 26 expressing envelope GP of Zaire Ebola virus species and modified vaccinia Ankara expressing 4 filoviruses nucleoproteins (GP for Zaire Ebola [Mayinga strain], Sudan Ebola, and Marburg viruses and nucleoprotein of Taï Forest Ebola virus)	1; currently recruiting for phase 2/3 trials.
ChAd3-EBOZ (monovalent) (GlaxoSmithKline, Belgium)	Non-replicative, recombinant chimpanzee adenovirus serotype 3 expressing envelope GP of Zaire (Mayinga strain) Ebola virus species	1/2a
ChAd3-EBOZ & MVA-BN-Filo (prime/boost) (University of Oxford, UK and National Institute of Allergy and Infectious Diseases, USA)	See previous descriptions	1
ChAd3 (bivalent) (National Institute of Allergy and Infectious Diseases, USA)	Non-replicative, recombinant chimpanzee adenovirus serotype 3 expressing envelope GP of Sudan and Zaire (Mayinga strain) Ebola virus species	1
DNA plasmid vaccines (National Institute of Allergy and Infectious Diseases, USA)	Several candidate vaccines that either encoded both Zaire and Sudan Ebola virus species GP or Marburg virus. *Trials carried out in 2004–2010 and none is currently active under NIAID.*	1 (inactive)
GamEvac-Combi (rVSV & Ad5, prime/boost) (Gamaleya Research Institute for Epidemiology and Microbiology, Russia)	Replicative, recombinant vesicular stomatitis virus and human adenovirus serotype 5 expressing envelope GP of Zaire (Makona strain) Ebola virus (prime & heterologous boost). *MOH of Russian Federation registered vaccine on 28/12/2016 (no. LP-003390).*	1/2, 4
rVSVΔG-ZEBOV-GP (Merck, USA)	Replicative, recombinant vesicular stomatitis virus expressing envelope GP of Zaire (Mayinga strain) Ebola virus species with or without homologous boost	1–3
rVSV N4CT1 EBOVGP1 (Profectus BioSciences, USA)	Replicative, recombinant vesicular stomatitis virus expressing GP of Zaire (Mayinga strain) Ebola virus species. (Trivalent Ebola/Zaire, Ebola/Sudan and Marburg candidate vaccine is also been developed.)	1
Nanoparticle recombinant Ebola GP vaccine (Novavax, USA)	Nanoparticle recombinant vaccine with and without our Matrix-M adjuvant; Zaire (Makona strain) Ebola virus species	1
DNA vaccine (INO-4212) (Inovio Pharmaceuticals, USA)	INO-4212 (with 2 components INO-4201 [past Ebola Zaire virus outbreak strains] & INO-4202 [2014–2015 Ebola Zaire virus outbreak strains]), delivered with electroporation	1
HPIV3-EbovZ GP (National Institute of Allergy and Infectious Diseases, USA)	Live-attenuated human parainfluenza virus type 3 vectored expressing Zaire Ebola virus GP. *Trial is completed.*	1 (inactive)

Data on safety and immunogenicity are accumulating for all candidate vaccines under active clinical development (see, **Appendix 2**). Trials have not reported serious adverse events definitely linked to any candidate vaccine. However, **safety profile** are still been 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 March 2017, the longest available interval is 12 months, which refers to the Ad26/MVA vaccine (published data from a Phase I conducted in the UK) and ChAd3-EBOV and rVSVΔG-ZEBOV-GP (unpublished data from a Phase II trials conducted in Liberia).(15) Surrogates of protection are not defined yet.

Figure 4. Humoral immune response to Ad26/MVA vaccine in a Phase I trial (15)



Efficacy and effectiveness data are only available for rVSVΔG-ZEBOV-GP.(16) In a Phase III trial mainly carried out in Guinea in 2015, this vaccine showed a 100% efficacy (95% confidence interval: 64–100%). **Table 2** details the efficacy and effectiveness results from this trial.

Vaccine approval

To date, no vaccine has been WHO-prequalified or completed the WHO Emergency Use Assessment and Listing (EUAL) procedure. The rVSVΔG-ZEBOV-GP candidate vaccine and a prime/boost candidate vaccine based on Ad26- and MVA-vectored components (Ad26.ZEBOV/MVA-BN-Filo) have submitted EUAL documentation to the WHO Secretariat. For both vaccines, submissions were accepted and evaluated on a rolling basis and the formal EUAL review by an ad-hoc Committee for the Emergency Use of Vaccines is planned for the second or third quarter of 2017.

Table 2. Effect of rVSVΔG-ZEBOV-GP on cases of Ebola virus disease in different study populations—Guinea and Sierra Leone (16)

	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

With regard to regulatory agencies, a vaccine (GamEvac-Combi) is licensed in the Russian Federation, its country of origin. Also, rVSVΔG-ZEBOV-GP was granted access to the Priority Medicine (PRIME) scheme by the European Medicine Agency and Breakthrough Therapy designation by the US Food and Drug Administration. Potentially, various licensure pathways exist for candidate vaccines. Developers are consulting individually with regulatory agencies to define the documentation and evidence that is needed.

Modelling of vaccination strategies

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

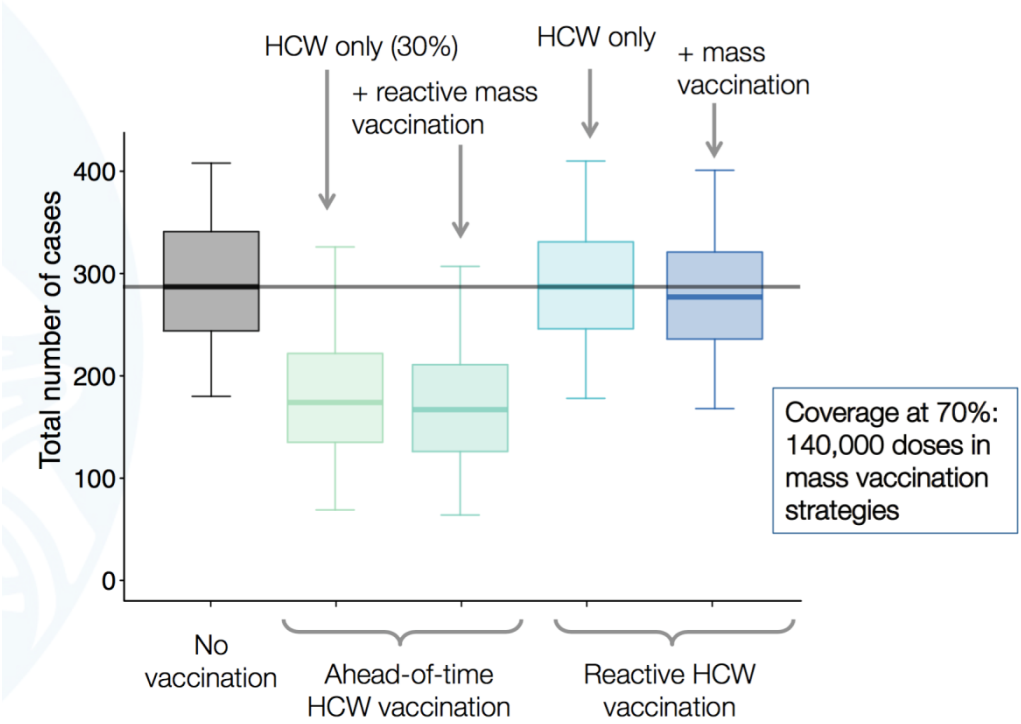
1. **Pre-emptive vaccination** of health-care workers (HCW). Front-line workers (FLW) are not included in HCW because they are recruited after an outbreak is declared.
2. **Reactive vaccination**
    a) Ring vaccination: contacts and contacts of contacts (CCC) of Ebola virus diseases cases;
    b) Targeted vaccination: HCW and/or FLW; and
    c) Mass vaccination: all people living in villages of Ebola virus disease cases plus random allocation of remaining doses in neighbouring areas.

The strategies were assessed on both **localised 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).

Figure 5 shows that pre-emptive vaccination of HCW, even at 30% coverage, can lead to a reduction around 40% of the total number of cases in a scenario similar to the one of Kikwit in 1995, where

HCW played an important role in amplifying the early spread of Ebola virus (see also **Figure 3**). By contrast, reactive vaccination targeting HCW 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.

Figure 5. Impact of different vaccination strategies on the 1995 Ebola outbreak in Kikwit (Democratic republic of Congo), while accounting for classical control measures implemented during the outbreak

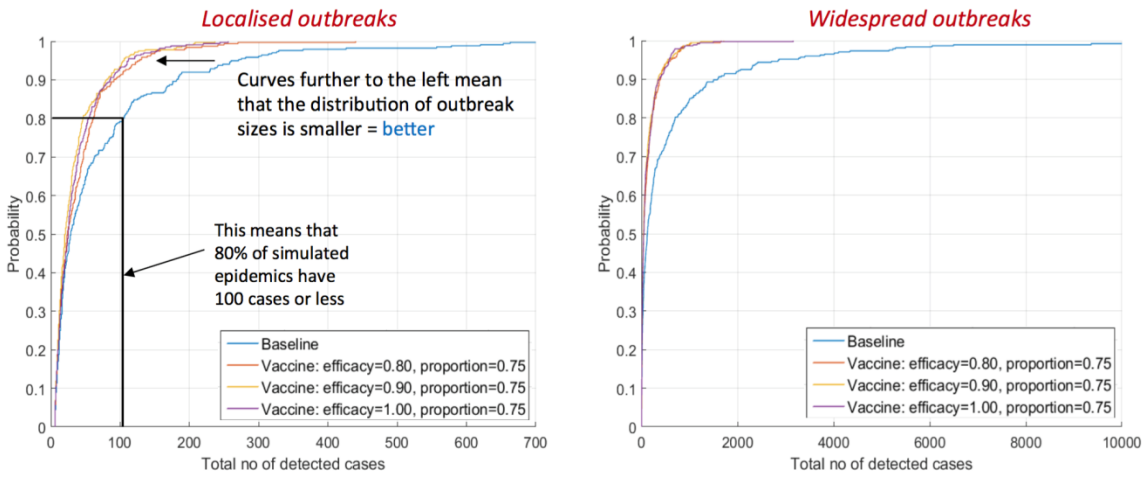


Notes: Each boxplot represents the distribution of the total number of cases expected for a given vaccination strategy, in comparison to the baseline scenario without vaccination (but with classical control measures). Variability arises from multiple stochastic simulations.
Source: Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, presented to the SAGE Working Group on 15 March 2017.

On the other hand, **Figure 6** shows that ring vaccination of CCC 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 localised 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.

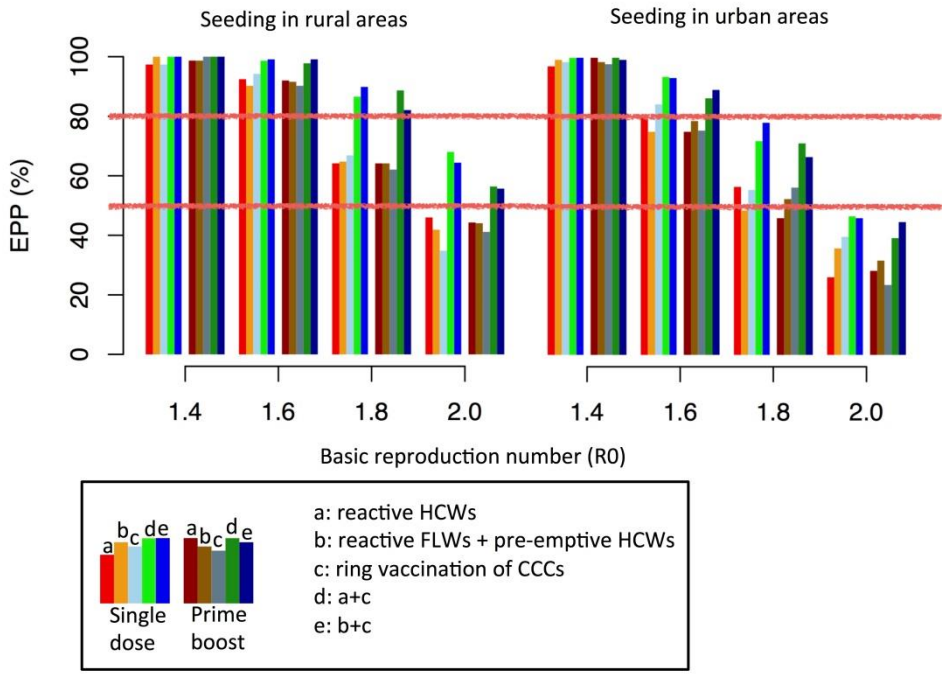
Figure 7 and **Figure 8** compare the impact of different combinations of pre-emptive and reactive strategies for both single-dose and prime/boost vaccines in either rural or urban areas and for different intensity of transmission (as measured by the basic reproduction number R0). This model is gauged 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 localised (left panel) and widespread (right panel) outbreaks



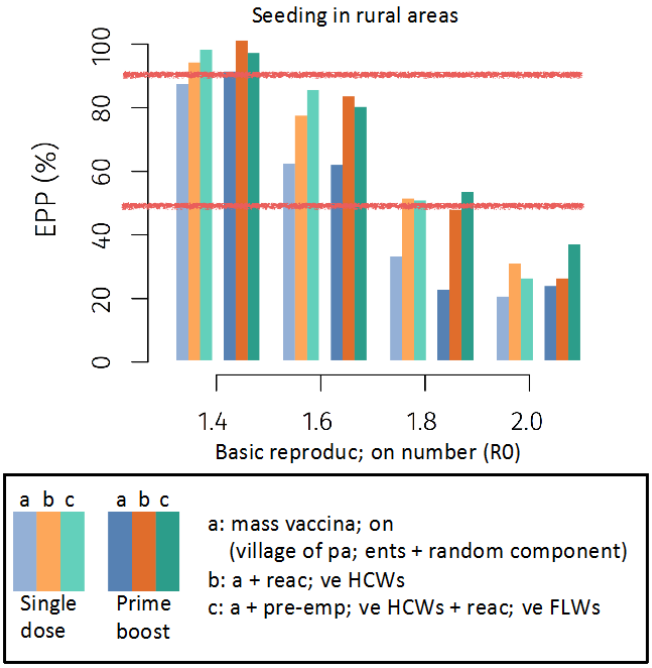
Note: Classical control measures are also implemented in this model.
Source: Centre for Outbreak Analysis and Modelling, Imperial College London, presented to the SAGE Working Group on 15 March 2017.

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 outbreaks (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 15 March 2017.

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 outbreaks (>300 cases).
Source: Center for Inference & Dynamics of Infectious Diseases, presented to the SAGE Working Group on 15 March 2017.

Taken together, the modelling estimates shows that combining a pre-emptive and/or reactive vaccination of HCW/FLW with ring vaccination of CCC is the most effective strategy as it reduces by more than 80% the risk of large outbreaks (>300 cases) when the epidemic is seeded in rural areas and R0 values are consistent with the 2013–2016 West African outbreak (R0 < 2). 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. Finally, 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.

Although the number of doses needed for pre-emptive vaccination of HCW 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 localised outbreaks, whereas 50,000 doses were sufficient to contain simulated widespread outbreaks. By contrast, mass vaccination required a tenfold number of doses.

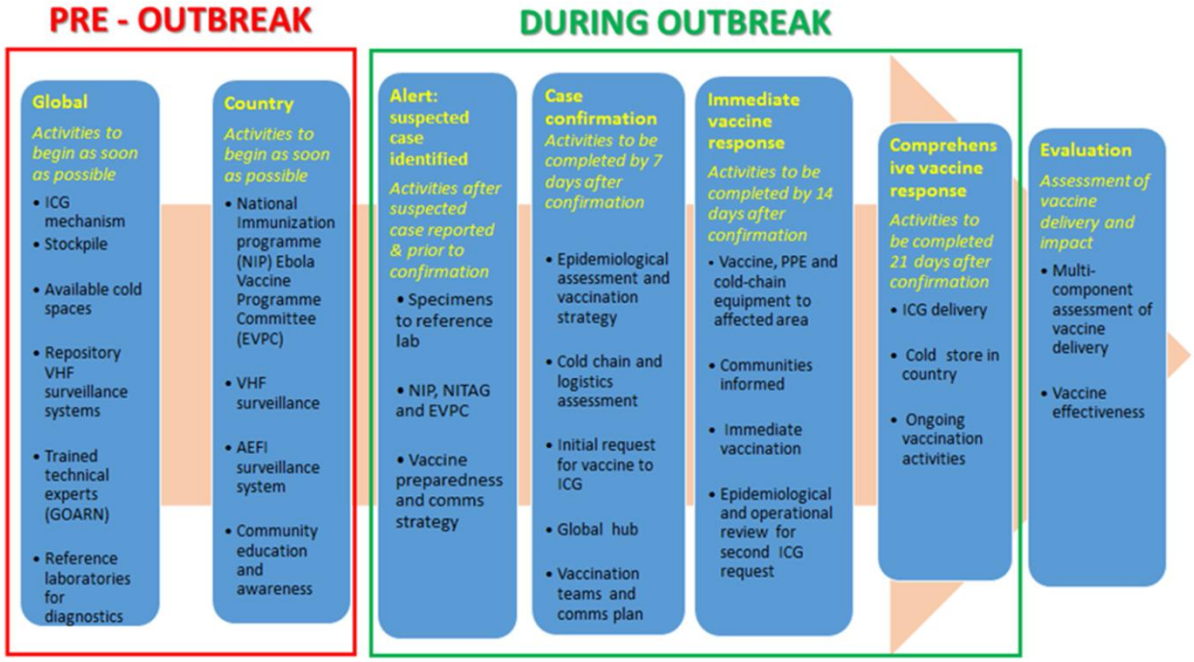
Overall, modelling suggests that pre-emptive vaccination of HCW combined with a reactive ring vaccination strategy is the most effective strategy to contain future Ebola outbreaks. Modelling estimates also support a vaccine stockpile of at least 100,000 doses for reactive ring vaccination. Importantly, ring vaccination requires effective case detection and contact tracing, thus acting synergistically with classical control measure of Ebola virus transmission.

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. 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 serious adverse events over 84 days after vaccination, adverse events over 28 days after vaccination, and pregnancy outcome. 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 9**).

Figure 9. Outline of Ebola vaccination phases proposed by the Global Ebola Vaccine Implementation Team



The GAVI Alliance and the manufacturer of the rVSVΔG-ZEBOV-GP candidate vaccine have entered an agreement to support the provision of a vaccine to protect against future Ebola outbreaks. Reserves of rVSVΔG-ZEBOV-GP are available with researchers and the manufacturer.

4 | RECOMMENDATIONS PROPOSED BY SAGE WORKING GROUP

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?

- SAGE notes and appreciates the momentous progress made in the development and evaluation of several vaccine platforms against Ebola and other filoviruses. SAGE wishes to recognize the invaluable contribution of the volunteers who participated in clinical trials, governmental institutions, researchers and their teams, research institutions, regulators and vaccine manufacturers from around the world.
- SAGE urges the WHO Secretariat and national regulatory authorities to intensify their efforts in reaching a consensus and clarity on specific aspects of regulatory pathways that would allow the development and registration of candidate Ebola vaccines, noting the changing Ebola epidemiology and the anticipated constraints in documenting clinical efficacy and effectiveness data. In particular, SAGE supports the role that the WHO Secretariat is playing in facilitating regulatory convergence through development of WHO Guidelines for Ebola vaccines evaluation that will be considered by the Expert Committee on Biological Standardization. Regulatory convergence on data requirements and wider understanding of various regulatory pathways such as the Animal Efficacy Rule that is unique to the US Food and Drug Administration.
- SAGE encourages developers seeking approval to engage relevant NRAs, in particular, national regulatory agencies and the regional regulatory structure (African Vaccine Regulatory Forum, AVAREF) of African countries, where Ebola vaccines are more likely to be deployed.
- SAGE acknowledges the national licensure of the vaccine GamEvac-Combi and would appreciate the submission of additional data, including the required evidence necessary to apply for prequalification status, should the developer wish to submit this. As the availability of several vaccines is generally beneficial, SAGE recommends that vaccine developers submit data in an application, as soon as they are available, to the WHO Secretariat according to established procedures (e.g., prequalification procedures).

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?

- Should an EVD outbreak occur, SAGE recommends the use of the rVSVΔG-ZEBOV-GP candidate vaccine for which clinical efficacy data are available. As this is an unlicensed candidate vaccine to date, this candidate vaccine should be deployed under the Expanded Access framework, with informed consent and in compliance with Good Clinical Practices. The recommended delivery strategy is the ring vaccination adapted to the social and geographic conditions of the outbreak and affected areas. The Expanded Access study protocol—that is being discussed with Member States by MSF, the vaccine developer, WHO, CDC, and other partners—should be implemented promptly after the confirmation of a case of Ebola virus disease. If the emerging outbreak was caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species. This Expanded Access should be used as an opportunity to accumulate additional information on vaccine safety, efficacy and effectiveness.
- Though SAGE recognizes the risks faced by health care workers and their potential role in the amplification of Ebola virus transmission early in an outbreak, current evidence is insufficient to

recommend pre-emptive vaccination of this group. There is incomplete information on the duration of the immune response for the vaccines that are under review, and uncertainty on vaccine cross-protection for the different Ebola virus species. There is also a need to generate more safety data on the rVSVΔG-ZEBOV-GP vaccine in African populations, noting the safety concerns of arthritis and arthralgia that occurred in the Phase 1 study in Switzerland. More finely grained sociological knowledge is required to appreciate the acceptability of vaccines used pre-emptively amongst health care workers, noting the low acceptability of Ebola vaccination by health care workers reported in Liberia. Lastly, additional modelling work should be done to refine estimates on the additional benefit of pre-emptive health care worker immunisation.

- SAGE also considers that available evidence is insufficient to recommend pre-emptive mass immunisation of the general population because of the still partial knowledge on the vaccine immunogenicity, efficacy, safety, and acceptability as well as the unpredictability of where Ebola may emerge next and the generally low attack rate observed to date in the general population. The existence of effective control interventions (including ring vaccination) when outbreaks are detected and responded to in a timely and decisive fashion is also a consideration.
- SAGE recommends that, once one or more Ebola vaccines are licensed and prequalified, a mechanism for stockpiling them should be put in place to ensure prompt and equitable access. Mathematical modelling estimates should be further refined to help inform the size and composition of the stockpile. At the present time, a stockpile of up to 300,000 doses can be recommended to cover the likely size of a large outbreak in high transmission settings.
- SAGE recommends taking all opportunities to generate or expand the evidence base that can broaden the indication and increase the acceptability of Ebola vaccination. This evidence that ongoing clinical studies, outbreak-related deployments, or operational research could generate should include:
- Safety, immunogenicity and efficacy of candidate vaccines in population groups not generally considered in clinical trials, such as infants and young children, pregnant women, children of breastfeeding mothers, people living with HIV, and other immune compromised persons;
- Vaccination perception and acceptability, especially among health care workers, front-line workers, and informal health care providers such as traditional healers, birth assistants, bone setters, and Ebola virus disease survivors; and
- Social mobilization and communication research to improve messaging and communication strategies in the event of an outbreak.

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Appendix A: Characteristics of Ebolavirus and Marburg virus outbreaks with ≥4 reported human cases, 1976–2016

Legend: EBOV, species *Zaire ebolavirus*; SUDV, species *Sudan ebolavirus*; BDBV, species *Bundibugyo ebolavirus*; MARV, species *Marburg marburgvirus*

Month & year started	Country	Virus species	Weeks to 1st peak	Weeks to extinction	Report cases	Reported deaths (CFR %)	Reference
Jun-76	South Sudan	SUDV	5	20	284	151 (53%)	WHO/International Study Team, 1978 (1)
Aug-76	Democratic Republic of Congo	EBOV	5	9	318	280 (88%)	Report of an International Commission, 1978 (2)
Jul-79	South Sudan	SUDV	2	10	34	22 (65%)	Baron et al., 1983 (3)
Nov-94	Gabon	EBOV	4	13	49	30 (61%)	Georges et al., 1999 (4)
Jan-95	Democratic Republic of Congo	EBOV	17	27	315	250 (81%)	Khan et al., 1999 (5)
Jan-96	Gabon	EBOV	0	5	29	18 (62%)	Georges et al., 1999 (4)
Jul-96	Gabon	EBOV	18	27	60	45 (74%)	Georges et al., 1999 (4)
Oct-98	Democratic Republic of Congo	MARV	13	100	154	125 (81%)	Bausch et al., 2006 (6)
Aug-00	Uganda	SUDV	5	20	425	224 (53%)	Okware et al., 2002 Trop Med Inter Health 2002 (7)
Oct-01	Gabon & Republic of Congo	EBOV	6	21	124	96 (77%)	World Health Organization, 2003 (8) Nkoghe et al., 2005 (9)
May-02	Gabon & Republic of Congo	EBOV	5	10	11	10 (90%)	World Health Organization, 2003 (8)
Dec-02	Republic of Congo	EBOV	N/A	19	143	128 (89%)	Formenty et al., 2003 (10)
Oct-03	Republic of Congo	EBOV	5	7	35	29 (83%)	Boumandouki et al., 2005 (11)
Apr-04	South Sudan	SUDV	1	10	17	7 (41%)	World Health Organization, 2005 (12)
Oct-04	Angola	MARV	24	42	252	227 (90%)	World Health Organization, 2005 (13, 14) US CDC, 2005 (15) Towner et al., 2006 (16)
Jun-07	Democratic Republic of Congo	EBOV	13	15	264	187 (71%)	World Health Organization, 2007 (17) Leroy et al., 2009 (18) Grard et al., 2011 (19)
Jun-07	Uganda	MARV	N/A	13	4	1 (25%)	Adjemian et al., 2001 (20)
Aug-07	Uganda	BDBV	14	18	149	37 (25%)	MacNeil et al., 2011 (21)
Nov-08	Democratic Republic of Congo	EBOV	3	5	32	15 (47%)	World Health Organization, 2009 (22) Rosello et al., 2015 (23)
Oct-12	Uganda	MARV	N/A	3	15	4 (27%)	Albariño et al., 2013 (24)
Aug-12	Democratic Republic of Congo	BDBV	N/A	8	36	13 (36%)	Albariño et al., 2013 (24)
Nov-12	Uganda	SUDV	N/A	1	6	3 (50%)	Albariño et al., 2013 (24)
Jul-12	Uganda	SUDV	N/A	1	11	4 (36%)	Albariño et al., 2013 (24)

Dec-13	West Africa & other countries in Africa, Europe and North America	EBOV	17	109	28,652	11,325 (40%)	WHO Ebola Response Team 2014, 2015 & 2016 (25-27)
Jul-14	Democratic Republic of Congo	EBOV	4	10	69	49 (74%)	Maganga et al., 2014 (28)

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Appendix B: Summary of published data on efficacy, immunogenicity and safety of candidate Ebola vaccines in clinical development

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 1.6×10^{11}, 4.0×10^{10} 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 immunity. Boosting provided greater antibody response, possibly with longer duration.	Mild and moderate solicited adverse reactions within 7d of vaccination reported at higher rate in both vaccine groups. No serious events recorded.	Completed
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	Randomised, placebo-controlled, double-blind trial; 2:1:1 randomisation to $8.0\text{x}10^{10}$, $1.6\text{x}10^{11}$ vp, or placebo; safety follow-up at 7d, immunogenicity follow-up at d14, 28 and	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	Rates of ≥1 adverse reaction within 7d of vaccination were similar in 3 groups; most reactions mild and	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			negative, no EVD history, no previous Ebola immunisation. 45% participants had pre-existing Ad5 immunity (titres >1:200).	168. Enrolment 10/2015.	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.	self-limiting. Injection-site reactions were more frequent in vaccine groups. No serious events related to vaccine.	
Ad5 expressing envelope GP of Sudan and Zaire Ebola virus species (bivalent)							
Ledgerwood et al., 2010 (4) (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 2×10^{11} or 2×10^{10} 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 present in both low- and high-dose vaccinees.	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
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 (5) Winslow et al., 2017 (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 (titres threshold not defined).	Randomised, placebo-controlled, observer-blind trial; 5:1 randomisation, with 4 vaccine groups (72 participants): primed with either Ad26 5×10^{10} vp or MVA 1×10^{8} infective dose and boosted with alternative vaccine at either d28 or d56. Also, open-label trial; 15 participants primed with Ad26 and boosted by MVA at d14. Follow-up for 12m 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 and 12m follow-ups. 60–83% vaccinees had T-cell persistent response at m12. 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
Enria et al., 2016 (7) (PMID: 27821112; NCT02509494)	3	Sierra Leone (Kambia)	*Stage 1:* 43 healthy adults aged ≥18y. *Stage 2:* 688 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 5×10^{10} vp and boosted with MVA 1×10^{8} infective dose at d28; vaccinated from 10/2015. *Stage 2:* randomised, controlled, double-blind trial; randomization to same prime/boost regimen as	N/A	N/A	Currently recruiting. Data collection for primary outcome measure finalized by 9/2018.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				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 serious adverse events for 36/12m for stage 1/2, respectively. Additional stages are being consulted with national and international stakeholders.			
ChAd3 expressing envelope GP of Zaire Ebola virus species (Mayinga variant, monovalent)							
De Santis et val., 2016 (8) (PMID: 26725450; NCT02289027)	1/2a	Switzerland (Lausanne)	120healthy 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 2.5×10^{10} (low dose), 5×10^{10} (high dose) or placebo. Allocation not concealed for deployable participants. Follow-up for 180d. Enrolment 10/2014–6/2015.	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 significant differences related to two dosages.	>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
Tapia et al., 2016 (9) (PMID: 26546548; NCT02231866)	1	USA (Maryland)	20 healthy participants aged 18–65y. Both sexes	Randomized, single-blind trial. 1:1 randomisation to ChAd3 (monovalent) 1×10^{10} or 1×10^{11} vp. Follow-up for 180d. Enrolment 11/2014.	100% vaccinees of both dose levels showed humoral response at d28. Titres were >2-fold higher in higher-dose group.	Local pain and tenderness, fatigue and headache were most frequently reported adverse	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
						events. No serious safety concerns identified.	
ChAd3 (monvalent) boosted with MVA-BN-Filo							
Ewer et al., 2016 (10) (PMID: 25629663; NCT02240875)	1	UK (Oxford)	76 healthy adults aged 18–50y.	Open-label trial. *Priming:* 20:36:20 participants each received ChAd3 at 1×10^{10}, 2.5×10^{10} and 5×10^{10} vp. *Boosting:* 46 participants in total boosted with MVA. At w1–2, 16 participants of ChAd3 2.5×10^{10} dose boosted with MVA 1.5×10^{8} plaque forming units (pfu). At w3–10, 10 participants of 3 ChAd3 dose groups boosted at either MVA 1.5×10^{8} (18 participants) or 3×10^{8} (12), stratified per priming dose group. Follow-up for 29d (primed only) or 180d (if boosted). Also, comparison of neutralizing antibody activity with that observed in ph1 trial of rVSV-ZEBOV. Enrolment in late 2014.	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 were superior to those induced by ChAd3 alone	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
Tapia et al., 2016 (9) (PMID: 26546548; NCT02267109)	1b	Mali	91 adults aged 18–50y (52 participants boosted with either MVA-BN-Filo [27] or saline	Open-label and double-blind, dose-escalation trial (ChAd3 prime); nested, randomised, placebo-controlled and double-blind trial (MVA 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	Most adverse events were mild. Predominant solicited adverse event was fever (10/11 episodes	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			[25]). Males & females not breast-feeding, not pregnant & not planning to become pregnant.	1:3:3:1 randomisation to ChAd3 1×10^{10}, 2.5×10^{10}, 5×10^{10} or 1×10^{11} vp. 52 participants were further 1:1 randomised to boost MVA 2×10^{8} pfu or placebo. Follow up for 180d after primary or booster vaccination. Enrolment 11/2014 (prime) and 2/2015 (boost).	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 1×10^{11} ChAd3 dose for reactive vaccination and MVA boosting for conferring long-lived protection.	resolved within 24h). Only one serious event observed in a Malian participant, but deemed unrelated to vaccine.	
ChAd3 expressing envelope GP of Zaire (Mayinga variant) and Sudan Ebola virus species (bivalent)							
Ledgerwood et al., 2014 & 2017 (11, 12) (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 2×10^{10} and 2×10^{11} 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
DNA plasmid vaccines							
Martin et al., 2006 (13) (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	100% vaccinees showed GP-specific humoral and cellular responses detected at 4w after 3rd dose. Responses	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
				Zaire and Sudan/Gulu species and nucleoprotein (VRC-EBODNA012-00-VP). Randomized, controlled, double-blind trial. 5:8:8:6 randomization to three injections (d0, d28, d56) of vaccine at doses 2, 4, 8mg or placebo. Followed for 12m. Enrolment in 11/2003–7/2004.	were also detectable after 2nd dose. Results of cellular responses also reported. Candidate DNA vaccine was immunogenic.		
Kibuuka et al., 2015 (14) (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
Sarwar et al., 2015 (15) (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	80% vaccinees showed GP-specific humoral response at w4 after 3rd dose. Titres peaked at w4 and were	Vaccines were well tolerated and no serious adverse events	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				homologous boost at ≥w32. Follow-up for 32/44w (w/o or w/ boost). Enrolled 6/2008–6/2009.	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.	were reported.	
GamEvac-Combi (rVSV & Ad5, prime & heterologous boost) expressing Zaire Ebola virus species (Makona variant)							
Dolzhikova et al., 2017 (16) (PMID: 28152326; zakupki.gov.ru no. 0373100043 215000055)	1/2	Russia	84 healthy adults aged 18–55y, both sexes (76% men)	Open-label, dose-escalation trial. GamEvac-Combi candidate vaccine (rVSV prime & heterologous Ad5 boost), each component alone or in combination at full (rVSV 2.5×10^{7} pfu & Ad5 2.5×10^{11} 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.	100% prime-boost vaccinees of both 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. Pre-existing 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 cross-reactive immunogenicity from Makona. 59–83% prime-boost vaccinees of both dose groups showed T-cell responses at d28, with	Pain at the injection site was most frequently reported adverse event. No serious adverse event was reported.	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
					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 (Gamaleay Research Institute, Russia) (PMID: N/A; NCT02911415 & NCT02911428)	4	Russia	120 healthy adults aged 18–56y, both sexes. 60 participants each as Ad5 prime only (NCT02911428) or rVSV prime & Ad5 boost (NCT02911415)	Both candidate vaccines GamEvac (Ad5 prime only, protocol 02-E-2015) & GamEvac-Combi (rVSV prime and Ad5 boost, protocol 01-COMBI-2015). Observational, prospective cohort study to evaluate 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.	Primary outcome measures relate to immunogenicity and safety. Study started in 10/2016, final data collection for primary outcome measure by 12/2017.	N/A	Ongoing; data collection for primary outcome measure finalized by 12/2017.
Russian Federation MOH briefing at WHO Executive Board meeting of 2/2016 (PMID: N/A; NCT03072030 & PACTR201702002053400)	2	Guinea (Kindia)	2,000 healthy adults aged 18–60y, both sexes	Candidate vaccine GamEvac-Combi: rVSV prime, $2.5x10^{7}$ pfu; Ad5 boost at d21, $2.5x10^{11}$ vp. Randomized, placebo-controlled, double-blind trial. 19:1 randomization to either prime/boost (1,900 participants) or placebo (100). According to epidemiological	Primary objective relates to immunogenicity. If an outbreak was to occur, efficacy would also be assessed.	N/A	Not yet recruiting. Anticipated study start 6/2017; data collection for primary outcome measure finalized by 6/2019.

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
				situation, option for ring vaccination around confirmed EVD cases. Follow-up for 12m. Enrolment expected from 7/2017.			
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSVΔG-ZEBOV-GP) with or without homologous boost							
Agnandji et al., 2016 (17) (PMID: 25830326; NCT02283099, NCT02287480, NCT02296983, and PACTR201411000919191)	1	Africa (Lambaréné, Gabon; Kilifi, Kenya) and Europe (Hamburg, Germany; Geneva, Switzerland)	*Gabon, Kenya, Germany:* 99 healthy adults aged 18–55y, both sexes (75% men). *Switzerland:* 59 healthy adults aged 18–65y, both sexes (61% men)	*Gabon, Kenya, Germany:* Open-label, uncontrolled, dose-escalation trial of single rVSV dose at $3x10^5$–$2x10^7$ pfu. *Switzerland:* randomized, placebo-controlled, double-blind trial at rVSV doses 1–$5x10^7$ pfu; first 19 participants open-label at $1x10^7$ pfu, then 1:1 randomization to 1 $x10^7$ or $5x10^7$ pfu for deployable participants or 1:1:1 randomization to 1 $x10^7$, $5x10^7$ pfu or placebo for non-deployable participants; unmasked after 3m. Follow-up for 28d (safety) and 180d (immunogenicity). Enrolled 11/2014–1/2015.	All vaccinees showed GP-specific antibody responses; similar titres for different doses that were sustained at 180d. Most vaccinees showed neutralizing antibodies, with higher titres at higher doses.	Within 1st day, mild-to-moderate adverse events, with fever being most frequent (up to 30% vaccinees). In 2nd week, 11/51 (22%) Geneva participants showed arthritis affecting 1–4 joints with 8d median duration, but only 2 (3%) vaccinees did at other three trial sites. No serious vaccine-related adverse events reported.	Completed (Germany, Switzerland); recruitment completed, but study ongoing (Gabon, Kenya)
Huttner et al., 2015 (18) (PMID: 26248510; NCT02287480)	1/2	Switzerland (Geneva)	67 healthy adults aged 18–65 years, of which 38 individuals were potentially	Randomised, placebo-controlled, double-blind trial. Non-deployable participants 5:1 randomised to rVSV dose	For preliminary results, see Agnandji et al., 2016; here interim results reported. Similar seropositivity rates were similarly (>90%), but	Mild, early-onset reactogenicity reported in 88%, 98% and 15% of low-, high-dose	Completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			deployable to areas with ongoing transmission	$5x10^7$ (9 participants), $1x10^7$ (17), $3x10^5$ pfu (38) or placebo (13); open-label for 38 deployable participants at 3 dose levels (13 at lowest dose). Follow-up for 12m. Enrolment 1/2015.	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.	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.	
Regules et al., 2015 & 2017 (19, 20) (PMID: 25830322; NCT02269423 and NCT02280408)	1	USA (Maryland)	78 healthy adults aged 18–50y, both sexes (71% men)	Placebo-controlled, double-blind, dose-escalation trial. Consecutive enrolment to $3x10^6$, $2x10^7$ and $1x10^8$ pfu (60 participants) or placebo (18). At one of two sites, participants received 2nd dose at d28. Follow-up for 28d (after either 1st or 2nd injection). Enrolment 10/2014–1/2015.	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 for further evaluation of rVSV at dose $2x10^7$ pfu and indicate that 2nd dose boost antibody responses.	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
Ebola ça suffit ring vaccination trial consortium, 2015 (21) Henao-Restrepo et al., 2015 & 2017 (22, 23)	3	Guinea, Sierra Leone	4,160 vaccinated participants (9,096 enumerated people) in 98	*Cluster-randomized trial:* Ebola Ça Suffit! trial. Cluster-randomized (ring) trial; single rVSV dose of $2x10^7$ pfu; randomization	*Cluster-randomized trial:* Vaccine efficacy was 100.0% (95% CI: 68.9–100.0%). *Front-line worker trial:* Only	*Cluster-randomized trial:* 54% of participants reported at ≥1	*Cluster-randomized trial:* completed

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
Soumah et al., 2016 (24) (PMID: 26215666 26248676 & 28017403; PACTR201503001057193)			clusters 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)	by cluster into immediate or 21d delayed vaccination. No immunological testing. Follow up for 84d. Enrolled 3/2015–1/2016. *Front-line worker trial:* non-randomized, open-label trial for safety and 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.	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.	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.	F*ront-line worker trial:* recruitment completed, but study ongoing
Widdowson et al., 2016 (25) Goldstein et al., 2016 (26) (PMID: 27387395 & N/A; NCT02378753)	2/3	Sierra Leone	8,600 clinical and nonclinical workers and other Ebola frontline workers (e.g., surveillance, burial, and ambulance	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	Preliminary data indicated 8,016 vaccinees in 5 districts, of whom 4,190 (52%) immediately vaccinated. 64 participants became EVD suspect, but 60 who gave sample tested all negative. 539 participants enrolled in immunogenicity sub-study,	No serious vaccine-related adverse events or deaths report among vaccinees. Safety profile similar to published studies.	Recruitment completed, but study ongoing

Published references (PMID; clinical trial registry reference)	Phase	Location	Population	Design	Efficacy/immunogenicity results (other findings)	Safety results	Trial status
			personnel)	period. Implemented as individually randomized trial of workers assigned to receive vaccine immediately or delayed by 18–24w. Follow-up monthly for 6m. Two sub-studies: safety in 400 participants (200 vaccinees, 200 placebo) 5 times within 28d post-vaccination; immunogenicity in 500 participants with 4 blood drawings up to 12m post-vaccination. Enrolled 4–8/2015, delayed vaccination completed in 12/2015.	but testing ongoing.		
Günther et al., 2011 (27) (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 (28) (PMID: 25742465; N/A)	N/A	USA	1 (post -exposure of 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	Ebola virus glycoprotein gene (both included in the vaccine) but Cytokine secretion and T lymphocyte and plasmablast activation were detected shortly after	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
				Leone in 9/2014. Vaccine administered 43h after accident	vaccination. Later, GP-specific antibodies and T cells were detected, but not antibodies against Ebola viral matrix protein 40 (not generated from vaccine). PCR was consistently negative for Ebola virus nucleoprotein gene (not in the vaccine).		
rVSV expressing envelope GP of Zaire Ebola virus species (Mayinga variant, rVSV N4CT1 EBOVGP1)							
Matassov et al., 2016 (29) (PMID: N/A; NCT02718469)	1	USA	39 healthy adults, aged 18–55, both sexes	Randomized, placebo-controlled, double-blind, truncated dose escalation trial. 10:3 randomization in 3 groups to either vaccine (at doses $2.5x10^4$, $2.5x10^5$ & $2.0x10^6$ pfu for each group) or placebo. Second dose administered at 28d interval. Follow-up for 26w (4m). Enrolment early 2016.	Preliminary results are from still blinded groups. GP-specific antibody responses 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.	Adverse events across all dose groups were generally mild. Most frequently reported events were pain at injection (13/39) and fatigue (5/39).	Completed
Multiple vaccines (Ad26, ChAd3, MVA [MVA-BN-Filo], rVSV [rVSVΔG-ZEBOV-GP])							
Kennedy et al., 2016 (30) Bolay, 2016 (31) (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 follow-up, which	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.	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.

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